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Editorial

MEXICO 1978

Now that the XI International Leprosy Congress has come and gone, many people will be asking awkward questions. Was it really worth it—the huge expenditure of money to bring together a thousand people?—the huge expenditure of effort and time for the detailed organization of the scientific sessions and the Workshops, the translation and printing of 333 abstracts in three languages, to say nothing of the social programme and the reservation of airplane seats and hotel rooms? Was it worth it? What was really accomplished? What will be its impact—if any—on the treatment and control of leprosy in the world? Will Mexico 1978 have any effect on the direction or content of leprosy research in the next five years?

The conventional stock-in-trade answers are unconvincing. Of course, "a good time was had by all". Of course, friend met friend, and had highly interesting conversation. Of course, like-minded people got together to discuss common problems. But with the long-distance telephone and air mail, is any additional benefit likely to accrue to the sufferer from leprosy or to those at risk of catching leprosy, from the masses of paper and the deafening Babel of multilingual communications?

Let us frankly admit that no unexpected or dramatic "breakthrough" was announced at Mexico. In any case, sober scientists do not usually conceal their research findings until they can allow them to burst upon a waiting world on such an occasion as an International Congress. Mostly, progress is made by the accumulation of small bits and pieces in which some genius will eventually discern a recognizable pattern.

Thus, in experimental leprosy, the immunologically deficient mouse has been joined by the armadillo, the nude mouse, the thymectomized rat, the hedgehog and the Korean chipmunk. Unimaginable quantities of *M. leprae* are now required, and obtained, by the World Health Organization cooperative IMMLEP programme, and progress is reported on the analysis of the complicated antigenic structure of cell-walls and cytoplasm. Interesting, and potentially important immunological comparisons between *M. leprae* and its nearest relations are being made, and further steps taken along the path that must lead to the making, appraisal and evaluation of specific skin tests and eventually to a specific protective vaccine. Perhaps some addition to, or modification of classical BCG vaccine will serve the purpose.

In microbiology, work was reported on the fascinating possibility that strains of organisms obtained from human lepromatous material may develop acid- and alcohol-fastness in culture. Over the years, successive claims to successful growth in artificial culture media have failed to find confirmation, and the use of the many accepted criteria for identification now available make the task of exclusion more precise and less difficult. In this connection, it is

now recognized that the addition of hyaluronic acid to special media may facilitate and enhance the growth of several mycobacteria, but "not proven" must be the verdict of some recent claims. The use of semi-solid agar, pyruvate, mycobactins and other possible adjuvants indicates the continuing interest in attempts to culture *M. leprae*.

Other important matters in this field were aired in Mexico, if not finally decided to the equal satisfaction of all interested parties. The occurrence of a leprosy-like disease, caused by a *M. leprae*-like organism, in wild armadillos in the southern United States is now generally admitted, and further work should indicate the epidemiological importance of this potential reservoir of infection, as well as confirm the intrinsic immunological interest of the armadillo.

The excellent investigations reported both at the scientific sessions and the pre-Congress Workshops, and the general air of scientific keenness and enthusiastic pursuit of new knowledge were met by no corresponding optimism by the clinicians and therapists. Here, the atmosphere was not quite one of unrelieved gloom and despondency, but certainly there was an air of sober—almost sombre—realism as the twin spectres of drug-resistance and persister organisms were cited and examined. Despite the availability for 30 years of an effective—and cheap—anti-leprotic drug, mycobacteriostatic (if not mycobactericidal) in standard therapeutic doses, an insufficient impact has been made on the worldwide prevalence of leprosy. The conclusions and recommendations of the WHO 5th Expert Committee on Leprosy were endorsed, and the recommendations of the LEPRA "Heathrow Report" were put forward as a series of practical measures for recognizing, treating and preventing drug resistance. Participants from countries where leprosy is most prevalent, countries facing other and more urgent problems of transmissible disease and nutrition, were in general far from hopeful that leprosy would be taken seriously enough by their governments (or by interested voluntary agencies) and resources made available to counter these two threats. Both the Workshop and the scientific session emphasized the urgent necessity for controlled trials of combinations of drugs, and for chemical modifications of some existing drugs to enhance their anti-leprotic activity. Knowledge is urgently needed on the most effective—and least costly—way to administer rifampicin, for instance; otherwise this valuable drug may be so misused that its potential wide usefulness may be seriously impaired.

Newer treatments designed to modify the immunological response, temporarily or for longer periods, by introducing substances like transfer factor, or clones of lymphocytes derived from healthy donors, or donors suffering from tuberculoid leprosy, or such products as levamisole, have given discordant or equivocal results, and no general recommendations are as yet forthcoming.

It is in this area of common interest that the clinicians and those responsible for programmes for leprosy control met the immunologists who are elucidating the complex antigenic structure of *M. leprae* and the unexpectedly complicated pattern of cellular and humoral immunity. The subject of immunology attracted more papers than any other, an indication of the widespread interest in and importance of leprosy as an investigative and demonstrative model. The

techniques of crossed immuno-electrophoresis and radio-immune-assay are being used in several laboratories as tools for identifying the antigenic patterns of *M. leprae* and related mycobacteria. Although at first sight this highly specialized and sophisticated type of investigation may appear to be far removed from the problems confronting the field worker in his day-to-day contacts with the defaulting patient or the uncooperative contacts, or the breakdown in the supply of dapsone—yet the solution of these questions, or perhaps the pursuit of "leads" arising during current investigations, will eventually provide the man-in-the-field with more effective weapons and strategies with which to attempt to treat and control leprosy.

Several reports were presented of the relation between skin tests with various antigens and past infection with leprosy, with active or quiescent disease, and with disease characterized by different degrees—or complete absence—of cell-mediated immunity. The search for the specific immune defect in patients with lepromatous leprosy continues, as well as the search for some field test that would readily and reliably (and inexpensively) identify those individuals who have this defect, and especially those individuals who are possibly exposed to viable *M. leprae* in the household or community. New studies are being made of the results of skin testing with armadillo-derived lepromin and human lepromin. A practical aspect of these studies is the light they may shed on the variable results of adequately controlled BCG prophylaxis programmes; it may be that previous exposure to opportunist mycobacteria may account for the difference in skin sensitization and protection rates afforded in the well-known trials.

The possible transmissible or hereditary factor in susceptibility to leprosy continues to baffle investigators. Blood groups, genetic markers, and now HLA (histocompatibility complex) antigen patterns do not provide any more than indications of present ignorance and future possible avenues of research. The well-known clustering of leprosy in families, and the reported apparent refractoriness of 95% of spouses of adult leprosy patients, provided the baselines for much theorizing and little solid progress.

The epidemiometric model recently developed is proving its usefulness and adaptability. In particular, the inputs concerning dapsone resistance, sub-clinical infections and persister viable organisms are modifying the whole picture of leprosy control. In the light of the increasing population in countries where leprosy is still virtually uncontrolled, the emerging picture is likely to cause deepening concern about the effectiveness of our present methods of control.

An upsurge of interest in nerve damage in leprosy is apparent in many quarters. The pathophysiologists are now in broad agreement concerning the main features of nerve function and malfunction in leprosy, and the pathogenesis and triggering mechanisms are now better understood. The relative importance of the various possible mechanisms, operative in the individual patient, merit more investigation. The relative importance of temperature, entrapment, trauma, immunological factors (such as immune complexes and complement) and possible sensitizing phenomena (like biochemical products derived from damaged nerve fibres or degenerating

mycobacteria)—will receive increasing attention from investigators approaching the subject from diverse standpoints. It was suggested that the whole subject of nerve damage in leprosy demands a full scientific session at the next Congress.

The role of surgery in the relief of nerve pain and the prevention of further nerve damage was studied in several well-documented papers, but such delicate surgery, it was urged, should be practised by medically-minded surgeons, and not by dabbling physicians. Convincing results of nerve-decompression, when practised for precise indications in appropriate surroundings, were presented. In this matter of reconstructive and plastic surgery, it was emphasized that the patient whose deformity or incapacity was due to leprosy should not suffer any discrimination on this account, but should wherever possible be admitted to a general ward. Yet reconstructive surgery in a leprosy patient demands high standards of knowledge, judgement and operative skill.

The rehabilitation of the sufferer from leprosy was sympathetically considered in more than one session. The surgeons and the social workers were as concerned as the clinicians in charge of leprosy programmes. Some were of the opinion that the abolition of stigma and the equal treatment of leprosy sufferers could be achieved only by the complete integration of leprosy into the health programmes of government, while others were equally convinced that integration would mean that the leprosy patient would cease to receive even the treatment and consideration he now enjoys in many "vertical" programmes. All were agreed, however, that education in its broadest sense was the common ground that must provide the essential *sine qua non* of any attempt to treat leprosy sufferers humanely and to ensure that all who needed help—medical, surgical, financial, social—could be sure of having access to it. The vicious circle of fear, stigma and prejudice can be interrupted only by effective health education.

The word "leprosy" and its derivatives came in for some critical examination. The crux of the matter is that in most linguistic groups, the real sting of leprosy resides in the disease and not in the name by which it is known. The members of the sessions on social aspects of leprosy faced this problem seriously in the course of the well-attended meetings, and the hope was expressed that some of the lingering old-style leprosaria might be utilized for the care of those disabled from whatever cause.

Not only in the special pre-Congress Workshop, but underlying many of the sessions on many diverse aspects of leprosy, was the urgent and continuing necessity for training for everybody concerned with leprosy; doctors and nurses, physiotherapists and laboratory technicians, and especially the auxiliary worker who is the keystone in most effective leprosy control programmes. Standardization of teaching materials is not nearly so important as the provision and availability of materials appropriate and adapted to the local needs of the situation, in language, pictorial or diagrammatic presentation, in content and in the down-to-earth practical nature of booklets, audio-visual aids, demonstrations, etc. The voluntary agencies were urged to continue their much-appreciated contribution, in this area, to the present

worldwide leprosy campaign, and to enlist the cooperation of technically qualified specialists to ensure the didactic acceptability of the materials they were publishing and disseminating.

A word must be said about the poster presentations. Despite initial misgivings on the part of some, it was evident that many authors welcomed the opportunity to present their work in this form, just as they welcomed the chance of discussion with interested individuals, unstressed by the demands of platform presentation within a strictly limited time.

Perhaps there were too many papers at Mexico, too many people, too little time for discussion. Perhaps there was a tacit acknowledgement that sophisticated research gains a greater popular rating than the humdrum activities of a good leprosy control programme. But research is the lifeblood of leprosy, and unless we can make available to the many the privileges of diagnosis, care and treatment enjoyed by the few, our leprosy programmes in the future will achieve no better results than they have in the past.

Where do we go from here?

I detect a note of sober—even sombre—realism in the papers and sessions. We are learning more of the complexity of the leprosy organism and of the immune response to challenge. And the twin spectres of drug resistance and persistently viable organisms dominate much of our thinking today. But I can also discern an excitement, an enthusiasm, as unforeseen and unimagined vistas of research are opening up to the research immunologist and microbiologist.

Coupled with the realism and the excitement, can we not all see, and welcome, the increasing interest in the whole social environment of the sufferer from leprosy? He is a fellow human-being, a man (or woman) like unto ourselves, with hopes and frustrations, with family contacts, with needs for food and housing and employment and the simple joys of life.

In this Congress, we met each other, and appreciated each other's work. And we are coming to realize, whatever our particular field of activity, that we need each other more than ever before as we face the common foe.

Highlights? Yes, a few. More importantly, a general intense glow of interest and cooperate effort, a warmth of mutual appreciation and understanding, and a realization of our interdependency in the One World, the global community. Coupled with all this, is the working together of the research scientist, the concerned therapist, and those deeply moved by the human plight of the sufferer from leprosy.

This spirit augurs well for the future—whatever the serious problems we may have to face. Let us put into practice what we already know, and strive after new knowledge that will help solve this intractable and challenging problem.

S. G. BROWNE

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Metabolic Disposition of Dapsone in African Leprosy Patients*

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In a preliminary study (Study 1) of 20 African leprosy patients receiving various doses of dapsone (DDS), we found a distribution of capacities to acetylate DDS that suggested the polymorphism of acetylation observed in other populations. A more detailed investigation (Study 2) in a subsequent group of 21 patients using sulfamethazine (SMZ) as the primary drug for determining acetylator phenotype as well as DDS clearly demonstrated that African patients exhibit the polymorphism of acetylation of these drugs. As in other populations studied previously, plasma clearance rates of DDS as expressed by the half-time of disappearance were unrelated to acetylator phenotype. Clearance rates or acetylation capacities were also unrelated to age, sex, or body weight of the patients, or to the dose of DDS administered per week. In 5 patients who participated in both Studies 1 and 2, no consistent marked differences in acetylation of DDS or plasma clearance rates of DDS were noted even though the two studies were separated by 11 months. A positive linear relationship between the 4-h level of DDS after the last dose and total dose of DDS per week was observed.

Introduction

Dapsone (4,4′-diaminodiphenylsulfone, DDS) has been for over 30 years and continues to be the principal drug for leprosy chemotherapy (Sansarricq, 1977). The repository form of this drug, acedapsone (4,4′-diacetamidodiphenylsulfone, DADDS), has also been employed as an effective intermittent treatment for leprosy (Russell *et al.*, 1975; Peters *et al.*, 1977*b*).

In a continuation of our efforts to define the characteristics of various human populations for metabolizing DDS (Gelber *et al.*, 1971; Peters *et al.*, 1972, 1975, 1976*b*, 1977*b*), we present in this paper the results of studies in African leprosy patients.

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Materials and Methods

The DDS used in these studies was in the form of 25- or 50-mg tablets (P.C.B., Brussels, Belgium) in which we previously found only minor sulfone contaminants (Gordon *et al.*, 1975). The SMZ was a crystalline material (Lederle Laboratories, Pearl River, New York, U.S.A.). Serum or plasma concentrations of DDS and monacetyl DDS (MADDS) were measured routinely by a fluorometric procedure (Peters *et al.*, 1970); in samples exhibiting levels near the limit of sensitivity of this method (0.01 μg/ml), we applied the more sensitive chromatographic-fluorometric technique of Murray *et al.* (1971). Plasma and urine concentrations of SMZ and *N*-acetyl SMZ (AcSMZ) were measured colorimetrically (Gelber *et al.*, 1971).

Study 1 was a preliminary survey of levels of DDS and MADDS in samples of serum collected from patients receiving various therapeutic regimens of DDS.* It was undertaken without detailed plans regarding any other subsequent evaluations and interpretations. Sera were obtained at 8, 24 and 96 h from 5 patients receiving 25 mg DDS, twice weekly; at 8, 24 and 72 h from 10 patients receiving 25 mg DDS, thrice weekly; and at 8, 24 and 48 h from 5 patients receiving 50 mg DDS, thrice weekly. From each patient, the last sampling of serum was taken immediately before the next dose of DDS. The serum samples were stored and shipped frozen over dry ice to the Menlo Park laboratories where analyses were performed within 8 weeks of the time of collection. We (Gelber *et al.*, 1971; Peters *et al.*, 1972) and others (Ellard *et al.*, 1971) had found that DDS and MADDS were stable in serum or plasma stored frozen for up to 12 months.

Eleven months later, Study 2 was carried out wherein 21 patients were phenotyped for acetylator status (Peters *et al.*, 1975) using an oral dose of 10 mg SMZ/kg after having been removed from their regular DDS regimens for 7 days. Following SMZ, urine was collected during 0 to 6 h, and a single 6-h heparinized plasma sample was taken from each patient. The patients were immediately returned to their DDS regimens. Five of these patients had been subjects in Study 1. All patients of Study 2 provided heparinized plasma at 4, 6, 8, 24 and 48 h after DDS administration. Nine of the 21 patients were receiving 25 mg DDS twice weekly; 8, 25 mg DDS thrice weekly; 2, 50 mg DDS twice weekly; and one each, 50 mg DDS thrice weekly and five times weekly. All plasma and urine samples were frozen after collection and shipped frozen to the Menlo Park laboratories for analysis.

Percentage acetylation of DDS and SMZ was calculated from the fraction: acetylated drug divided by the total of parent and acetylated drug. In all computations, acetylated drug was expressed in parent drug equivalents. In studies with DDS, the mean percentage acetylation was the average of values obtained from all plasma samplings in each patient. Relationships between groups of data were examined by calculating linear regression equations and correlation coefficients (r) to determine whether the slopes of the lines were significantly different from zero (Goldstein, 1964). Half-times of disappearance ($T_{\frac{1}{2}}$) for

* We are indebted to Dr C. H. Binford, Armed Forces Institute of Pathology, Washington, D.C., for acting as intermediary in this preliminary study.

TABLE 1
Results of Study 1

Treatment group	Study-patient designation	% Acetylation of DDS Mean ± S.E.	$T_{\frac{1}{2}}$ value* (h) DDS	$T_{\frac{1}{2}}$ value* (h) MADDS
25 mg DDS, 2 × per week	1– 1	19 ± 2	24	28
	1– 2	19 ± 2	38	47
	1– 3	23 ± 2	33	36
	1– 4	18 ± 1	83	62
	1– 5	27 ± 1†	—†	—†
25 mg DDS, 3 × per week	1– 6	45 ± 1	35	32
	1– 7	42 ± 2	27	32
	1– 8	15 ± <1	24	24
	1– 9	13 ± 1†	—†	—†
	1–10	13 ± 1	26	30
	1–11	16 ± 1	28	34
	1–12	36 ± <1	41	37
	1–13	14 ± <1	56	48
	1–14	13 ± <1	38	48
	1–15	14 ± 1	61	49
50 mg DDS, 3 × per week	1–16	34 ± <1	30	32
	1–17	14 ± 1†	—†	—†
	1–18	30 ± <1	18	16
	1–19	33 ± 2	22	27
	1–20	20 ± <1	16	18

* $T_{\frac{1}{2}}$ values were calculated from regression equations of levels of DDS at 8 and 24 h and either 48, 72 or 96 h following administration; r values $\geqslant -0.95$.

† Only 2 specimens of serum were collected.

DDS and MADDS were calculated from the regression equations representing the logarithmic decay of the compounds with time. The Student t-test was used to determine the significance of differences between mean values (Goldstein, 1964).

Results

From the results of analyses of the sera of Study 1, we calculated the mean percentage acetylation of DDS and $T_{\frac{1}{2}}$ values of DDS and MADDS*. These are listed in Table 1, wherein the patients are grouped by dosage of DDS. Each patient exhibited nearly the same acetylation of DDS at the various times of sampling of serum as shown by the very small variations around the mean. From these results, we tentatively classified patients 5, 6, 7, 12, 16, 18 and 19 as rapid acetylators, and the other 13 patients as slow acetylators by assuming an antimode of between 23 and 27% acetylation. Within the various treatment groups of Table 1, we calculated that 20% of the low dosage group, 30% of the

* Raw data from these patients and those from patients of Study 2 are available on request from the senior author.

TABLE 2
Results of Study 2

Treatment group	Study-patient designation	% Acetylation of SMZ* Plasma	% Acetylation of SMZ* Urine	% Acetylation of DDS Mean ± S.E.†	$T_{\frac{1}{2}}$ value‡ DDS	$T_{\frac{1}{2}}$ value‡ MADDS
25 mg DDS, 2 × per week	2–1	16	52	10 ± <1	18	20
	2–02	71	88	26 ± <1	25	27
	2–03	68	89	32 ± 2	24	31
	2–04	36	60	19 ± <1	24	21
	2–05	24	54	13 ± <1	23	22
	2–8	24	53	15 ± <1	18§	21§
	2–09	24	56	12 ± 1	33	54
	2–010	56	91	31 ± 1	32	35
	2–011	33	50	16 ± <1	34	39
25 mg DDS, 3 × per week	2–7	87	94	41 ± 1	24	27
	2–012	38	70	21 ± <1	22	23
	2–013	74	88	32 ± <1	25	24
	2–014	73	88	31 ± 1	36	36
	2–015	24	67	12 ± 1	40	44
	2–017	23	59	19 ± <1	33	33
	2–018	29	59	15 ± <1	40	31
	2–019	32	64	15 ± 1	29	26
50 mg DDS, 2 × per week	2–16	71	85	35 ± <1	35	36
	2–020	27	65	18 ± <1	29	35
50 mg DDS, 3 × per week	2–6	75	87	37 ± 1	23	27
50 mg DDS, 5 × per week	2–021	70	86	25 ± 1	27	34

* Values are from plasma collected at 6 h and urine collected during 0–6 h following an oral dose of 10 mg SMZ per kg.

† Mean value from levels of DDS and MADDS in plasma at 4, 6, 8, 24 and 48 h.

‡ $T_{\frac{1}{2}}$ values were calculated from regression equations of levels of DDS and MADDS at 8, 24 and 48 h unless otherwise noted; r values $\geqslant -0.95$.

§ $T_{\frac{1}{2}}$ values were based on plasma levels at 4, 6, 8 and 24 h.

intermediate dosage group, and 60% of the high dosage group were rapid acetylators. The last two columns of Table 1 list the $T_{\frac{1}{2}}$ values for DDS and MADDS in these patients. No definitive relationships between dosage of DDS or percentage acetylation of DDS and these $T_{\frac{1}{2}}$ values were clearly indicated, although the 5 patients receiving the highest DDS dosage apparently exhibited, on the average, shorter $T_{\frac{1}{2}}$ values than the other groups.

The results of Study 2, which was more detailed than Study 1, are shown in Table 2. Again, patients are grouped by the DDS dosage and the patients that participated in both studies are indicated by employing the same patient numbers as those shown in Table 1. The percentage acetylation of SMZ in plasma and urine are shown in columns 3 and 4, respectively. From the acetylation of SMZ in plasma—the most discriminating test for acetylator phenotype (Peters *et al.*, 1975)—we divided these patients into 9 rapid acetylators, i.e. those exhibiting a percentage of acetylation of SMZ ranging from 56 to 87%; and 12 slow acetylators, i.e. those exhibiting a percentage of acetylation of SMZ ranging from 16 to 38%. The acetylation of SMZ in urine and of DDS in plasma agreed with the assignment of acetylator phenotype for each patient. Also, the 5 patients of Study 2 (1, 8, 7, 16 and 6), who were also subjects of Study 1, were found to be the same phenotype as that suggested by the results of Study 1. Again, variability of the acetylation of DDS at the various times in individual patients of Study 2 was small (column 5) indicating that acetylation was stable during the time of this study. In the groups of patients receiving 50 and 75 mg DDS per week, 33 and 38% were rapid acetylators, respectively. In the 4 patients receiving $\geqslant$100 mg DDS per week, 3 (75%) were rapid acetylators. Columns 6 and 7 of this table list the $T_{\frac{1}{2}}$ values of DDS and MADDS in these patients. Evaluations of these values will be subsequently discussed.

Table 3 summarizes the distribution of acetylator phenotypes in both Studies 1 and 2. Column 5 shows that the antimode of DDS acetylation assumed for patients of Study 1 was found to occur also in those of Study 2. Nevertheless, it is clear from the distribution of acetylation of SMZ in plasma (column 3) and in urine (column 4) that this drug is far superior to DDS for discriminating between acetylator phenotypes. The 5 patients of Study 2 (last

TABLE 3
Distribution of acetylator phenotypes in Studies 1 and 2

Study*	Acetylator phenotype*	% Acetylation (mean, range) SMZ, plasma	SMZ, urine	DDS, plasma
1 (20)	Rapid (7)	—	—	35, 27–45
	Slow (13)	—	—	16, 13–23
2 (21)	Rapid (9)	72, 56–87	88, 85–94	32, 25–41
	Slow (12)	28, 16–38	59, 52–70	15, 10–21
2 (5)†	Rapid (3)	78, 71–87	89, 85–94	38, 35–41
	Slow (2)	20, 16–24	52, 52–53	12, 10–15

* The number of patients is shown in parenthesis.
† These 5 were subjects in both Studies 1 and 2.

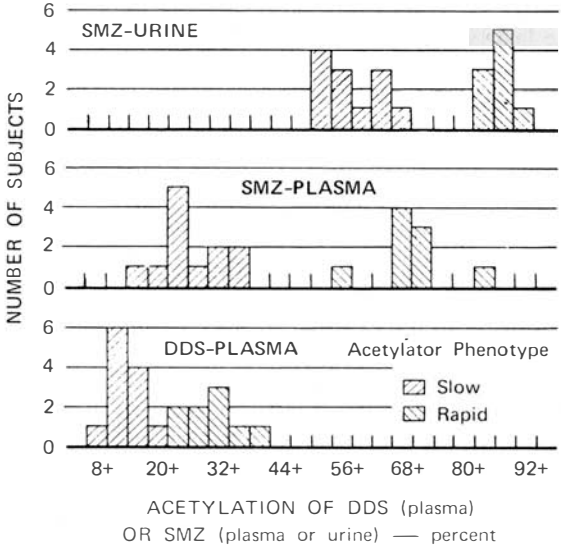

Fig. 1. Distribution of acetylator phenotypes of the patients of Study 2. On the abscissa each division represents a range of 3 percentage units, e.g. 8+ = 8–11%.

line), who were participants in Study 1 also were more clearly phenotyped with SMZ than with DDS. This point is strikingly emphasized by Fig. 1, a plot of the distribution of acetylation capacities for SMZ and DDS of the patients of Study 2.

More detailed comparisons of the results in the 5 patients of both studies are shown in Table 4. Only patients 1 and 7 were on the same dosage schedule of DDS in the two studies. Significant differences ($P < 0.001$) in the mean percentage of acetylation in the two studies were noted in patients 1 and 6, but not in the other 3 patients. However, these differences did not alter the classification of phenotype in patients 1 and 6 and therefore, within these limits, we can conclude that the acetylation capacity of the individuals was sufficiently stable with time to yield the same phenotype. Patient 7, on the same dosage schedule, and patients 8 and 16, on different schedules, exhibited identical mean values in the two studies. These results indicate that acetylation capacity is relatively stable with time and is not influenced by the dosage schedules employed in these studies. Similarly, the $T_{\frac{1}{2}}$ values of DDS and MADDS in the two studies did not differ consistently or substantially, indicating also that these parameters were relatively stable and not influenced by the dosages of DDS employed.

The mean (±S.E.) age and body weight of the 21 patients in Study 2 were 38 (± 2) years and 54 (± 2) kg, respectively. The 8 female patients of the group had a mean age of 34 (±3) years and a mean body weight of 52 (±2) kg; the 13 male patients averaged 40 (±3) years and 55 (±2) kg. Neither the mean ages nor the body weights of the two sexes differed significantly. The group of

TABLE 4
Comparison of results from 5 patients in Studies 1 and 2

Patient number*	% Acetylation of DDS Mean ± S.E.		$T_{\frac{1}{2}}$ of DDS (h)		$T_{\frac{1}{2}}$ of MADDS (h)	
	Study 1	Study 2	Study 1	Study 2	Study 1	Study 2
1	19 ± 2	10 ± <1	24	18	28	20
6	45 ± 1	37 ± 1	35	23	32	27
7	42 ± 2	41 ± 1	27	24	32	27
8	15 ± <1	15 ± <1	24	18	24	21
16	34 ± <1	35 ± <1	30	35	32	36

* The dosages of DDS administered were identical in Studies 1 and 2 for patients 1 and 7. Patient 6 received 25 mg DDS, 3 × per week, in Study 1 and 50 mg DDS, 3 × per week, in Study 2. Patient 8 received 25 mg DDS, 3 × per week, in Study 1 and 25 mg, 2 × per week, in Study 2. Patient 16 received 50 mg DDS, 3 × per week, in Study 1 and 50 mg DDS, 2 × per week, in Study 2.

9 rapid acetylator phenotypes consisted of 3 female and 6 male patients; that of the slow characteristic comprised 5 female and 7 male patients. These distributions of sexes within phenotypes were judged to be random by the chi-square test (Goldstein, 1964). Finally, the average age (35 ± 3 years) and body weight (53 ± 3 kg) of the 9 rapid acetylators did not differ significantly from the mean age (40 ± 3 years) and body weight (55 ± 2 kg) of the 12 slow acetylators. Thus, phenotype was not related to sex, age, or body weight.

Table 5 presents similar comparisons of $T_{\frac{1}{2}}$ values of DDS and MADDS for the entire group of patients of Study 2, for the sexes and acetylators, and for the various groups receiving different dosage schedules of DDS. None of the various sub-classes differed significantly from any other, indicating that the disappearance rates of DDS or MADDS were unrelated to any of these characteristics.

TABLE 5
Comparison of the $T_{\frac{1}{2}}$ values for DDS and MADDS in various groups of patients in Study 2

Group*	Mean (±S.E.) $T_{\frac{1}{2}}$ (h)	
	DDS	MADDS
All patients (21)	28 ± 1	31 ± 2
Females (8)	26 ± 2	26 ± 2
Males (13)	30 ± 2	34 ± 2
Rapid acetylators (9)	28 ± 2	31 ± 2
Slow acetylators (12)	29 ± 2	31 ± 2
Patients receiving 25 mg DDS; 2 × per week (9)	26 ± 2	30 ± 4
Patients receiving 25 mg DDS; 3 × per week (8)	31 ± 2	31 ± 2
Patients receiving 50 mg DDS; 2, 3, or 5 × per week (4)	29 ± 3	33 ± 2

* The number of patients in each group is shown in parenthesis.

TABLE 6

Examination of various correlations of the data obtained from the patients of Study 2

Correlation examined	*N*	Correlation coefficient	Significance of confidence interval
% acetylation of SMZ in plasma versus:			
% acetylation of SMZ in urine	21	0.9378	<0.001
plasma SMZ	21	–0.9270	<0.001
plasma AcSMZ	21	0.8166	<0.001
% acetylation of DDS versus:			
% acetylation of SMZ in plasma	21	0.9434	<0.001
% acetylation of SMZ in urine	21	0.9102	<0.001
dose-adjusted plasma DDS at 4, 6, 8, 24 or 48 h in patients receiving DDS 2 × weekly	11*	–0.1876 to 0.5309	N.S.
dose-adjusted plasma DDS at 4, 6, 8, 24, or 48 h in patients receiving DDS 3 × weekly	9†	–0.5422 to –0.0090	N.S.
dose-adjusted plasma MADDS at 4, 6, 8, 24, or 48 h in patients receiving DDS 2 × weekly	11*	0.8988 to 0.9750	<0.001
dose-adjusted plasma MADDS at 4, 6, 8, 24, or 48 h in patients receiving DDS 3 × weekly	9†	0.8736 to 0.9150	<0.005
$T_{\frac{1}{2}}$ of DDS	21	–0.0841	N.S.
$T_{\frac{1}{2}}$ of MADDS	21	–0.0861	N.S.
age	21	–0.1930	N.S.
body weight	21	–0.2638	N.S.
$T_{\frac{1}{2}}$ of DDS versus:			
$T_{\frac{1}{2}}$ of MADDS	21	0.7460	<0.001
age	21	0.1567	N.S.
body weight	21	0.2594	N.S.

* This group consisted of the 9 patients receiving 25 mg DDS, 2 × per week, and the 2 patients receiving 50 mg DDS, 2 × per week.

† This group consisted of the 8 patients receiving 25 mg DDS, 3 × per week, and the patient receiving 50 mg, 3 × per week.

The results of examination of various correlations of the data of Study 2 by linear regression analysis are shown in Table 6. The first three entries indicate that acetylation of SMZ in plasma and in urine were positively related and the variation of the percent acetylation in plasma was a result of decreased amounts of SMZ (negative correlation) and increased amounts of AcSMZ (positive correlation) in plasma. The next two entries indicate that, in individual patients, acetylation of DDS was directly related to acetylation of SMZ in both plasma and urine.

For the next evaluations, we calculated plasma levels of DDS and MADDS in units of μg of compound per mg of DDS per kg of body weight to correct for different dosages used and the different body weights of the subjects. Because the plasma samples were obtained after the last dose of DDS given during the week, we employed that dose of DDS for the different schedules to obtain these dose-adjusted values. Also, for brevity, and because the results of the correlation analyses for different times after administration were the same, we have presented evaluations of the dose-adjusted levels versus acetylation of DDS as ranges of the correlation coefficients (column 3). No significant correlation between percent acetylation of DDS and dose-adjusted levels of DDS in patients receiving 25 or 50 mg DDS, two or three times per week was found. However, similar evaluations employing dose-adjusted levels of MADDS, as shown by the next two entries, were always directly related to the percentage acetylation of DDS. These evaluations indicate that the varying percentage acetylation of DDS resulted from varying amounts of MADDS in plasma, without concomitant changes in the amounts of DDS.

Subsequent entries show that the percentage acetylation of DDS in the individual patients was not related to the $T_{\frac{1}{2}}$ of DDS or of MADDS, or to the age or body weight of the subjects. However, the last group of entries clearly indicates that the $T_{\frac{1}{2}}$ of DDS and of MADDS were directly related but that the $T_{\frac{1}{2}}$ of DDS was unrelated to age or body weight of the patients.

Finally, the different DDS regimens received by these patients allowed an evaluation of the influence of total dose during the week on the levels of DDS observed shortly after the final administration. The first sample collected from these patients, irrespective of the schedule, was at 4 h. At this time, different $T_{\frac{1}{2}}$ values of DDS in the patients would tend to have minimal effect on the level observed. Figure 2 shows that the levels observed at 4 h were directly related to the total mg of DDS given per week and that the plasma levels at 4 h were elevated by approximately the same multiple as that used to increase the total dosage.

Discussion

As we discussed previously (Peters *et al.*, 1975), assignment of acetylator phenotype on the basis of single tests with SMZ presumes that acetylation capacities of individuals are stable characteristics. Our current finding that the 5 patients of Studies 1 and 2 exhibited the same phenotype for the acetylation of DDS adds more evidence to that already accumulated for the stability in man of the acetylation characteristics for INH (Peters *et al.*, 1965), SMZ (Peters *et al.*, 1972), and DDS (Gelber *et al.*, 1971). In addition, our

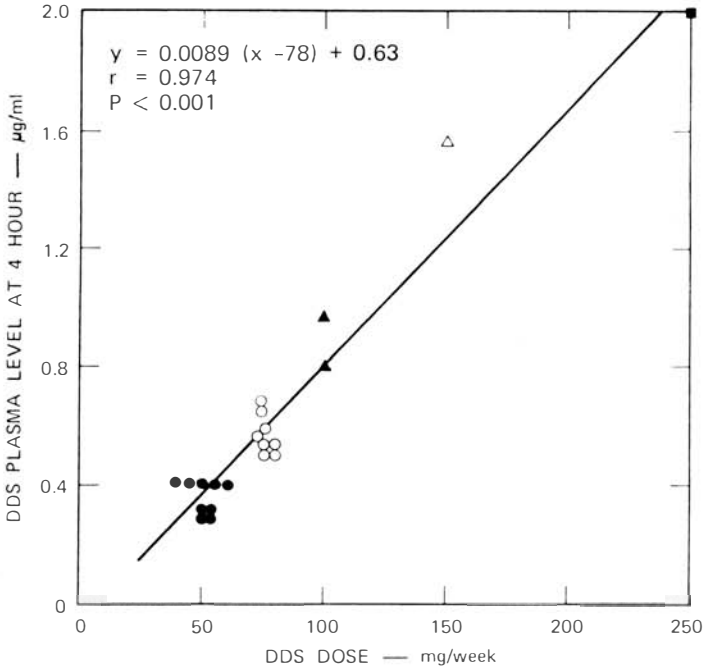

Fig. 2. Relationship between dosage of DDS (mg/week) and plasma levels of DDS at 4 h in the 21 patients of Study 2 (●=25 mg, 2 × per week; ○=25 mg, 3 × per week; ▲=50 mg, 2 × per week; △=50 mg, 3 × per week; ■=50 mg, 5 × per week). The regression equation is in the form $y = b(x-\bar{x}) + \bar{y}$ in which b is the slope of the line and $\bar{x}$ and $\bar{y}$ are the mean values of x and y.

observation of nearly the same $T_{\frac{1}{2}}$ values of DDS and MADDS in these 5 patients in Study 1, and 11 months later in Study 2, confirms similar results we obtained earlier in 6 Filipino subjects (Peters *et al.*, 1972), and indicates that clearance rates of DDS and MADDS from the circulation are also stable individual characteristics even though unrelated to acetylator phenotype.

The clear parallel between the acetylation of DDS and SMZ in all the patients of the current studies adds this ethnic group to those previously studied in the United States (Gelber *et al.*, 1971), the Philippines (Peters *et al.*, 1972), South India (Peters *et al.*, 1975), Costa Rica (Peters *et al.*, 1976*b*), and New Guinea (Peters *et al.*, 1977*b*), wherein acetylation of SMZ and DDS were found to be directly related. In addition, earlier reports of direct parallels among the acetylation of INH, SMZ, and DDS (Gelber *et al.*, 1971) and between INH and SMZ (Evans *et al.*, 1960; Evans and White, 1964) support the conclusion that the same genetic polymorphism for acetylation of all three of these drugs is operative in man. This fact is further supported by comparisons of proportions of the rapid phenotype in the current studies with those reported earlier in various Negro populations. In Studies 1 and 2, we found that 7 of 20 patients (35%) and 9 of 21 patients (43%) were rapid

acetylators, respectively. These are quite similar to the frequency of the rapid phenotype for INH or SMZ of 47% of 95 (Dufour *et al.*, 1964) and 46% of 31 (Mitchell *et al.*, 1960) American Negroes; 35% of 102 Sudanese (Evans, 1962); 45% of 204 East African (Ellard *et al.*, 1975); and 51% of 109 Nigerian Negroes (Fawcett and Gammon, 1975).

Other aspects of the results found in the current studies are the same as those found earlier in other population groups (Gelber *et al.*, 1971; Peters *et al.*, 1972, 1975, 1976*b*, 1977*b*). These include a poorer definition of acetylator phenotype with DDS than with SMZ; the finding that DDS acetylation and levels of MADDS were directly related but that extent of acetylation was not related to levels of DDS; that age or body weight of the patients was unrelated to either acetylation of DDS or the $T_{\frac{1}{2}}$ value of DDS; and that $T_{\frac{1}{2}}$ values for DDS and MADDS were directly related. This last relationship reflects the stability of DDS acetylation with time.

Recently, Olson *et al.* (1978) reported that $T_{\frac{1}{2}}$ values of SMZ in man were dependent upon the dose of SMZ employed in tests for acetylator phenotype. Thus, increasing single doses of SMZ from 5 to 40 mg/kg gave consistent increases in $T_{\frac{1}{2}}$ values, with the maximum increase being 3.5-fold in one subject. Percentage acetylation was not consistently affected by dosage. In the current studies with DDS, we did not observe any consistent dose-effect on either percentage acetylation of DDS or $T_{\frac{1}{2}}$ of DDS in the 3 patients of both Studies 1 and 2 who received different weekly dosages of DDS (Table 4). In addition, no statistical differences in the $T_{\frac{1}{2}}$ values for DDS and MADDS were observed in the sub-groups of patients of Study 2 receiving various weekly doses of DDS (Table 5). Therefore, our observations do not suggest any dose-effect on the acetylation or clearance of DDS. Further support for this conclusion is derived from the linear relationship between the weekly dose of DDS and the level of DDS found 4 h following the last administration (Fig. 2).

In a study of DDS levels in whole blood of patients in Brazil, receiving 100 mg DDS daily, Beiguelman *et al.* (1974) concluded that variations of DDS levels in their patients were not related to the polymorphism of acetylation of DDS. These authors measured only DDS levels. We have emphasized repeatedly in our earliest (Gelber *et al.*, 1971; Peters and Levy, 1971) and subsequent studies (Peters *et al.*, 1972, 1975, 1976*b*, 1977*b*) that the polymorphism for the acetylation of DDS can only be detected by measurements of both DDS and its acetylated metabolite, MADDS, and that rapid and slow acetylators do not exhibit related variations in DDS levels. This conclusion is reinforced in the current studies by the lack of correlation between dose-adjusted DDS levels and percentage acetylation shown in Table 6. As in all previous work in other populations, this table shows that levels of MADDS were directly correlated with percentage acetylation and therefore determine the extent of acetylation of DDS. These aspects of DDS acetylation differ from the polymorphic acetylation of SMZ (Table 6) and INH (Peters *et al.*, 1965) wherein parent drug levels are always negatively, and acetylated drug levels are always positively related with extents of acetylation. Thus, acetylator phenotype can be determined for INH and SMZ by simply measuring levels of the parent drug. This is not true for DDS.

As recently emphasized by Ellard (1975), DDS clearly surpasses all other bacteriostatic drugs for antileprosy activity. Thus, peak plasma or serum concentrations of approximately 300 times the minimal inhibitory concentration (MIC) of DDS for *M. leprae* and maintenance of levels in excess of the MIC for about 10 days are achieved following a single dose of 50 mg of DDS. Also, no tissue barriers to DDS are apparent from results of studies in rodents and man (Peters *et al.*, 1976*a*). However, in patients receiving adequate DDS or DADDS chemotherapy no relationships between lack of response to chemotherapy and metabolic characteristics of poor responders could be discerned (Peters *et al.*, 1977*b*). Furthermore, both earlier (Ellard *et al.*, 1972) and more recent studies (Gelber and Rees, 1975; Peters *et al.*, 1976*b*; Balakrishnan and Ramu, 1977) concluded that the occurrence of DDS-resistance was not related to the metabolic characteristics of the resistant patients. Thus, none of the metabolic characteristics of patients receiving adequate monotherapy with DDS or DADDS have been shown to be responsible for poor response or relapse with DDS-resistant disease.

This may not be the case in patients receiving combination therapy because recent findings indicate that rifampin added to DDS regimens causes accelerated plasma clearance of DDS (Gelber and Rees, 1975) and dramatic decreases in the levels of DDS in plasma, skin, and radial nerve (Peters *et al.*, 1977*a*, 1978). Whether or not these decreases in DDS levels will have an adverse effect on therapeutic response has not been determined. Interactions between DDS and other drugs used for leprosy chemotherapy have not been studied.

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A New Operation Hand Splint for Intrinsic Replacement Tendon Transfers

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For many years in several units which are practising tendon transfer surgery for the intrinsic minus hand in leprosy, a splint has been used to ensure the equalization of the tensions on the four slips of the transplanted tendons during suture (Fritschi, 1971).

This splint has been proved extremely useful, but it has had one major defect namely, that the transverse metacarpal arch has not been maintained during the suturing of the tendons. This has tended to result in a lower tension on the medial fingers because the palm has been stretched out flat as it were. For this reason this splint has perhaps contributed to the tendency towards reversal of this very important arch.

Several workers have at various times stressed the importance of this arch (Antia, 1971; Boilean, Grant and Basmajian, 1965; Brand, 1958; Fritschi, 1971). Some operations have been devised to correct the arch (Beine, 1974; Ranney Donald, 1973), and have given some good results. The positioning splint has at one time been modified by tilting the axis of the metacarpo-phalangeal joints to the ulna side, but this does not seem to have made much difference, and it necessitated different splints for the left and right hands.

The accompanying illustration shows a new splint designed for the flexor approach which has been carved out of solid wood (Fig. 1) and which is now in use (Fig. 2). This splint has the same positions of wrist and M.P. joints as its antecedents, but provides a very definite curve in the metacarpal regions of the palm. Six grooves are provided for the fingers so that the same splint can be used for both hands by leaving two spare grooves empty between the index finger and the thumb. The thumb is also included in the splint and the opponens procedure is done in the same splint, by tilting it over on its side.

The splint is sterilized, just as its metal precursors were, by wrapping it in a cloth wrapper and autoclaving at 120°C for 20 min, as is done for our wooden operating blocks and wooden skin stretchers for skin grafting. The use of wood for these purposes has been well and truly tried over many years, and has not been found wanting.

This splint has been in use for the past 6 months in this institution and we have found it very helpful indeed. It should also be said however, that the

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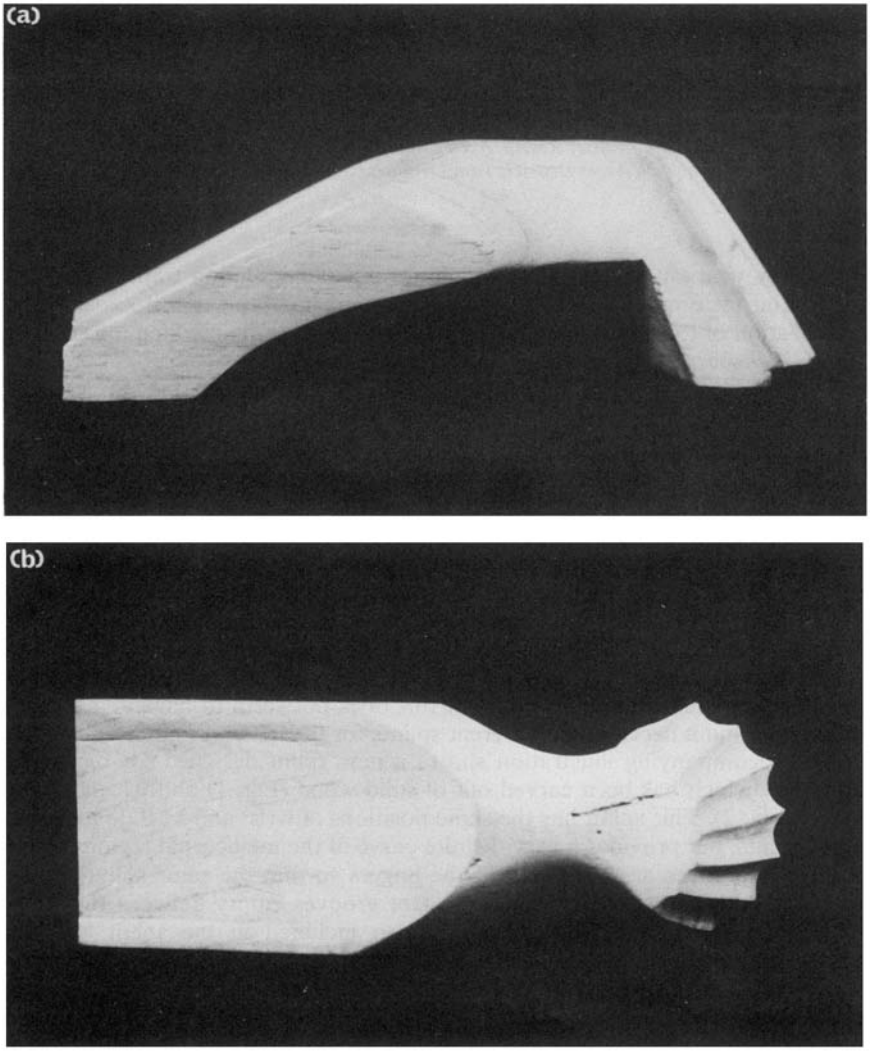

Fig. 1. (a), (b) The new positioning splint which preserves the metacarpal arch during tendon sutures.

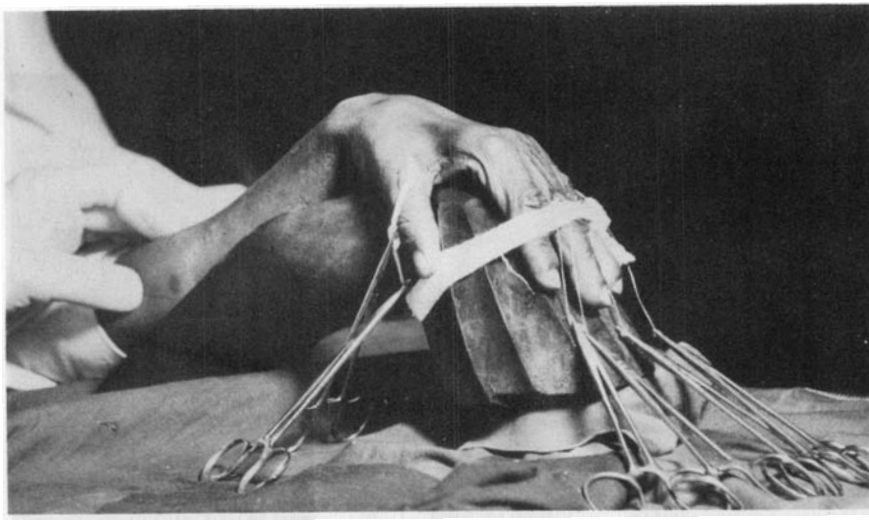

Fig. 2. The splint in use at operation.

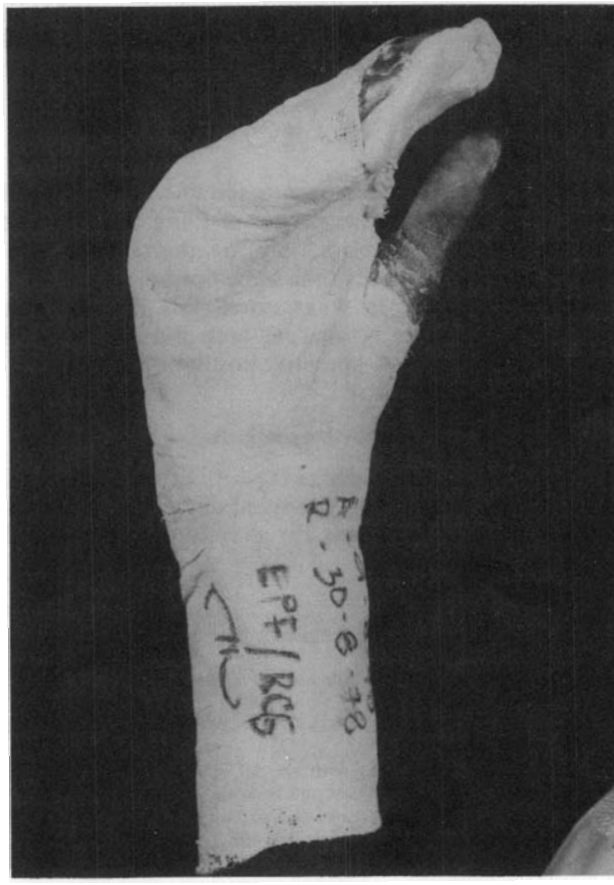

Fig. 3. Position of immobilization in plaster.

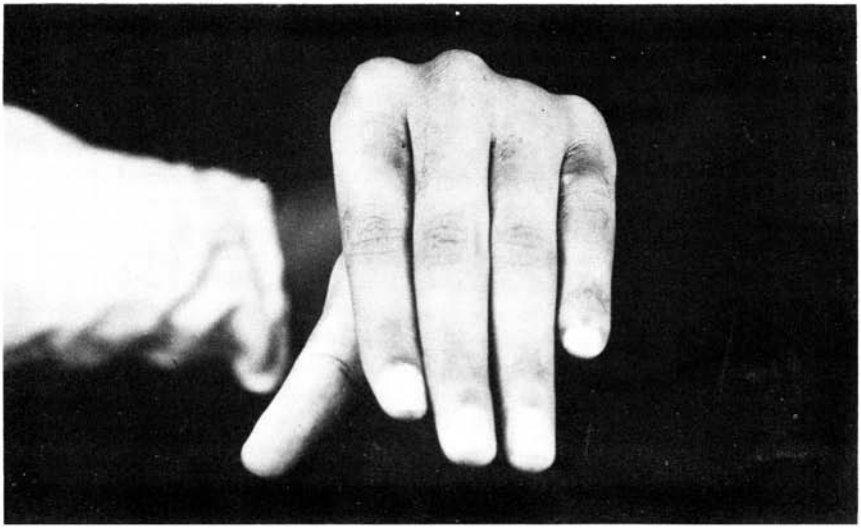

Fig. 4. Post-operative picture showing excellent arch position.

position of the metacarpal arch has been maintained throughout the healing process by applying a post-operative plaster of Paris cast with the arch very carefully preserved (Fig. 3). Thus not only are the tendons sutured in this position but also healing takes place in the same position.

It is still too early to state to what extent this has contributed to the maintenance of the transverse metacarpal arch but the early results have shown some very satisfactory post-operative positions (Fig. 4).

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A Clinical Study of the Mouth in Untreated Lepromatous Patients

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The mouth in 40 consecutive, unselected bacilliferous leprosy patients has been examined. The frequency and various types of lesion are reported. Twenty-three patients showed lesions inside the mouth. Although all parts of the mouth were found to be affected in a varying percentage of patients, the hard palate was involved in all 23 patients. Further, of these 23 patients, 21 showed acid-fast bacilli on the surface of mouth as judged by surface smears and mouthwash. A review of the literature concerning oral lesions in lepromatous leprosy is also presented.

Introduction

Cutaneous manifestations of leprosy are well known. However, detailed descriptions of oral lesions of the disease are lacking in most of the standard text-books. This is possibly on account of the fact that only a few studies primarily dealing with mouth involvement have been published in the past. In recent years, some work has been reported (Lighterman *et al.*, 1962; Epker and Via, 1969; Reichart, 1974, 1976). Other recent publications are either in Japanese or in German and a few have appeared in the *Journal of Oral Surgery*. As such, none of the reports have found an entry into the text books on leprosy, and the subject has not been reviewed in the leprosy journals.

The present work has therefore been undertaken to report on the frequency and type of lesions occurring in the mouths of untreated lepromatous patients from North India and also to review the literature on the oral manifestations of leprosy.

Material and Methods

The study comprised of 40 consecutive, mainly untreated, multibacillated patients examined by the authors at Central JALMA Institute for Leprosy, Agra. Thirty-seven of these had lepromatous leprosy, while the remaining 3 had borderline (BL) type of leprosy. Five cases had just started their treatment. Four had received DDS for 3 days to 4 weeks and the fifth patient had taken the drug (DDS 100 mg daily) for 7 weeks only. On account of the very brief duration of treatment, these cases were included in the study.

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A detailed history of the disease was obtained and complete clinical examination done in each case. The mouth was subjected to a thorough examination and details recorded on a proforma prepared for the study. Teeth were not included in the present work.

Surface smears from 3 sites in the mouth (tongue, palate and gums) were examined in all cases for acid-fast bacilli (AFB). Mouthwash for enumeration of AFB was also obtained in each case. The techniques of surface smears and mouthwashes are described elsewhere in this issue of *Leprosy Review*.

Results

As already mentioned all but 5 of the patients were untreated and were picked up consecutively as they reported to the out-patient department. There was thus no selection of the cases. Twelve patients had disease for less than 3 years, while there were 23 who had the disease for 3 to 10 years and 5 for more than 10 years (Table 1). It is seen from the table that 4 out of the 12 cases (33.3%) with disease of less than 3 years duration had lesions inside the mouth. On the other hand 15 out of the 23 patients (65.2%) in the group of 3 to 10 years duration and 4 out of 5 patients (80%) with disease of more than 10 years duration had clinical involvement inside the mouth. In all, 23 patients (57.5%) had lesions of the oral mucosa. Various clinical lesions, as observed in different parts of the mouth are described.

PALATE

This was the most commonly affected site inside the mouth and all the 23 patients (57.52%) who had involvement of the oral mucosa, had lesions on the palate. The midline of hard palate bore the brunt of the disease, being involved in all the 23 cases. Twelve of these cases showed in addition, involvement of the soft palate while in 10 cases the uvula was also affected. None of the patients had lesions of the soft palate or the uvula without the hard palate being also involved.

Lepromatous lesions in the form of multiple papules and nodules were seen in 10 cases over the hard palate (Fig. 1). Three cases had solitary nodules. The nodules were moderate in size. Five patients had plaques over the hard palate (Fig. 2) with superficial erosion in 2 of them. One patient had diffuse infiltration with obliteration of the mucosal folds of palate. Extensive scarring in 2 patients and superficial ulceration in another 2 patients were also seen.

Seven patients showed papulo-nodular lesions over the soft palate. One had diffuse thickening and 2 others had erosions. Five of the above patients also had scarring — 2 with extensive fibrosis had problems of phonation, 3 with slight atrophy.

In the present study no case of perforation of the palate was seen. However, perforation of the palate is quite often seen in lepromatous leprosy. Figure 3 illustrates a large perforation in the hard palate of a case of lepromatous leprosy not included in the present study.

TABLE 1

Frequency of oral lesions in lepromatous leprosy

Duration of illness	Total no. of patients	No. of patients showing lesions inside the mouth	No. of patients showing lesions on palate		No. of patients with uvula affection	No. of patients with tonsillar pillar/or post-pharyngeal wall lesions	No. of patients with gum affection	No. of patients with buccal involvement	No. of patients showing tongue lesions	No. of patients with lesions +ve for AFB
			Hard	Soft						
1	2	3	4	5	6	7	8	9	10	11
0–3 years	12	4	4	3	2	2	2	0	1	5
4–10 years	23	15	15	6	4	8	8	2	6	13
More than 10 years	5	4	4	3	3	2	3	1	3	3
Total	40	23	23	12	9	12	13	3	10	21

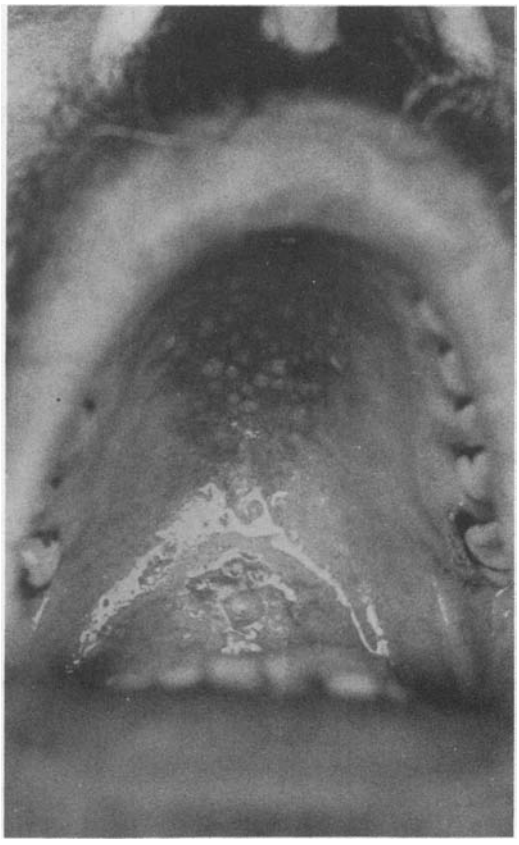

Fig. 1. Papules on the hard palate.

UVULA

As mentioned earlier, the uvula was involved in 10 cases. There was complete destruction of the uvula in 3 cases and scarring with partial loss in 4 patients. Two patients had nodules over the uvula. One patient showed an ulcer.

TONSILLAR PILLARS AND POSTERIOR PHARYNGEAL WALL

Twelve patients had lesions of tonsillar pillars. Papules and nodules were seen on the tonsillar pillars in 5 cases (Fig. 4). One of these patients had mild scarring of tonsillar pillars as well. Two patients showed shallow ulcers. Gross scarring was observed in 4 patients. One had diffuse thickening of the pillars. It was mainly the anterior pillar which was affected.

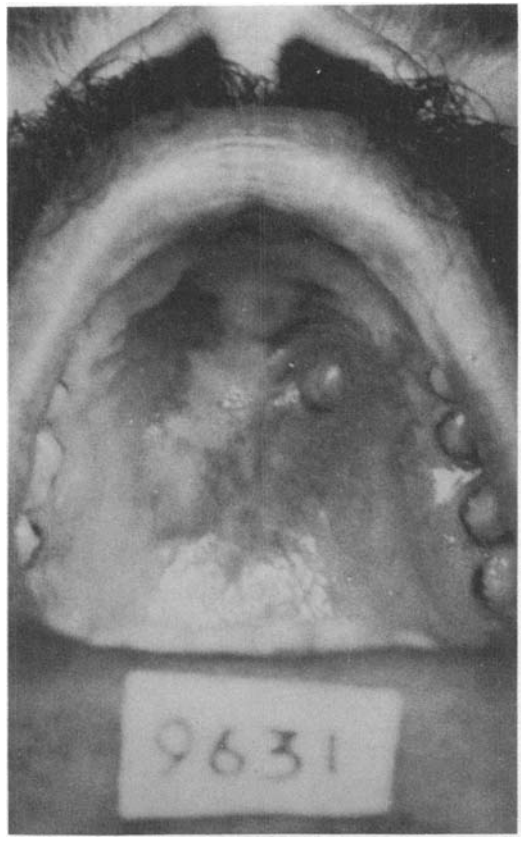

Fig. 2. Plaque on the hard palate.

Posterior pharyngeal wall was involved in 3 cases and appeared irregular with small pin-head sized papules. One patient had excessive dryness of the posterior pharyngeal wall.

GUMS

Thirteen patients showed gum lesions in one or the other form. Inner gums of the upper jaw were involved in 9 cases and in all these cases the lesions appeared to be in continuity with those of lesions on the hard palate. The lesions were in the form of papules and nodules. Four patients had no involvement of the adjoining area of the hard palate. Three of these 4 had swelling and infiltration and the remaining one had retraction of the gums.

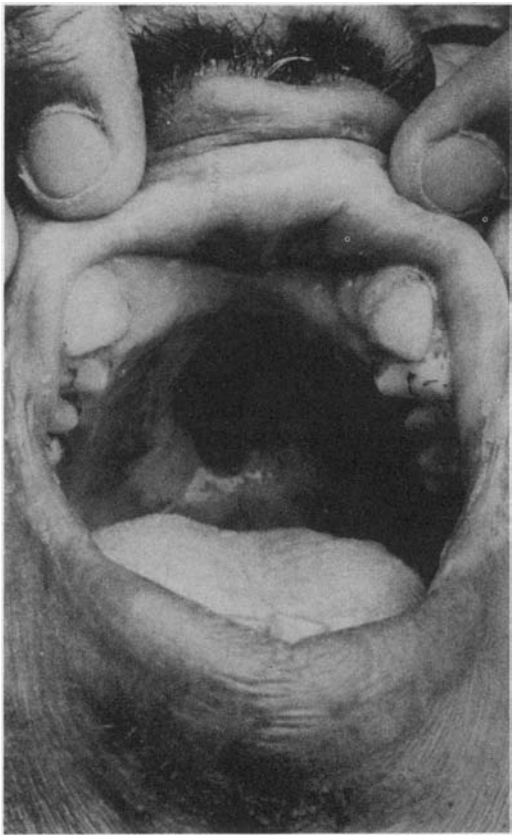

Fig. 3. Perforation hard palate (patient not from the present series).

BUCCAL MUCOSA

Only 3 patients showed lesions over the buccal mucosa. In 2 of these, there were discrete, moderate-sized papulo-nodular lesions predominantly over the line of contact of teeth. The third patient had hyperemia but no other lesions.

TONGUE

Gross lesions of the tongue were seen in 10 of the 40 cases. Two had very extensive lesions consisting of multiple big nodules giving a cobble-stone appearance (Figs 5 and 6). In 2 other patients there were a few nodules and 2 patients had solitary nodules on the tip of the tongue (Fig. 7). One had diffuse thickening of the tongue while another had marked scarring. The remaining 2 had shallow longitudinal fissures.

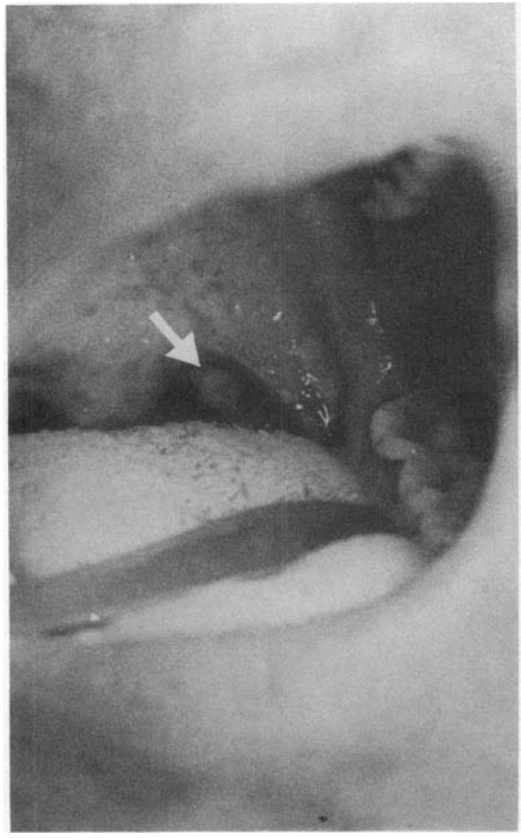

Fig. 4. Nodule on the left posterior tonsillar pillar.

Fissures of the tongue were a striking finding in lepromatous patients. Fissures of varying depths were seen in 6 cases. Four had shallow fissures while 2 had deep fissures. In all cases tongue involvement was limited to the dorsal surface and anterior two-thirds only. In no case was the ventral surface of the tongue and floor of the mouth affected.

Bacteriological examination of the mouth showed that in 21 of the 23 patients with oral lesions, AFB were seen in either the smears prepared from the surface of lesions or in the mouthwash specimens.

Discussion

Lepromatous leprosy is known to result in a variety of clinical manifestations in the oral mucosa. The lesions inside the mouth develop insidiously and in most patients there are no attributable symptoms. However,

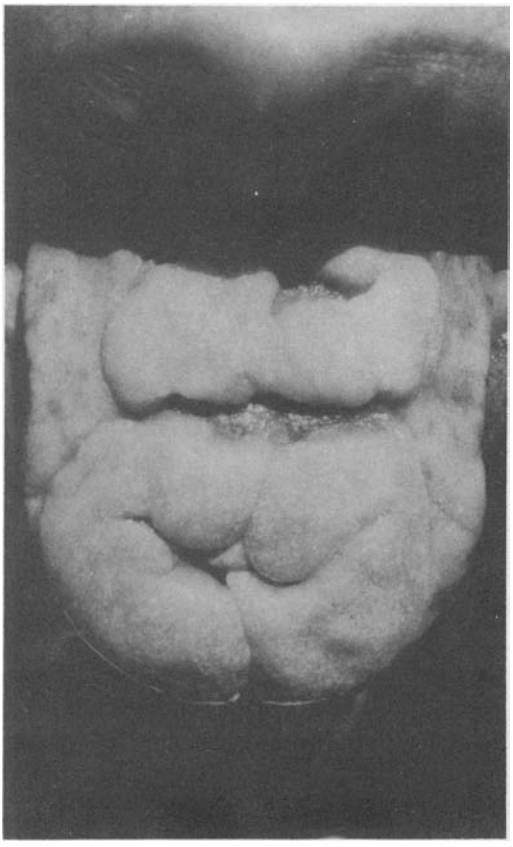

Fig. 5. Big nodules on the dorsum of tongue.

when there is fibrosis and shrinkage of the soft palate or perforation of the hard palate, the condition may become symptomatic with problems of phonation and nasal regurgitation of food.

The sequence of changes, as it occurs in oral mucosa in lepromatous patients, is well described by Pinkerton (1932, 1954) who lists the stages as congestion, infiltration, nodule formation, possible ulceration, atrophy and scarring. A similar sequence of events has been described by Job *et al.* (1966) in nasal mucosa which appears to be affected earlier than the oral mucosa (Bertelli and Sacheri, 1961).

Oral involvement has been reported to occur in 19% (Bechelli and Berti, 1939) to 60% (Lighterman *et al.*, 1962) of lepromatous leprosy patients. Although all the structures inside the mouth can become involved, the premaxillary gingiva, hard and soft palate, uvula and tongue have been shown to be more commonly affected (Prejean, 1930, 1936, 1943; Lighterman *et al.*,

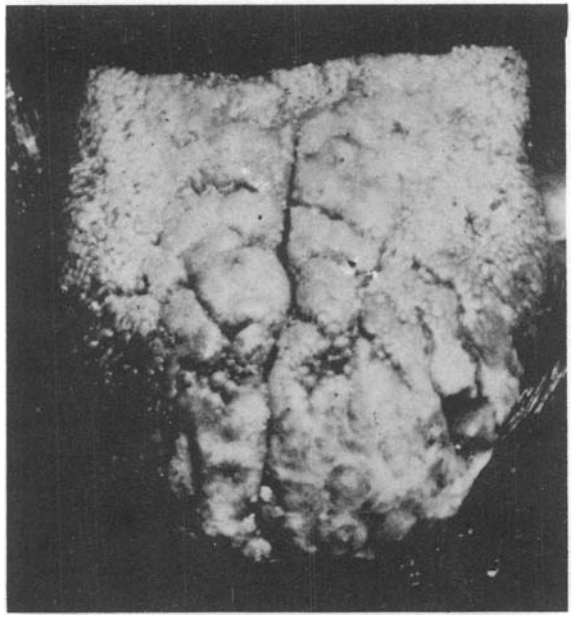

Fig. 6. Multiple nodules with fissures on the tongue.

1962; Reichart, 1976). In Itakura's series (1940), the hard palate was involved in 53.5% of patients examined. Lighterman *et al.* (1962), quoting Serra, have reported that nodules on the soft palate were observed in 48% of cases and uvula affection was seen in 20% of cases. Hikada (1958), on the other hand, found that 42.2% of his patients had late changes affecting the uvula. Tongue lesions, which appear to be less common than those of the palate, have been reported to occur in 17.3% of cases by Lighterman *et al.* (1962) and in 29.5% of cases by Mathis (1955).

In the present series, which comprised 40 unselected patients, intra-oral lesions were seen in 57.5% of cases. Frequency of oral lesions, as recorded in Table 1, appeared to increase with the duration of illness. The hard palate was the most commonly affected site and was involved in all 23 patients. The midline of the hard palate was the site of predilection. The possible cause of its greater involvement may be its relatively low temperature, because as a separating media between the nasal and oral cavities, it is constantly exposed to a cooling air stream on both its surfaces. The frequency of palate affection in the present series is higher than in those of Itakura (1940) and Hikada (1958). Involvement of the soft palate and the uvula was a less common finding, as observed by Serra (quoted by Lighterman *et al.*, 1962).

Gum involvement was next in frequency to the palate and in a majority of patients gum lesions were seen as an extension of those of the palate. Buccal mucosa appeared to be rarely involved. Occurrence of lesions over the anterior

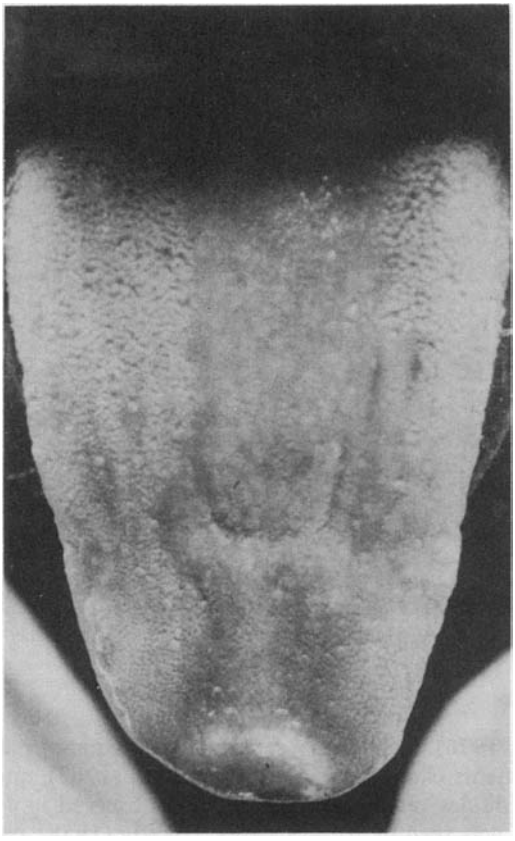

Fig. 7. Solitary nodule on the tip of the tongue.

tonsillar pillar as also occasional involvement of the posterior pharyngeal wall were rather unexpected observations. The tonsillar pillars seemed to be more often involved with gross lesions or scarring of the soft palate and uvula.

Tongue involvement, in the present study, was seen in 25% of cases. These findings are very similar to those of Lighterman *et al.* (1962) and Mathis (1955). An additional finding in the present study, is the occurrence of fissures on the tongue which, to the best of our knowledge, has not been reported in the literature.

The present study indicates that involvement of oral mucosa is quite significant in lepromatous leprosy. These lesions could be the source of discharge of bacilli into the mouth as 21 of 23 patients with clinical lesions in the mouth showed bacilli on the surface. The epidemiological significance of this feature is obvious particularly in communities where spitting is common. It is important that the mouth should be carefully examined in all lepromatous cases and that patients should be educated in oral hygiene.

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The Histopathology of Tongue Lesions in Leprosy

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A histopathological study of the tongue lesions in 8 cases of lepromatous leprosy is presented. The salient histopathological changes in these lesions are described and the implication of the findings discussed.

Introduction

Involvement of the oral cavity in cases of lepromatous leprosy is well known (Dharmendra, 1967; Cochrane, 1964). The various structures in the oral cavity commonly affected are the gums, the hard and soft palates, the uvula and the tongue (Reichart, 1976). Although clinical descriptions of these are available (Reichart, 1976; Lighterman, 1962), reports of the histopathology of these lesions, however, are very few (Ishihara, 1975; Reichart, 1974).

The present report describes the histopathological changes seen in the tongue lesions of lepromatous leprosy.

Material and Methods

Eight patients were biopsied for the purpose of the study. All of them were patients with lepromatous leprosy. Six of them had disease of more than 10 years' duration, while the other 2 had a shorter duration of 7 and 2 years respectively. Three patients had taken dapsone irregularly for varying periods of 2 to 4 years. The others had not received any treatment.

Gross lesions were present on the tongue in all 8 cases but none had any symptoms attributable to its involvement. Tests for sensation of touch and taste were not performed. One patient had large nodules (1 cm diameter) on the dorsum of the tongue which were separated by deep fissures giving a "cobble-stone" appearance. Two had diffusely scattered small papules more on the anterior two-thirds of the tongue. Three had solitary nodules over the tip of the tongue, one of them showing atrophic scarring in addition. Two patients had diffuse thickening of the tongue, one of them with loss of papillac as well.

Biopsies of tongue lesions were performed under local anaesthesia. The tissues were fixed in Formol-Zenker for 24 h, processed, embedded in paraffin

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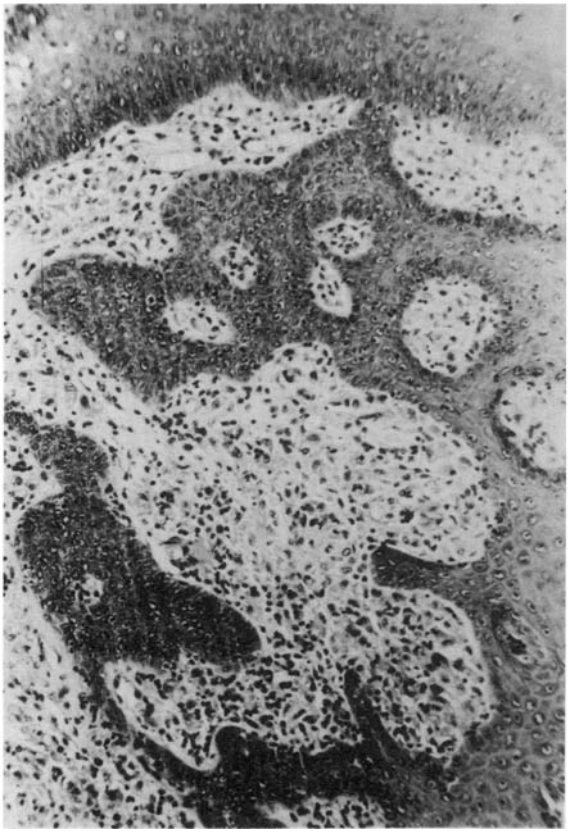

Fig. 1. Tongue lesions in lepromatous leprosy showing epithelial hyperplasia. H & E. × 100.

and 5-μm-thick sections were cut and stained with H & E, Fite's modification of Ziehl-Neelsen's stain and Picro-Mallory's stain.

Results

All the 8 biopsies showed lepromatous granulomata histologically. The histological findings are described below.

EPITHELIUM

In all 8 cases, the epithelium was continuous and no ulcerations were seen. Four cases showed evidence of mild to moderate epithelial hyperplasia (Fig. 1). No epithelial dysplasia was observed. Of the rest, 3 had normal epithelium while only one showed flattening of the epithelium.

The inflammatory infiltrate extended into the epithelium in one case. In this

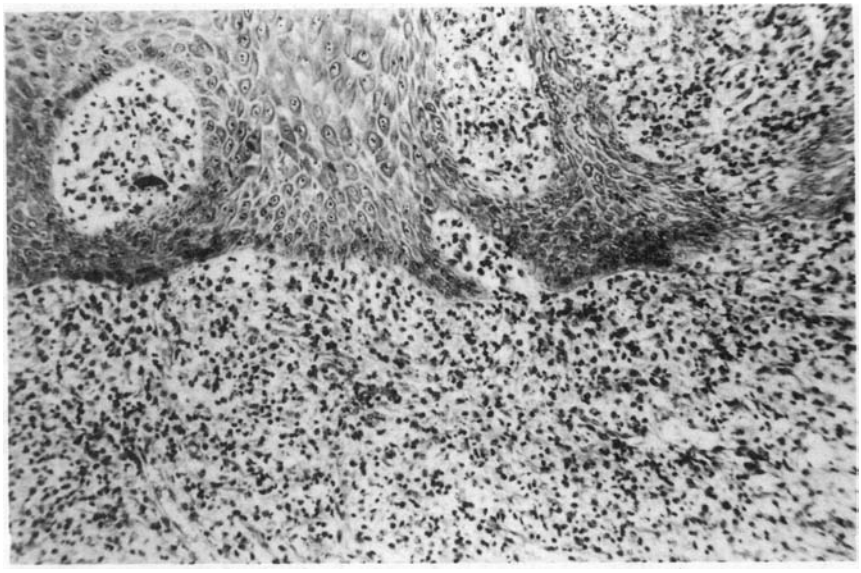

Fig. 2. Lepromatous granuloma of tongue showing extension up to basal layer of epithelium encroaching on the sub-epithelial zone. H & E. × 100.

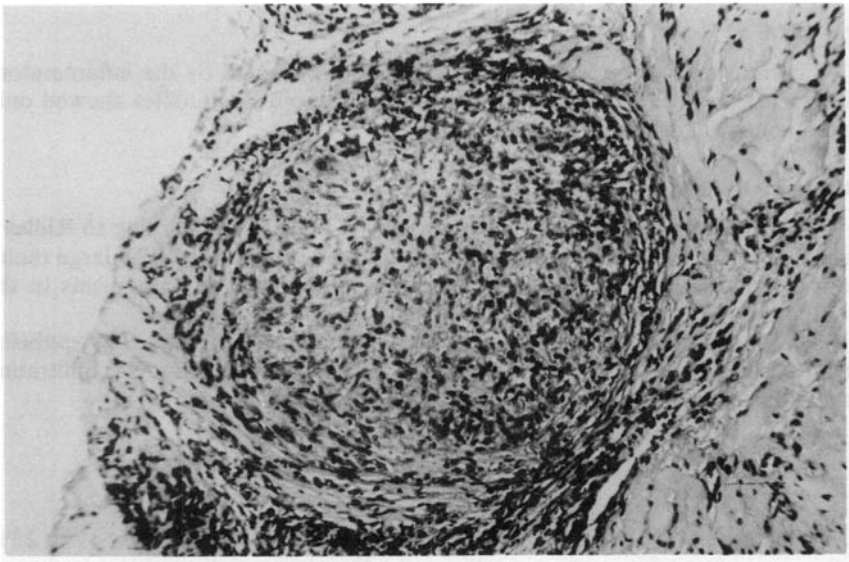

Fig. 3. A nerve in the tongue showing infiltration and destruction. H & E. × 400.

the epithelium was thin at some places while in other places long proliferating rete pegs were seen. The picture suggested the edge of an ulcerating lesion.

SUB-EPITHELIAL ZONE

None of the cases with diffuse infiltration showed any evidence of a clear sub-epithelial zone as seen in the skin lesions of lepromatous leprosy. In all cases the granuloma extended right up to the basal layers (Fig. 2).

SUB-EPITHELIAL TISSUES

Extensive lepromatous granulomata composed of sheets of macrophages were seen in 5 cases. One case had an irregularly branching granuloma whilst the remaining 2 had only slight to moderate patchy granulomatous infiltration of the sub-epithelial layers.

The infiltrate in all the cases was richly vascular. It comprised mainly of vacuolated and non-vacuolated macrophages, scant to moderate numbers of plasma cells, lymphocytes and occasional polymorphs.

NERVES

Nerve twigs could be identified in 4 cases. In all the 4 they were infiltrated by exudate cells. In 2 of these cases, the nerves were found in the midst of a large granuloma. Here the nerve showed lamination, infiltration by foam cells and destruction (Fig. 3). In the other 2 cases, the cellular infiltration was patchy and mainly around the nerves. One of these cases also showed large multi-nucleated foamy giant cells with large single vacuoles in the neurovascular bundles.

MUSCLE

The muscular tissues were compressed and infiltrated by the inflammatory infiltrates (Fig. 4). In the cases with less infiltration, the bundles showed only mild non-specific changes.

BACILLARY POPULATION

The bacillary content could be graded as 4+ to $6\frac{1}{2}$+ according to Ridley's scale (Fig. 5). Bacilli were found in macrophages and nerves. The large multi-nucleated cells seen in one case contained several broken organisms in the vacuoles.

The muscle fibres were not found to contain any organisms. The epithelial layers were devoid of bacilli except in one case where the histiocytes infiltrating these layers contained some organisms.

Discussion

Reichart (1976) has reported that the tongue is involved in about 17 to 25% of cases of lepromatous leprosy. Since the literature on this subject is sparse,

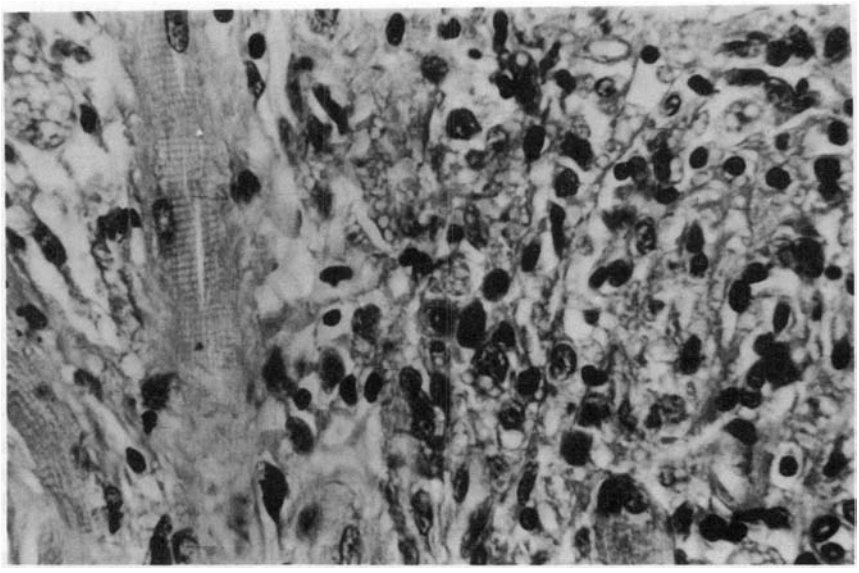

Fig. 4. Lepromatous granuloma showing infiltration of cells in between muscle bundles. H & E. × 400.

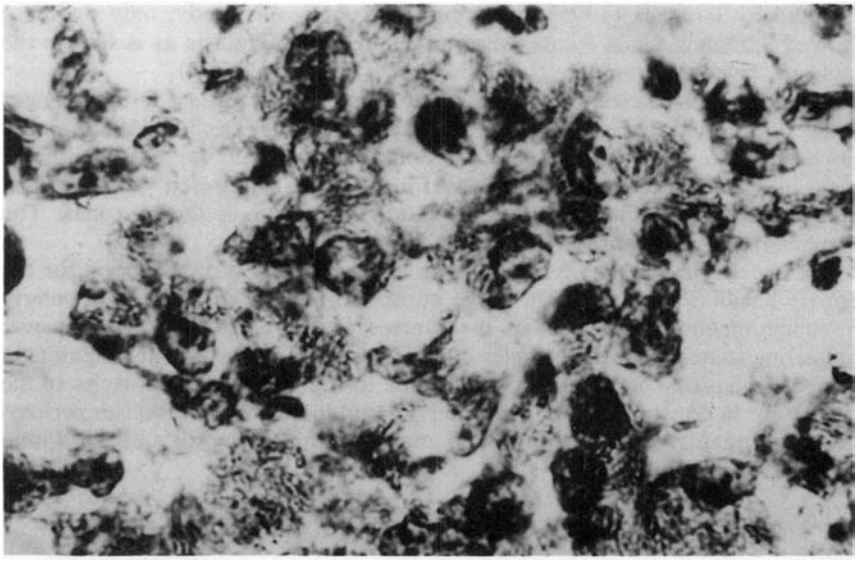

Fig. 5. Microphotograph showing the heavy bacillary population present in the lesion. Fite's stain. × 1000.

details of the pattern of microscopic involvement are still not clear. The salient features of the tongue lesions as observed in this study are: (i) all the cases which showed clinical evidence of tongue involvement had definite histopathological lesions of leprosy; (ii) the composition of the infiltrate and the pattern of the granuloma was similar to that seen in skin lesions; (iii) the sub-epithelial zone was encroached in all cases with a heavy infiltration of exudate cells; (iv) nerves were preferentially affected; (v) the epithelium showed hyperplasia; (vi) all the lesions were heavily bacillated; (vii) the muscles were compressed or infiltrated by the granuloma but bacilli were not seen in large numbers as is found in muscles similarly located elsewhere e.g. Dartos and Arrectores Pilorum etc.

These findings lead to certain important considerations. Extensive involvement of the nerve twigs as seen even in the relatively less infiltrated lesions could well lead to sensory and/or motor loss of function of the tongue. These functions, unfortunately, were not tested in the present study. Earlier studies also do not mention any loss of taste function. Reichart (1974) in his study of the soft palate in leprosy has found motor impairment to be associated with infiltration in the palate. However, he has not described destruction of the nerves histologically in these cases.

Extension of the granuloma up to the basal layers, heavy bacillation in all cases and presence of bacilli-laden histocytes in the epidermis strongly suggest that the leprosy bacilli from the lesions of the tongue could easily be extruded into the mouth secretions and discharged through the saliva while spitting.

The epithelial changes are in contrast to that seen in the skin lesions of lepromatous leprosy. Atrophy and flattening is the normal reaction of the epidermis in skin lesions. Flattening of the epithelium of the tongue is also reported by Ishihara (1975) in his case report. In this study, only one case showed flattening while 4 cases showed epithelial hyperplasia as is seen in the epidermis over the granulomas in tuberculosis (Nirmala, 1977).

The absence of a clear sub-epithelial zone is also in contrast to the changes in the skin. In autopsy studies on lepromatous patients (Desikan, 1968) and in biopsy specimens of oral and palatal lesions (Reichart, 1974) the sub-epithelial zone in the larynx and palate was found to be infiltrated. Conjunctival lepromatous lesions also fail to show any clear sub-epithelial zones. The significance of this finding is however still not clear.

The muscle has been described as an important site of predilection for the leprosy bacilli (Pearson, 1970). Large numbers of bacilli are found particularly in subcutaneous muscles as in the Dartos (Pandya, 1974). It is however interesting to note that the muscles of the tongue do not exhibit any significant number of leprosy bacilli. This may be due to the fact that the muscles of the tongue are in constant action, their activity and increased metabolism perhaps militating against the lodgement and multiplication of leprosy bacilli within them.

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Discharge of *Mycobacterium leprae* from the Mouth in Lepromatous Leprosy Patients

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A bacteriological study of the mouths of 40 lepromatous patients, 35 of them untreated, has been undertaken. In each case a mouth wash was done and acid-fast bacilli were counted in the washing. Surface smears taken from 3 sites (tongue, palate and gums) were examined for acid-fast bacilli. Inoculation of surface scrapings into Lowenstein-Jensen media was also performed. The results show that non-cultiviable acid-fast bacilli were present in the mouths of 85% patients with a mean count of 1.59×10^6 per mouth wash. The possible significance and the epidemiological implications of these findings in communities where spitting is a common habit, are discussed.

Introduction

The nose in leprosy has been a subject of thorough study in the recent years. It has been shown that nasal washings (Shepard, 1960, 1962), nasal smears (Davey and Barton, 1973) and nose-blows (Davey and Rees, 1974) are all positive for *Mycobacterium leprae* in a large proportion of lepromatous patients. Further Desikan (1977) has shown that *M. leprae* shed from nose, in the nose-blows, remain viable for 9 days — indicating an obvious epidemiological significance and potential hazard of the nasal discharge in leprosy.

In some Asian countries, indiscriminate spitting is common. The present study has therefore been undertaken to see whether there is a discharge of bacilli from the mouth of lepromatous patients as happens from their nose. Hitherto, no such study has been undertaken.

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Material and Methods

Forty bacteriologically positive cases of leprosy formed the subjects of study. Except for 5, all were practically untreated. Of the treated cases 4 had received DDS 50 to 100 mg for 3 days to 4 weeks and the fifth patient had received DDS for 7 weeks. Thirty-seven cases belonged to lepromatous type and 3 to borderline (BL) type. There was no evidence (clinical and in some cases radiological) of pulmonary tuberculosis in any of the cases. A detailed history of disease with particular regard to duration, treatment received, if any, was noted in all cases. All the patients were assessed for their leprosy status by clinical examination, skin smears from 4 sites and skin biopsies. In each patient the mouth was subjected to a thorough clinical examination.

(a) BACTERIAL COUNTS FROM MOUTH WASH

Patients were given 40 ml tap water and were asked to take it into the mouth and swill it around for 30 s before spitting it out into a wide-mouth container. To this mouth wash, 1 to 2 ml of N/10 NaOH was added for breaking excess of mucus. The specimen was then centrifuged for 15 min at 3000 rev/min. The supernatant was discarded and the deposit resuspended in about 1 ml of 0.1% B.S.A. The exact volume of the suspension was recorded. In the suspension thus prepared, counting of acid-fast bacilli (AFB) was done by standard procedure.

(b) SURFACE SMEARS

Surface smears were obtained from 3 sites in the mouth, from the lesions, if they were present, or from the apparently normal mucosa if lesions were not found. The 3 sites chosen were the tongue, palate and gums. Only surface material was obtained without traumatizing the mucous-membrane. This was done by gently scraping the surface with a blunt, smooth-edged instrument. After air-drying, the smears were fixed by passing the slides over a flame. The slides were then stained by Ziehl-Neelsen technique and examined for AFB.

(c) INOCULATION OF LOWENSTEIN-JENSEN (L.J.) MEDIUM

In all the first 24 patients, scrapings from the sites mentioned above were also inoculated into L.J. medium. Scrapings were first introduced in 1 ml of 0.1% B.S.A. to which a few drops of N/10 NaOH was added. The resulting suspension, after neutralization, was inoculated into 2 tubes of L.J. medium. One tube was incubated at 37°C and the other at 25°C.

(d) NOSE-BLOW EXAMINATION

In 16 consecutive cases nose-blow specimens were taken directly on the glass slides. Smears were prepared, stained and examined for AFB.

Results

Twenty-three patients showed lesions in the mouth seen as papules or nodules, some with ulcerated surface. Seventeen patients did not show any

TABLE 1
Summary of results

Groups	No. of patients	By smear		By mouth wash		Positive by either method	Negative by both methods
		Positive	Negative	Positive	Negative		
Patients with oral mucosal lesions	23 (57.5%)	19 (82.6%)	4	17 (73.9%)	6	21 (91%)	2 (6.1%)
Patients with no oral lesions	17 (42.5%)	7 (41.2%)	10	10 (58.8%)	7	13 (76.4%)	4 (23.5%)
Total	40	26 (65%)	14	27 (67.5%)	13	34 (85%)	6 (15%)

TABLE 2
Quantum of bacillary discharge per mouth wash

No. of bacilli recovered per mouth wash	No. of patients
More than 10^6	4 (10%)
10^5–10^6	15 (37.5%)
Less than 10^5	8 (20%)
Nil	13 (32.5%)

Mean 1.6×10^6.

lesions (Table 1). From among the cases showing lesions in the mouth, bacilli could be detected by either of the methods in 21 patients. In 19 cases surface smears of the mucosa were positive for AFB. In 17 cases bacilli were found by mouth wash.

From among the patients not having any lesions in the mouth, 7 patients showed AFB in the smears and 10 in the mouthwash specimens, 13 being positive by either of the methods.

As mentioned earlier, only surface material was obtained from the mucous membrane without traumatizing the mucosa. However, in one case, the mucosa was accidentally abraded. Smears thus examined showed inflammatory cells, mainly macrophages, some of which contained intracellular bacilli in the classical "cigar bundle" arrangement. Very few epithelial cells showed intracellular bacilli.

The number of bacilli recovered in the mouthwash varied considerably (Table 2) — the range being 2.6×10^4 to 2.9×10^7 with a mean of 1.6×10^6 per mouth wash. The data related to duration of disease is presented in Table 3. It is apparent that the longer the duration of the disease, the higher the bacteriological positivity in smears as well as mouth washings.

Of the 24 inoculations into L.J. medium, none showed any cultiviable AFB. In this group of 24 patients, 21 showed AFB on smear/mouth wash.

In 16 consecutive cases, nose-blows were also taken at the time of examination. Eight of them showed bacilli in the nose-blows. Of these 8 patients, 7 had bacilli in the mouth too. In other words, one patient who had bacilli in the nose-blow, did not show organisms in the mouth. Further, in 4

TABLE 3
Duration of illness and bacteriological positivity

Duration of illness	No. of cases	Mouth smear positivity	Mouth wash positivity
0 to 3 years	12	6 (50%)	6 (50%)
4 to 10 years	23	16 (69.6%)	17 (73.9%)
More than 10 years	5	4 (80%)	4 (80%)

patients whose nose-blows were negative for bacilli, the organisms could be seen in the mouth. Five patients were negative for AFB in both nose-blows and mouth smears washings.

Discussion

The present study shows that AFB, which did not grow on Lowenstein-Jensen medium, were present in the mouth of 34 of the 40 lepromatous patients studied (85%). As could be expected, mouth positivity was higher in patients with clinical lesions in the mouth than in those with no lesions. Further, where clinical lesions were present, mouth smears were positive more often than mouth washes. This could be due to the selection of an affected site for obtaining smears. In patients without any clinical lesions, mouth wash appeared to be more sensitive as it could sample a larger area of mucosa.

The bacillary discharge per mouthwash ranged from 2.6×10^4 to 2.9×10^7 (mean 1.6×10^6). This indicates that a large number of bacilli may be discharged into the environment by lepromatous patients in spitting as also while speaking, coughing, sneezing etc., causing a potential hazard to the community. It has been shown by Davey and Rees (1974) that bacilli discharged in the nose-blows remain viable up to 7 days. Desikan (1977) has shown that bacilli shed into the environment, could be viable for 9 days or even longer. This further highlights the epidemiological significance of the discharged bacilli from the nose in the earlier studies and possibly also from the mouth in the present study.

In addition to its public health importance, the other important findings are that unlike the nose (Davey and Rees, 1974) mouth positivity appears to increase with the duration of the disease.

In 16 cases, simultaneous study of mouth smears, mouth washes and nose-blows was conducted. Percentage of mouth positivity was a little higher than nose blows, but almost all patients who were positive for nose-blows were also positive for AFB in the mouth. Though the possibility of nasal secretions trickling into the posterior part of the mouth cannot be ruled out, higher positivity of the mouth may well indicate discharge of bacilli from oral mucosa itself. This has been confirmed in a subsequent study (see accompanying publication) where biopsy specimens from the tongue were found to be loaded with AFB. Similar findings have been observed in the histopathological study of the soft palate (Reichart, 1974).

The results of the study thus show that discharge from the mouth, like that of nose, contains a large number of acid-fast bacilli in significant proportion of lepromatous leprosy patients. Further, the unhygienic habit of indiscriminate spitting, especially while chewing tobacco, betal leaves or betal nuts (which possibly also cause minor trauma to the oral mucosa), enhances the possibility of bacillary dissemination. Bacilli are probably sprayed from the mouth of the lepromatous patient into the environment during sneezing, coughing and speaking.

Acknowledgement

Stefan Hubscher is indebted to the British Leprosy Relief Association (LEPRA) for sponsoring his elective period at JALMA. The authors are grateful to Dr R. J. W. Rees of Medical Research Council, London for his continued support and cooperation in this project.

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XI International Leprosy Congress, Mexico City 1978

(1) WORKSHOP ON EXPERIMENTAL LEPROSY

Chairman: C. H. Binford

Participants: M. E. Amescua; L. M. Balina; J. C. Convit; S. Innami; W. F. Kirchheimer; G. Klingmueller; K. Kohsaka; K. Nakamura; D. Opromolla; E. E. Storrs; G. P. Walsh; J. Lew—unable to attend; M. J. Colson (representing H. L. Fieldsteel); A. C. McDougall (representing R. J. W. Rees)

Observers: J. Delville; Dr Elsler; Dr Makino

At the X International Leprosy Congress, 1973, in Bergen, the Committee on Advances in Experimental Leprosy reported the developments in the use of the normal mouse, the thymectomized irradiated mouse, the neonatally thymectomized Lewis rat and the nine-banded armadillo, *Dasypus novemcinctus*. Also initial results with the Korean chipmunk were reported.

During the past 5 years there has been intense activity in experimental leprosy and several new models were introduced. The members of the workshop who reported on experiments in new animals brought several sets of appropriately stained histopathological sections for study under the 12 microscopes which were generously provided by the Organizing Committee.

EUROPEAN HEDGEHOG (*Erinaceus europaeus*)

In Germany, experimental inoculation with *Mycobacterium leprae* was initiated in the European hedgehog, a small animal (less than 1 kg) with a body temperature of 35 to 36°C when not in hibernation. This animal is readily adjusted to a laboratory environment and will breed in captivity. In some animals intracutaneous and subcutaneous inoculation with *M. leprae* resulted, after many months, in local lesions that histopathologically showed epithelioid cell granulomatous reactions with small numbers of AFB. Investigators in the United Kingdom, stimulated by the work in Germany, inoculated a group of hedgehogs in footpads and another group intravenously. Two intravenously infected hedgehogs sacrificed 20 months post-inoculation showed widespread dissemination with large numbers of AFB in macrophages. The lepromatous lesions were found in lymph nodes, liver, spleen, tongue, footpads and ears. Intraneural involvement with *M. leprae* was observed in dermal and sciatic nerves.

The members of the Workshop were impressed by the results obtained in these initial experiments with this small animal which is readily available in Europe and easily adjusted to laboratory environment, and recommended that the investigators vigorously continue their experiments.

NUDE MOUSE

The nude athymic mouse (BALB/C—nu/nu) was presented by investigators from Tokyo and Osaka as a model for experimental lepromatous leprosy. The mice were maintained under specific pathogen-free conditions. Severe lepromatous lesions were obtained in liver, lung, spleen, nerves, bone marrow, testis, ears, tail and the inoculated foot. Eight months after inoculation, up to 10^{10} *M. leprae* could be recovered from footpads.

The investigator from Tokyo reported enhancement of the development of the lepromatous disease in the nude mouse by inoculating the animal with young thymic cells (1 to 2 weeks). The members of the Workshop were convinced that with further study the nude mouse gives promise of becoming a valuable model for immunological investigations and experimental chemotherapy.

NEONATALLY THYMECTOMIZED LEWIS RAT

An account was given from the U.S.A. of the widespread dissemination of bacilli in this model following the intravenous injection of 10^7 *M. leprae* 12 months previously. Moreover, in contrast to the mouse footpad in which the maximum inoculum is 10^4 bacilli (more than this being immunogenic), it is possible to inoculate 10^7 bacilli into the footpad of the NTLR and still detect bacillary growth. Heavily infected NTLR are being used in chemotherapy experiments in order to provide information on persistence of *M. leprae*. This information would be useful in the design of therapeutic regimens for patients with multibacillary leprosy. Monitoring of therapy in this experimental model and in human patients is being carried out by inoculation of large numbers of bacilli into the footpads of NTLR.

ARMADILLOS

The use of the armadillo in leprosy research has advanced rapidly during the past 5 years. For the first time in the history of leprosy, sufficient quantities of *M. leprae* could be made available for basic research in microbiology, immunology and biochemistry. WHO has seized this opportunity by developing an extensive, comprehensive programme in immunology (IMMLEP), utilizing lepromatous tissue of armadillos captured in southern U.S.A.

In May 1977, the Pan American Health Organization conducted at the Instituto Nacional de Dermatologia, Caracas, Venezuela, a 5-day Workshop on the Armadillo as an Experimental Model in Biomedical Research. The report of this Workshop will be made available in December 1978, in PAHO Scientific Publication No. 366 (178 pages).

Stimulated by the Workshop in Caracas, programmes to use armadillos in leprosy research are developing in many countries of the Americas. In addition to *D. novemcinctus*, several other species found only in South America are being investigated. Active programmes utilizing nine-banded armadillos from southern U.S.A. are being carried out in countries where armadillos are not naturally available.

Reports on progress of leprosy research with armadillos were made by several participants of this Workshop.

Venezuela

Very encouraging results were reported in the *Dasypus sabanicola*, the eight-banded armadillo, native to certain regions of Venezuela and Colombia. This animal is much smaller (1.5 kg) than *D. novemcinctus* and more easily handled in the laboratory. On inoculation with *M. leprae* a very significant number of *D. sabanicola* develop severe lepromatous leprosy, while some animals develop near-tuberculoid lesions, suggesting that this model may be useful in studying the several types of leprosy found in man.

United Kingdom

The report from the U.K. revealed that it is possible to successfully maintain colonies of the nine-banded armadillo (*D. novemcinctus*) in a country where this animal is not naturally available. Fifty-six percent of 16 armadillos surviving from a group of 20 which were donated by the Gulf South Research Laboratory, New Iberia, Louisiana, within 2 years after inoculation developed disseminated lepromatous lesions involving major tissues and organs. Dermal nerves were frequently involved. Large nerve involvement was seen in some animals. Histopathologically the lesions were similar to those reported from Carville and New Iberia, La.

Argentina

In Argentina, 3 species native to the country, *Zaedus pichey*, *Chaetophractus villosus* and *Dasypus hybridus*, were inoculated by intradermal and intracardiac routes. Repeated inoculations were done in some animals. In *Z. pichey* and *C. villosus*, granuloma developed at the sites of inoculation. Some granulomas histopathologically showed tuberculoid changes. The lesions did not advance locally or disseminate. The results of inoculation in *D. hybridus* could not be learned because no animals survived more than 6 months.

Brazil

A large programme for using armadillos in leprosy research is in progress. After unsuccessful results in several species, the project now is principally concerned with determining the susceptibility of the native *D. novemcinctus* to leprosy. Eight *D. novemcinctus* were found not to be infected after periods of observation up to 18 months. Much longer periods of observation will be used.

Paraguay

In Paraguay, the inoculations of *Chactophractos vellerosus* and *Euphractus septicinctus* were unsuccessful. The first trials with *D. novemcinctus* were interrupted by loss of the colony from an epizootic infection. An extensive programme using principally *D. novemcinctus* is now underway.

Mexico

In Mexico, facilities for use of the native *D. novemcinctus* have been provided and 18 animals have now been adapted to the laboratory environment. Basic information on the natural bacterial flora of these armadillos and haematologic profiles have been obtained.

Carville, La

At Carville, programmes previously reported have been continued and valuable information has been provided on results of massive intravenous inoculation to produce early harvests of lepromatous tissues for basic research.

An interesting report was made on the results obtained from vaccinating armadillos with heat-killed whole *M. leprae* in incomplete Freund's antigen 8 months prior to challenge with viable *M. leprae*. The results in a small group of animals were promising and it is hopeful that further experimental vaccination of armadillos will be done.

New Iberia, La

Inoculation with *M. leprae* of two *Dasypus hybridus* obtained from Argentina resulted after 24 months in severe, disseminated lepromatous leprosy in one animal and no infection in the other. Histopathologically, the lesions were indistinguishable from those seen regularly in infected *D. novemcinctus*. The positive result in this animal should provide impetus for effectively using *D. hybridus* in programmes of experimental leprosy in Argentina where this species is readily available.

Experience with the inoculation of approximately 500 *D. novemcinctus* showed that up to 60% will develop disseminated leprosy at doses of 10^7 to 10^8 *M. leprae*. Histopathological evaluation of tissues from the experimentally-inoculated animals provided experience that later was invaluable in the study of armadillos naturally infected with mycobacteria later identified as *M. leprae*.

Studies of the tissues and organs from normal newborn and adult armadillos showed the reticuloendothelial system (thymus, spleen, lymph node, tonsils, and Peyer's patches) of *D. novemcinctus* to be well developed and morphologically intact. From these studies it was concluded that the susceptibility of the nine-banded armadillo to leprosy was not a result of malformation of organs or tissues needed to mount an effective immune response.

A shift in programme emphasis from the experimental disease to the naturally acquired disease was made following the discovery in 1974 of indigenous leprosy in wild-caught nine-banded armadillos.

Indigenous leprosy in wild armadillos

The most recent data on indigenous leprosy in *D. novemcinctus* captured from the wild were presented. Sixty animals from 11 locations in Louisiana and one location in Texas have been found by the Gulf South Research Institute, New Iberia, La to have lepromatous leprosy. Confirmation of indigenous leprosy in armadillos has been reported by the CDC, Atlanta, the University of Texas, Galveston and the USPHS Hospital, Carville, La. An

armadillo captured in Texas and kept for 2 years in the zoo at San Diego, California was found to have disseminated lepromatous leprosy.

At New Iberia, the best method for identifying leprosy in a live animal was by examination of slit smears from the base of ears. Lymph nodes were consistently involved but obtaining biopsy specimens of lymph nodes from live animals during a survey study is not practical.

By the criteria proposed at the London Congress (1968) and methods subsequently developed (pyridine extraction; fluorescent antibody methods) the cause of the indigenous disease is indistinguishable from *M. leprae.*

The indigenous leprosy found in *D. novemcinctus* in the U.S.A. provides an opportunity for comprehensive studies on the epizootiology of this disease and from such studies it is hoped that some answers to problems in the epidemiology of human leprosy will be found.

Reproduction of armadillos in captivity

A scientist from the Medical Research Institute, Melbourne, Florida, reported current studies in reproduction being carried out in that institute and previous studies carried out at New Iberia. Reproduction was given top priority at the PAHO Workshop in Caracas in 1977 and there is general agreement that the full potential of the armadillo in biomedical research will not be obtained until breeding in captivity can be achieved and laboratory-bred animals provided in numbers sufficient for experimental work.

It was emphasized that the stress of captivity is probably responsible for interrupting the normal ovulation phases of the female. Sperm cells of males in captivity, although lower than from males when captured, appear adequate to fertilize ova of females ovulating regularly. Although artificial stimulation of ovulation is possible, it has not resulted in successful impregnation and gestation. Modification of the environment of captivity to reduce stress may prove to be the solution to reproduction.

At the Zoonosis Paramedical Center (CEPANZO) in Argentina in an area where *D. hybridus* is readily available, facilities have been developed for experimental breeding and it is hoped that successful breeding of *D. hybridus* in numbers adequate for experimental use will result.

KOREAN CHIPMUNK

Unfortunately, because of transportation difficulties, Joon Lew MD PhD who was scheduled to present his progress in experiments with the Korean chipmunk, *Eutamias sibricus Asiaticus*, arrived after the conclusion of the Workshop, but presented his finding to some members of the Workshop. In these animals inoculation of 10^7 *M. leprae* in footpads resulted in gross nodules appearing 7 to 17 months post-inoculation in 10 to 20% of the animals. Histopathologically, the lesions were advanced lepromatous. Nerves were distinctly involved. Lymph nodes were massively involved and liver and spleen less involved.

These chipmunks, while readily available in nature so far, have not bred in captivity. Obviously, work with this animal that without immunosuppression develops lepromatous leprosy should continue.

Conclusion

This Workshop has provided information on several new models for the study of lepromatous leprosy. During the period since the last Congress, significant progress has been made on the use of the nine-banded armadillo (*D. novemcinctus*) in leprosy research. At this Workshop, the eight-banded armadillo (*D. sabanicola*) has also been shown to be a model for lepromatous leprosy and hopefully, for other types of leprosy.

With the opportunities now available for investigators in experimental leprosy, the use of these models in studying the pathogenesis, prevention, epidemiology and treatment of human leprosy appear unlimited.

(2) WORKSHOP ON MICROBIOLOGY

Chairman: Dr S. Pattyn
Rapporteur: Dr P. Draper
Participants: Dr M. Abe; Dr O. Closs; Dr W. M. Meyers; Dr R. Navalkar; Dr K. Prabhakaran; Dr H. Sansarricq; Dr O. Skinsnes; Dr J. Stanford; Dr N. Morrison; Dr C. C. Shepard

MORPHOLOGY

Mycobacterium leprae, when stained by the Ziehl-Neelsen procedure, is an acid-alcohol-fast, weakly curved bacillus, 0.3 to 0.4 μm × 2 to 7 μm, sometimes showing a metachromatic granule of unknown nature. In all mycobacteria-rich tissues it is possible to find some non-acid-fast organisms. The significance of these, and particularly the possibility that they may be young forms, should be investigated.

In human lepromatous tissues, leprosy bacilli frequently occur in round to oval clumps called globi, the organisms being situated in cigar-shaped bundles.

Commonly the majority of bacteria stain irregularly. Provided that staining techniques are carefully standardized, there is a strong correlation between regular (solid) staining in smears and viability, measured by the mouse footpad model. Harada (1977) has shown that batches of fuchsin having particular light absorbance characteristics give the most satisfactory staining.

Fisher and Barksdale (1971, 1973) and Convit and Pinardi (1972) reported that the acid-fastness of *M. leprae* was extractable with pyridine, and that this was specific for the species. However, Skinsnes *et al.* (1975) have shown that pyridine extractability of acid-fastness is a characteristic of aging, non-viable bacilli, and not unique to the leprosy bacillus. Šula *et al.* (1978) also found that the reaction was not specific.

In the electron microscope, shadowed preparations of *M. leprae* are seen to contain both uniformly dense and beaded forms of the bacilli. After shadowing or negative staining of *M. leprae* suspensions, intertwining paired fibrous structures 10 to 30 nm in width, forming a network in the walls, can be seen. Nishiura *et al.* (1969) have described "band-like structures" parallel to the short axis of the cell.

In ultrathin sections, *M. leprae* has a cell wall 15 to 20 nm thick apparently

consisting of an inner electron-dense and an outer electron-transparent layer, surrounding the cytoplasmic membrane. Large mesosome-like structures are frequently observed, continuous with the cytoplasmic membrane. In tissues, at least, bacterial division is by transverse fission. There have been numerous reports of spheroplasts and other aberrant forms in leproma-derived material. It is important to establish the nature of these and their relation to leprosy.

BIOCHEMISTRY, METABOLISM AND GROWTH

The presence of mycolic acids in *M. leprae* was first demonstrated by Etémadi and Convit (1974). The large amounts of *M. leprae* obtainable from armadillo tissue allowed a chemical study of the cell walls (Draper, 1976). Like other actinomycetales, *M. leprae* has in its wall mycolic acids, arabinogalactan and peptidoglycan. The mycolic acids resemble 2 of the 3 found in *M. tuberculosis*, and differ from those found in *M. avium, M. lepraemurium, M. vaccae* and *M. smegmatis*. The peptidoglycan contains diaminopimelic acid, D-alanine, glutamic acid, glucosamine, muramic acid and substantial amounts of glycine. The simultaneous occurrence of glycine and meso-diaminopimelic acid in bacteria is rare and does not occur in other mycobacteria analysed so far. At the present time this is an important differential characteristic of *M. leprae*.

Knowledge of metabolic processes in *M. leprae* remains limited. Among enzyme activities reported to occur are dopa oxidase (Prabhakaran, 1967), glutamate decarboxylase (Prabhakaran and Bragança, 1964), β-glucuronidase and *N*-acetyl-β-glucosaminidase (Matsuo and Skinsnes, 1974). In each case controversy persists about the origin of the activity, whether it is bacterial or host-derived. More investigation is needed.

The organism is reported to take up, and to incorporate into insoluble products, radiolabelled thymidine and dopa (Ambrose *et al.*, 1978). Uptake is apparently inhibited by dapsone and rifampicin, and by diethyldithiocarbamate in the case of dopa.

The drug dapsone is bacteriostatic for *M. leprae* in very low concentrations: MIC = 0.003 µg per ml. This high sensitivity is an unusual property.

M. leprae can be readily transmitted to animals, normal mice, rats and hamsters (limited infections); armadillos, immunosuppressed mice and rats and congenitally athymic (nu/nu) mice (disseminated infections). The evolution of the infection, particularly in the mouse footpad, is characteristic for *M. leprae* when compared with other mycobacteria. The generation time during the exponential phase of multiplication in the mouse footpad is 11 to 13 days. Isolates of *M. leprae* in mouse footpads vary slightly in only two properties: the average rate of growth between inoculation and harvest, and the number of bacilli in the harvest.

ANTIGENIC STRUCTURE

Abe *et al.* (1970, 1972) found 2 antigens in human lepromatous nodules: a protein antigen thought to be specific for *M. leprae* and a polysaccharide antigen common to other mycobacteria. Abe *et al.* (1976) has also

demonstrated an insoluble antigen specific for *M. leprae* by indirect immunofluorescence. This has been useful in identifying organisms as *M. leprae*. Navalkar (1971, 1976) found 4 antigens common to other mycobacteria and one protein antigen specific for *M. leprae*.

Stanford (1976) was able to detect 12 antigens in disrupted *M. leprae* from infected armadillo tissue. Six of these were common to all mycobacteria, 4 were apparently species-specific and 2 of uncertain specificity. Closs detected 20 to 30 antigen components in *M. leprae*. None of these has been demonstrated to be specific for *M. leprae*, but at least some of them possess *M. leprae*-specific determinants as part of the molecule.

CULTURE

Criteria that should be applied to claims of *in vitro* culture of *M. leprae* are:

(a) The isolation procedure should ideally be successful in a percentage of attempts when bacilli-rich material, derived from untreated humans or experimental animals, is used.
(b) Multiplication should be regular and significant (taking into account experimental errors and possible artifacts of the techniques used).
(c) Ideally it should be shown that the bacilli can be passaged indefinitely.

Attempts to grow *M. leprae* in tissue culture have sometimes indicated limited multiplication but results were irregular. Recently Talwar's group have shown limited but continuous incorporation of thymidine into bacteria derived from human biopsies, cultured in macrophages.

There have been several recent reports on organisms cultivable from human and armadillo leprosy tissues, notably that of Skinsnes *et al.* (1975). Proof acceptable to all workers that these organisms are identical with *M. leprae* has not yet been obtained. Among criteria that should be used to demonstrate identity are:

(i) All *in vitro*-grown strains obtained should be identical in most if not all characters, including drug-sensitivity patterns. Strains may differ in a small number of tests (biotypes).
(ii) Strains should be identical with *M. leprae* in antigen components known to contain *M. leprae*-specific determinants.
(iii) The possibility of contamination from the environment should be considered; isolates should differ from currently known mycobacterial species.
(iv) The strains obtained should behave in experimental animals in a similar way to *M. leprae* derived from human tissue, particularly with respect to nerve invasion.
(v) Standardized suspensions of killed organisms prepared from the cultures should give negative Mitsuda reactions in lepromatous forms of the disease and positive reactions in tuberculoid cases.
(vi) The cell-wall skeleton of the cultivated strains would be expected to resemble that of tissue-derived *M. leprae* in its chemical composition.

(vii) 3,4-Dihydroxyphenylalanine (dopa) oxidase has been reported to be active in *M. leprae* and has been proposed as a specific test. Several workers have attempted to use this test, but with contradictory results. It is important that procedures for preparing bacterial suspensions and for performing the test are standardized, so that its significance may be established.

The greater the number of characteristics in which the proposed isolate differs from *M. leprae*, the greater the possibility that it is, in fact, a contaminant. Up to the present no cultures have been shown to satisfy all the above criteria, though not all have been fully tested.

Recommendations

(a) In order to accelerate progress towards *in vitro* cultivation of *M. leprae*, the setting up of multidisciplinary teams of investigators as recommended, so that the most recent progress in such areas as cell physiology and molecular biology is applied to the problem. Studies on electron-microscope histochemistry, incorporation of radioisotopes, DNA homology and other genetic investigations and characterization of cell components should be stimulated.
(b) Detailed antigenic characterization of *M. leprae* should be pursued to determine its taxonomic relation with other mycobacteria.
(c) Difficulties have arisen over the use of techniques for determining viability based on morphology in different laboratories, in spite of attempts to ensure that standard methods are used. Additional objective techniques for identifying viable organisms should be sought.

(3) WORKSHOP ON IMMUNOLOGY OF LEPROSY

Chairman: W. E. Bullock
Rapporteurs: T. Buchanan; Indira Nath
Participants: M. Abe; R. StC. Barnetson; S. Estrada-Parra; C. K. Job; R. Lai A. Fat; M. Lefford; T. H. Rea; D. S. Ridley; M. Ulrich.

IMMUNOCHEMISTRY AND LEPROSY

With greater quantities of *Mycobacterium leprae* made available from infected armadillo tissues during the past 5 years, there have been advances in the characterization of *M. leprae* antigens. There is now evidence that protein antigens specific for *M. leprae* exist.

Specific goals for the coming 5-year period should include studies to confirm this evidence and to characterize putative *M. leprae*-specific antigens with respect to:

(a) The methodology for purification of these antigens.
(b) Defining the physicochemical properties of these antigens that may help to increase their yields from bacilli and infected tissues.

(c) Development of antigen-specific assay systems to allow quantitation either of antibody to these antigens or of antigens present in infected tissues.
(d) Assessment of the role of these antigens in the stimulation of delayed-type hypersensitivity (DTH) and cell-mediated immunity (CMI) specific to *M. leprae*.
(e) Assessment of the role of these antigens in ENL, reversal reactions and the Lucio phenomenon, with emphasis on the search for antigen within lesion sites and within circulating immune complexes.
(f) Determining the significance of antibody to *M. leprae*-specific antigen(s) as an indicator of subclinical leprosy in contacts of lepromatous patients who have positive or negative lepromin skin tests as compared to contacts of tuberculoid patients.

EXPERIMENTAL STUDIES OF IMMUNOREGULATORY MECHANISMS IN LEPROSY

A significant advance in immunology during the past 5 years has been the identification of functionally specific subpopulations of lymphocytes that modulate the immune response in the mouse. The availability of markers for specific immunoregulatory cell function provides a powerful tool for more precise study of the complex cell-to-cell interactions that result in net help or suppression of the cell-mediated immune defence mechanisms in chronic infectious disease models.

Future studies should first be directed to resolving the nature of the immunoregulatory disturbances evoked by chronic infection of the mouse with *Mycobacterium lepraemurium*.

Much needed are detailed immunological studies of the normal and *M. leprae*-infected armadillo with special efforts directed to the identification of specific markers for immunoregulatory cell subpopulations in this genus.

Knowledge gained from these models will have direct application to studies of the immunoregulatory disturbances in human leprosy. Critical will be the development of techniques for recognizing specific markers on human regulatory cell subpopulations. As these techniques are perfected, they will yield information of great value in permitting clinical investigators to assess the impact of both chemotherapy and immunotherapy upon the immune functions of leprosy patients; these studies in turn can be expected to aid in the design of therapeutic approaches that will provide maximum long-term benefit.

THE IMMUNOLOGY OF HUMAN LEPROSY

A complex series of immunological perturbations has been delineated in leprosy patients during the past 5 years. In general, the DTH and CMI responses to contact sensitizing agents and a variety of "recall" antigens, including *M. leprae*, are not impaired substantially in patients with tuberculoid forms of disease. Conversely, in borderline and especially in lepromatous forms of infection, significant impairment of the immune response is observed frequently. Both non-specific generalized impairment of cellular immune

function occurs as well as a highly specific impairment of *M. leprae*-specific immunity. These abnormalities are frequently associated with disturbances in the ratio of T and B lymphocytes in the peripheral blood of lepromatous patients. The non-specific abnormalities of CMI appear to be reversible by chemotherapy of at least several months' duration, whereas impairment of the responses to *M. leprae* antigens is long-lasting.

Additional advances in the immunology of human leprosy include:

(a) the finding that antibodies that appear to be *M. leprae*-specific are detectable in a large percentage of tuberculoid patients as well as in lepromatous patients;
(b) the finding that circulating immune complexes may be present in patients with leprosy, more commonly in those with lepromatous disease; and
(c) evidence that patients with reversal reactions demonstrate increased lymphocyte transformation responses to *M. leprae*.

Goals of high priority during the next 5 years include:

(1) Definition of immunoregulatory subpopulations in man and the assessment of abnormalities within these subpopulations in patients with leprosy.
(2) Extensive studies of macrophage function in leprosy, with emphasis upon the mechanisms of the processing of *M. leprae* antigen.
(3) Longitudinal studies of circulating immune complexes in leprosy patients, and immunopathological studies of tissue reactions evoked by these complexes.
(4) Further exploration of the possibility of a genetic predisposition to leprosy by studying the distribution of HLA antigens in the population of leprosy patients and their families.
(5) Development of a vaccine against leprosy. The availability of *M. leprae*-specific antigens and of quantitative assays for these antigens, and antibody responses to these antigens, will aid in this pursuit.
(6) Exploration of the thesis that peripheral nerves may serve as "protected sites" for multiplication of *M. leprae*.

(4) WORKSHOP ON EXPERIMENTAL CHEMOTHERAPY

Chairman: Dr R. J. W. Rees
Rapporteur: Dr G. A. Ellard
Participants: Prof. J. Ambrose; Dr M. J. Colston; Prof. L. Levy; Dr N. E. Morrison; Prof. S. R. Pattyn; Dr J. M. H. Pearson; Dr J. H. Peters; Prof. J. K. Seydel; Dr C. C. Shepard

Progress in the last 5 years has largely resulted from exploitation of mouse models for the further evaluation of drugs and the demonstration of both drug-resistant and persisting drug-sensitive *M. leprae* in patients.

ANIMAL MODELS

In view of the continued failure to cultivate *M. leprae in vitro*, the activity of antileprosy drugs must be assessed using animal models. The 2 established animal models are:

(i) *Normal mouse*

This, the standard experimental model, enables the minimal inhibitory concentrations (MICs) of drugs against *M. leprae* to be determined, the nature of their antibacterial activity to be assessed, the rate at which viable leprosy bacilli are eliminated in patients during treatment to be measured, and the occurrence of drug-resistant organisms to be detected. Whether drugs have significant antileprosy activity is determined by ascertaining whether continuous administration in the diet prevents multiplication of *M. leprae* in the mouse footpad. Administration of drugs in graded doses allows the minimal effective dose (MED) to be measured. Following the growth of bacilli after administering a drug for a limited period reveals whether or not its activity is purely bacteriostatic (kinetic method), whereas the degree of bacterial killing engendered by drugs displaying potential bactericidal activity can be quantified using the proportional bactericidal test method. The normal mouse can be used to monitor the loss of viability of leprosy bacilli in lepromatous patients early in chemotherapy: when inocula from biopsies are no longer infective at least 99% of the original viable population must have been killed. The level of drug resistance of strains of *M. leprae* can be determined from their ability to multiply in mice fed graded doses of drugs that are normally inhibitory.

(ii) *Thymectomized-irradiated mouse (T/R mouse)*

This immunologically suppressed mouse enables the killing of *M. leprae* to be followed in treated patients to the time when the proportion of viable bacilli has been reduced to less than 0.1% of its original value.

PHARMACOKINETICS

Measurement of serum and tissue levels of drugs in mice fed with the MED enables their MICs to be determined. Pharmacokinetic studies in man indicate by how many fold the peak serum/tissue concentrations are likely to exceed the MIC, the duration after a single dose that inhibitory levels will be maintained, and whether treatment will be actively bactericidal.

CLINICAL TRIALS

Studies of the treatment of lepromatous leprosy extending from 6 months to 10 years have been monitored in the mouse to assess the rapidity with which viable bacilli are initially killed either by single drugs or by combinations of drugs, and whether drug-sensitive survivors ("persisters") can be eliminated by continued treatment.

DRUG RESISTANCE SURVEYS

Because of the importance of dapsone resistance, investigations have been undertaken in various parts of the world to estimate the prevalence of dapsone-resistant strains of *M. leprae* among patients who have relapsed during continuing treatment (secondary resistance) and in those with previously untreated leprosy (primary resistance).

DAPSONE

The exceptional sensitivity of *M. leprae* to inhibition by dapsone is indicated by its MIC of only 0.003 μg/ml. At concentrations near to its MIC, dapsone is essentially bacteriostatic; but at concentrations in excess of 100 times this value it is weakly bactericidal. Studies in both experimental animals and man show that it penetrates readily into all tissues including nerves. A dose of 100 mg dapsone results in peak concentrations that exceed the MIC by a factor of about 500-fold and maintains inhibitory levels for about 10 days.

Several studies have shown that 30% or more of leprosy out-patients are grossly irregular in self-administering their dapsone treatment. A reliable method of maintaining inhibitory levels of dapsone is to treat patients with acedapsone, the repository form of dapsone, since 225 mg intramuscular injections of acedapsone maintain dapsone concentrations well in excess of the MIC for over 3 months.

Viable dapsone-sensitive leprosy bacilli ("persisters") can be recovered from up to 50% of lepromatous patients after as many as 10 years of continuous dapsone monotherapy. Estimates of the prevalence of dapsone-resistant strains of *M. leprae* among lepromatous patients have ranged from 3% to 20%. In the worst situation new dapsone-resistant cases were occurring at a rate of about 3% per annum of those at risk. Dapsone-resistance is a stable characteristic of *M. leprae* and resistant strains are clearly infectious for man, since dapsone-resistant strains of *M. leprae* have been isolated from previously untreated patients. Although dapsone is a weak carcinogen in the male rat, epidemiological studies indicate that it is probably not carcinogenic in man. Furthermore neither dapsone nor any of its known metabolites displays mutagenic activity *in vitro*.

RIFAMPICIN

The extremely powerful bactericidal activity of rifampicin against *M. leprae* has been demonstrated in the mouse by both the kinetic and proportional bactericidal test methods. Rifampicin is fully active against dapsone-resistant strains, and experimental studies indicate that it penetrates excellently into nerves. In man it reduces the levels of dapsone in the body but this is probably without therapeutic significance. In clinical treatment the bactericidal activity of rifampicin is so powerful that single doses of 1200 mg or as few as 4 consecutive daily doses of 600 mg of the drug killed over 99% of the viable bacilli. However even 5 years continuous treatment with rifampicin plus thiambutosine failed to eliminate the remaining persisters. Drug-sensitive persisters were also isolated after combined treatment with daily dapsone plus

rifampicin. Patients have relapsed with rifampicin-resistant strains of *M. leprae* after treatment with 3 years rifampicin monotherapy, but no such relapses have occurred among patients treated up to 5 years with rifampicin plus thiambutosine.

CLOFAZIMINE

Because of marked tissue accumulation, it is impossible to determine the MIC of clofazimine against *M. leprae*. Clofazimine treatment is less effective when doses are given at intervals of a week or more. Patients with dapsone-resistant leprosy have been treated for up to 10 years with daily or thrice weekly clofazimine monotherapy without relapses occurring, although the relatively small number of patients treated in this way does not exclude the possibility that clofazimine resistance might eventually emerge in a pattern similar to that originally observed with dapsone. Persisters can also be isolated after many years of continuous clofazimine treatment.

ETHIONAMIDE/PROTHIONAMIDE/THIACETAZONE/ THIAMBUTOSINE

The most important results of studies of the antileprosy activities of these drugs in the normal mouse and investigations of their pharmacology in man are summarized in Table 1. The corresponding data for rifampicin and dapsone are included for comparison. Strains of *M. leprae* exhibit cross-resistance between these drugs, but are not cross-resistant with dapsone.

STREPTOMYCIN/SULPHAMETHOXYPYRIDAZINE

A pilot clinical trial has shown that the antileprosy activity of streptomycin is inferior to that of dapsone. Experimental and pharmacological data relevant to the antileprosy activity of sulphamethoxypyridazine are given in Table 1.

POTENTIAL NEW DRUGS

The antileprosy activities of a series of dihydrofolate reductase inhibitors, antithyroid compounds, interferon inducers, chaulmoogric-, clofazimine- and long-acting rifampicin-analogues have been investigated experimentally. The rifampicin derivatives appeared the most promising for further investigation.

FUTURE STUDIES

In vitro *models*

M. leprae has been shown to incorporate radioactive thymidine and DOPA in a cell-free system and in human macrophage culture. These systems may provide more rapid means of testing the activity of new drugs and identifying drug-resistant strains.

Animal models

The neonatally-thymectomized rat and the athymic "nude" mouse may be useful for detecting persisting *M. leprae* and for studies of drug combinations and microbial persistence. A newly-discovered nude rat may also be useful for

these studies. The armadillo is currently the only source of the large numbers of bacilli required for enzymatic studies of drug action, and represents the only model in which the development of drug resistance can be studied. The pharmacokinetics of dapsone and rifampicin have been studied in the armadillo, but more developmental work will be required before the armadillo can be evaluated as a model for long-term chemotherapeutic studies.

Drug development

Employing new methods for drug screening, computer-assisted techniques for studies of quantitative structure-action relations, and new analytical methods for studies of enzyme activity, it may be possible to develop new drugs specifically active against *M. leprae*. Employing two experimental models of ENL, it may now be possible to develop an active compound that is non-teratogenic.

Clinical and field studies

Surveys of the point-prevalence of secondary and primary dapsone resistance must be conducted in various parts of the world. Surveillance programmes should be initiated immediately for rifampicin resistance, in view of the increasing use of rifampicin, which is often irregular and unsupervised. The efficacy of rifampicin administered intermittently and of ethionamide, prothionamide and thiacetazone must be established in short-term trials monitored by inoculation of normal mice. Combined regimens of drugs in dosage schedules already shown to be effective in short-term monotherapy trials must be tested among patients with lepromatous leprosy in formal clinical trials monitored by inoculation of immunosuppressed rodents. Finally, those combined regimens that appear most promising in formal clinical trials must be tested in the field to determine their acceptability to patients, the ease of their application to leprosy control programmes and, most importantly, their ability to interrupt the transmission of *M. leprae*.

Implications for Present Treatment

The widespread emergence of dapsone resistance has emphasized the necessity of using combinations of at least two antileprosy drugs for the treatment of lepromatous leprosy. The experimentally determined antileprosy activity and pharmacological characteristics of the available drugs are shown in Table 1. For previously untreated patients, dapsone administered at a dosage of 50 to 100 mg daily must remain the primary drug, and the maintenance of inhibitory levels of dapsone could be guaranteed by the administration of acedapsone in addition to daily doses of dapsone. Of the drugs available for use in combination with dapsone, rifampicin with its rapid bactericidal activity is the first choice. Clofazimine is less costly than rifampicin and its antileprosy activity is of the same order as that of dapsone. Thiacetazone might be a suitable drug for inclusion in drug combinations, although the experimental data suggest that one of the thioamides, ethionamide or prothionamide, would be more effective. However, the

TABLE 1

Minimal inhibitory concentration against M. leprae *(MICs), peak serum concentrations, durations of coverage and bactericidal activities of antileprosy drugs*

Drug	MIC (μg/ml)	Dosage (mg)	Ratio* peak serum MIC	Duration† which serum concs exceed MIC (days)	Bactericidal‡ activity
Rifampicin	0.3	600	30	1	+++
Dapsone	0.003	100	500	10	+
Acedapsone	0.003§	225	15	200	—
Ethionamide	0.05	500	60	1	++
Prothionamide	0.05	500	60	1	++
Thiacetazone	0.2	150	8	2	—
Sulphamethoxypyridazine‖	30	1000	3	3	—
Thiambutosine¶	0.5	1500	1	<1	—

* Ratio of peak serum concentration in man after a single dose to MIC determined in the mouse.

† Serum concentrations in man after a single dose.

‡ Purely bacteriostatic; +, ++, ++ +, relative degrees of bactericidal activity.

§ Acedapsone is inactive against *M. leprae* but is converted to dapsone—the figures for MIC and peak serum concentration refer to the values for dapsone.

‖ Cross-resistant with dapsone.

¶ Manufacture discontinued.

antileprosy activity of the thioamides in patients has yet to be fully evaluated. The cross-resistance demonstrated between the thioamides and thiacetazone indicates that only one drug from this group should be used in combination with other antileprosy drugs.

The role of combinations of drugs for eliminating or decreasing the number of persisting bacilli has yet to be determined. The current THELEP trials should establish the best possible combinations.

(5) WORKSHOP ON EPIDEMIOLOGY AND CONTROL INCLUDING FIELD THERAPY

Chairman: S. K. Noordeen

Participants: A. Alvaranga; F. Gjalt; V. Ekambaram; J. C. Gatti; J. Languillon; J. Walter; M. F. R. Waters; Unable to attend—A. A. Juscenko; W. F. Kirchheimer; M. F. Lechat; T. Meade; D. V. Opromolla Aranjo

EPIDEMIOLOGY

Only a limited amount of additional information on the epidemiology of leprosy has accumulated since the last Congress, and there is a continuing need for more planned studies on various aspects of the problem. One of the important requirements for field studies is clear and comparable terminology, so that geographical comparisons are possible. There is also a need for more information on mortality rates of leprosy patients and also on spontaneous inactivation of the disease in certain types of leprosy.

One of the major handicaps in the study of the epidemiology of leprosy, particularly on transmission, is the lack of a simple and dependable test to identify subclinical infection in the field, despite the considerable progress which has been made in developing immunological tests. The available information indicates that leprosy is a disease of high infectivity and low pathogenicity. With regard to transmission of the disease, there is more and more evidence of the importance of airborne spread, although other modes of transmission cannot be ruled out. The available evidence on arthropod transmission is inadequate to permit definite conclusions. However, there is less and less justification for insisting on the necessity for direct, prolonged, intimate contact for transmission of the disease. There is also the possibility of a carrier state in leprosy in view of the occurrence of acid-fast-bacilli in the skin and nose of apparently healthy persons, and studies on the occurrence of such bacilli should be repeated in combination with mouse footpad and serological studies. Regarding possible extra-human reservoirs of infection, it is difficult to evaluate the significance of the occurrence of leprosy or leprosy-like disease in armadillos in certain parts of the U.S.A., and it may be worthwhile to look for similar reservoirs in other parts of the world, using modern methods.

The role of genetic predisposition in leprosy is not clear in view of the inadequacy of the available information. Further precise studies on the importance of genetics in leprosy are indicated.

One area of research in leprosy that could be fruitful is "risk factor" studies, where association of leprosy with certain variables related to environment or host could be studied prospectively with the hope that it may be possible to contribute to disease prevention through intervention or manipulation of the risk factors identified.

LEPROSY CONTROL

In leprosy control, programme planning is vital for successful control work. Programme formulation provides a logical process to ensure a full analysis of the current epidemiological, operational, and managerial problems. Such a formulation requires specially trained staff. A programme should include precise objectives, targets, manpower requirements, physical facilities, financial resources, timings of activities and their interrelations. Programming incorporates implementation and evaluation; the latter should include specification of the subject, verification and analysis of information support, review of original programme planning, and review of progress on (a) operational efficiency, such as staff competence, case detection activities, case holding, bacteriological monitoring, etc; (b) epidemiological effectiveness, such as reduction of prevalence and incidence rates and of deformity rates.

The programme planning should lead to a gradual integration of specialized programmes into the general and primary health services, which should eventually take full responsibility. This is a task for which the general health workers must be trained and motivated in order to prevent failures.

For the analysis of the leprosy situation and to make the comparison between data from different regions possible, it is recommended that a uniform leprosy information system be developed.

Case detection methods should, among others, include methods to encourage voluntary reporting through health education of the community utilizing, among others, mass media such as radio, TV, etc. In urban areas, motivation of general practitioners could be useful for case detection; they should coordinate with health authorities. Where facilities are available, lepromin testing is useful for identifying early cases which are lepromin negative.

With regard to release of patients from control, the recommendations of the Fifth WHO Expert Committee on Leprosy were considered to be valid. However, further studies on optimal duration of chemotherapy of paucibacillary leprosy were considered necessary.

Regarding treatment delivery, while the mode of treatment delivery will depend upon individual situations, it is necessary to carry out periodic checks on drug intake through urine tests. Every effort should be made to maintain regularity of treatment of patients, particularly of patients with multibacillary leprosy. In this connection it is necessary to ensure high standards in patient care.

Regarding primary prevention, although studies on chemoprophylaxis have established their moderate protective value, the application of chemoprophylaxis on a mass scale will not be practicable. Notwithstanding the difficulties, chemoprophylaxis can still be recommended in individual

situations, where the risk of contracting leprosy is considered to be unduly high. Considering the limited prophylactic value of BCG, there is a need to develop a specific antileprosy vaccine.

FIELD THERAPY

The Workshop reviewed field therapy of leprosy in the light of the recent advances in the pharmacology of the antileprosy drugs, the increasing incidence of dapsone resistance reported from different parts of the world, and the need for effective, acceptable, practicable, simple and supervisable therapy, both for infection with *Mycobacterium leprae* and for the treatment of reactions.

The group reviewed the drugs available, and confirmed the importance of using bactericidal drugs, namely dapsone in full dosage, rifampicin, clofazimine and ethionamide or prothionamide.

Dapsone remains the basis of treatment, at a dosage of 6 to 10 mg per kg body weight per week. The drug should be commenced in full dosage, without any initial "build-up", and this dosage should be kept unchanged throughout treatment, and should not be interrupted or altered during reactions.

In tuberculoid (TT and BT), borderline (BB) and indeterminate (I) leprosy, monotherapy with dapsone is acceptable. In lepromatous (LL and BL) leprosy, it is recommended that an initial intensive phase of combined therapy should be given.

Recommended adult regimens for the treatment of lepromatous leprosy include:

(a) rifampicin 600 mg daily for a minimum of 2 weeks, plus dapsone 100 mg daily, indefinitely;
(b) rifampicin 1500 mg in a single dose on the first day of treatment, plus dapsone 100 mg daily, indefinitely;
(c) clofazimine 100 mg daily for 2 months, then 100 mg three times a week for 4 months, plus dapsone 100 mg daily, indefinitely;
(d) ethionamide 375 mg daily for 3 months, plus dapsone 100 mg daily, indefinitely.

Pre-programme studies of ethionamide are recommended in any area, before the drug is introduced generally.

Choice of regimen depends upon cost, cultural acceptance and toxicity. If none of the above regimens can be afforded, the alternatives are:

(e) thiacetazone 150 mg daily for 1 year, plus dapsone 100 mg daily;
(Thiacetazone may have an unacceptably high incidence of toxic side-effects, especially in East Asia; its cost over 1 year equals that of a single dose of rifampicin, and thiacetazone-resistant *M. leprae* show cross-resistance with ethionamide.)
(f) dapsone 100 mg daily indefinitely, ensuring regularity of treatment.

Dapsone resistance

Secondary dapsone resistance has to date only been reported in lepromatous (LL and BL) leprosy. The diagnosis should be confirmed by a medical officer. It is appreciated that mouse footpad confirmation is not widely available. However, random specimens of the patient's urine should normally be tested to confirm the presence of dapsone. Further information is needed on the incidence and prevalence of dapsone-resistant leprosy in different geographical areas.

Recommended adult regimens for the treatment of dapsone-resistant patients include:

(a) rifampicin 600 mg daily for 1 month, plus clofazimine 100 mg daily for 6 months, then 100 mg three times a week indefinitely;
(b) rifampicin 600 mg daily for 1 month, plus ethionamide 375 mg daily, indefinitely;
(c) ethionamide 375 mg daily for 3 months, plus clofazimine 100 mg daily for 6 months, then 100 mg three times a week indefinitely;
(d) clofazimine 100 mg daily for 6 months, plus ethionamide 375 mg daily indefinitely.

Primary dapsone resistance may occur in any type of leprosy, and this possibility should always be kept in mind, especially among contacts of known cases of secondary resistance.

Field therapy of reactions

Effective treatment of reactions is essential for the well-being of patients, and to retain their cooperation with drug therapy. This involves improved training of field staff, and the provision of referral centres for the treatment of severe reactions. Mild reactions should be treated in the field, the patient being seen regularly; patients suffering from severe reactions should be sent immediately to the referral centre, antileprosy treatment being continued unchanged.

Prevention of deformities

Prevention of deformities depends on the early diagnosis of leprosy, effective antileprosy treatment, effective treatment of reactions to prevent (further) nerve damage, and education of the patients in the care of anaesthetic limbs.

(6) WORKSHOP ON HUMAN ASPECTS IN THE TREATMENT OF LEPROSY PATIENTS

Chairman: Mr Marcel Farine
Rapporteur: Dr Ernest Fritschi
Participants: Dr Gilberto Rodriguez Ochoa; Sr Gebre Mariam Senkenesh; Dr (Mrs) Turkan Saylan; Dr V. P. Macaden; Mr R. S. Mani; Mr D. Von der Weid; Dr (Miss) Grace Warren; Mrs Alicia E. Kaufmann de Swiec; Rev. Rocco Serra; Mr Iman Bijleveld

Observers: Mr A. D. Askew; Dr L. M. Baliña (in place of Dr Manuel M. Gimenez)

1. INTRODUCTION

Mass treatment and case-finding in any endemic area tends to have the effect of dehumanising the individual patient. Therefore, each member of the team, medical, paramedical and social, while bringing to bear on the patient his own particular expertise, must constantly remind himself of the patient's total needs —physical, emotional and social, and treat him as a fellow human being. The effective moments for the application of the human element to the treatment of leprosy patients are during the first contacts of the team with the patient.

2. GENERAL CONSIDERATIONS

The extent of the trauma inflicted on the patient by the diagnosis of leprosy is very important. The word "leprosy" is to be used with caution, since it tends to have a socio-historical, in addition to a medical connotation.

The stigma attached to leprosy can only be overcome by a continuous programme of health education at all levels and for all target audiences. The shock of the first diagnosis should be communicated to the patient with kindness. The patient often may not believe it until the deformities appear. This lack of acceptance of the diagnosis is a significant factor, along with socio-economic considerations, in chronic absenteeism from treatment by the patient.

3. CASE FINDING AND CASE HOLDING

Finding patients in the community and holding their confidence during treatment is a continuing concern. The whole team must be imbued with an attitude of sympathy for the patient. His privacy must be respected and his identity preserved. The method of door to door delivery of medication, and unscheduled follow-up visits to ensure that the patient is taking his tablets has proved useful.

There are many factors which render regular clinic attendance difficult for the patient, and the health education team should take account of these problems in their presentation.

The continuing health education of the patient, his family and society should be accepted as requiring the highest priority.

Well qualified social workers with carefully defined job descriptions must be engaged. They should ensure that the other members of the team are trained, not merely in the detection of early lesions and medical aspects, but in psychology, techniques of communication and counselling.

4. CENTRES FOR PATIENT CARE

The old pattern of institutional care has largely given place to field clinics. Institutions however, still remain a necessity. The nature of the institution is important, and the difference in the psychological impact on patients in a leprosarium and a hospital is considerable. Emphasis must be given to the need

for understanding the patient's emotional reactions, and in the hospital set-up, the staff must take time to care for these too.

It is important to establish an interdisciplinary team participation in planning the treatment of the patient.

Hospitalization should be short-term and interrupted. Each admission should be for a specific and documented objective, such as the healing of an ulcer, operation of a hand, treatment of neuritis, etc., the patient being discharged after this target is achieved, to be re-admitted later for another reason if necessary. Patients should be taught self-care of their hands and feet at home.

5. REHABILITATION AND RE-INTEGRATION

In relation to this subject, health education was again the line strongly advocated by all the participants. The need was stressed to implement the Havana Congress' (1948) decision to educate all levels: the medical profession, politicians and the State administration, schools and society at large, of which of course the patient is also a member. The central place of domiciliary rehabilitation has to be emphasized and the team approach is required to keep the patient in his home environment.

The beggar presents a real problem of socio-economic failure in developing countries. Rehabilitation of these patients is difficult but not impossible. However, efforts and resources should also be used to prevent patients from descending to this level.

Rehabilitation and re-integration of the patient in society, especially if he has deformities, can only be achieved by sustained efforts on the part of the patient, the medical, paramedical and social team, and society as a whole. It is necessary to discover and harness the patient's abilities and not be distracted by his disabilities.

Rehabilitation should be planned after careful consideration as to whether further displacement is essential or not. All measures taken for persons disabled because of leprosy should be in the context of resolutions already adopted by ECOSOC, WHO, and ILO (see reference). Care must be taken not to make leprosy a qualification for special privileges.

It has also been proved that it is less expensive to provide appropriate rehabilitation services than to provide the necessary care for an individual who, without rehabilitation, depends on public help.

6. BASIC PRINCIPLES FOR THE HUMANE TREATMENT OF LEPROSY PATIENTS

(1) Health education, both general and specific, must be the basis of all rehabilitation.
(2) A natural and empathetic approach to the patient is required to reduce psychic trauma and loss of identity to the minimum.
(3) Hospitalization should be for short periods, each with definite objectives. Long-term treatment should be interrupted by periods at home from time to time, to avoid long separations from the family.

(4) Much time should be spent by the team in instructing the patient in the care of his hands and feet and the prevention of injuries.
(5) The approach to rehabilitation should not be confined to one channel, such as sheltered industry or domiciliary employment, but all efforts should be made to find out the type of rehabilitation must suited to the country, the environment, the patient's aptitude, skills and social status, and the available funds for capital costs per work place.

Recommendations

To encourage further investigation and to carry out the above basic principles (see para. 6), it is particularly necessary:

(a) To organize a research centre and/or referral library, to collect a bibliography of all publications on social aspects of leprosy patient care, and to make these available to those interested.
(b) To inform on a continuing basis and with discernment, every section of the population, especially in areas and countries where leprosy is endemic, utilizing mass media about the leprosy problem and its social aspects, where possible in the context of general health education, in order to facilitate the acceptance of leprosy patients.
(c) To produce articles, TV and radio features, as well as booklets in different languages on the human aspects of leprosy.
Wherever false concepts are being propagated in the mass media, the concerned organizations must contact the authors, request the withdrawal of any misleading ideas and offer in their place the accepted facts of the disease. If necessary a public protest may be made, utilizing the same media.
(d) To organize in endemic areas and countries regular courses in schools, universities, medical schools, etc., not only on the medical aspects of the disease, but also on its historical, social and economic aspects, pointing out the necessity for humane treatment of the patients.
(e) To train in social aspects (by courses, conferences, seminars, etc.) the personnel engaged in case-finding and working in health centres, hospitals or other services, and to engage qualified social workers, especially for important projects.
(f) To bring to the notice of everybody concerned (especially social, medical, commercial and pharmaceutical agencies) these important aspects of leprosy programmes; in particular, to encourage investment in research and development, and lower prices of anti-leprosy drugs.
(g) To awake the conscience of governments to provide all facilities for the production of anti-leprosy drugs and equipment, and where necessary to waive customs duties and other formalities connected with the import of these drugs and equipment.
(h) To draw the attention of intergovernmental organizations such as UNO, WHO and ILO, international non-governmental organizations such as ILA and ILEP, as well as governments and private organizations, to the need for a concern for the social and human aspects in the treatment of

leprosy patients, as outlined in this report, taking into consideration recommendations and guidelines already adopted. To achieve these objectives, it is essential that all these agencies act together in close cooperation.

Reference

No. 99 of ILO (1955).
No. A29.68 of WHO (1976).
No. 1921 (LVIII) of ECOSOC (1975).

(7) WORKSHOP ON TEACHING MATERIAL FOR LEPROSY WORKERS

Chairman: Dr W. Felton Ross
Rapporteurs: Miss Jane Neville; Dr Ken Seal; Dr B. Landheer
Participants: Dr Joe J. Arvelo; Dr M. Aschhoff; Dr Wanda Blenska; Dr M. Bourges; Dr J. A. Cap; Med Général A. Carayon; Dr C. J. G. Chacko; Dr D. S. Chaudhury; Dr N. Desikan; Mrs Soledad S. Griño; Dr E. D. Kelly; Dr Do Il Kim; Mr Herman Kober; Dr A. C. McDougall; Dr Sandy Ritung; Med Général P. B. Saint Andre; Dr H. W. Wheate; Dr Yo Yuasa; Dr J. A. K. Clezy; Dr Schaller; Dr Roy E. Pfaltzgraff

Purposes

(1) To review currently available teaching material in the leprosy field.
(2) To identify the main training needs, not met by existing material.
(3) To develop plans and coordinate efforts to meet those needs.

1. INTRODUCTION

The production and distribution of suitable teaching/learning material in leprosy is of increasing importance as:

(a) more and more states adopt the principles of community health and widen the range of health personnel engaged in leprosy patient care and leprosy control;
(b) the technologies of leprosy patient care, leprosy control and health programme management become more advanced;
(c) new developments in education offer the possibilities of greatly increased effectiveness in teaching.

2. PROCEDURE

Members of the workshop brought copies of over 100 different pieces of teaching material in a number of languages.

As a basis for reviewing this material, the workshop adopted the following categories of tasks in leprosy work: The Public, Patients, Health Work I, Health Work II, Health Work III and Specialists (see Annex). Limited by time, members of the workshop concentrated on material for Health Work I, II and III. The members divided into groups to review the literature, using a literature assessment form, a copy of which is attached.

Pieces of literature were reviewed by up to six participants.

3. CONCLUSIONS

(a) A great deal more teaching material exists than is generally known and available.
(b) There are still parts of the world where shortage of currency limits the availability of teaching material.
(c) Serious needs for more material exist in the following areas:

(i) basic leprosy for village level workers;
(ii) supervision;
(iii) programme management;
(iv) laboratory technology;
(v) a periodical for middle level workers to fill the gap existing between the magazine "*Partners*" and "*Leprosy Review*".

Recommendations and Actions

4. ADVERTISEMENT

(1) In order to begin to make existing literature more widely known, members of the workshop agreed to:

(a) collate and publish the list of material available at the workshop;
(b) prepare an annotated bibliography of literature reviewed at the workshop;
(c) prepare more complete bibliographies in French, Spanish and English.

(2) The workshop welcomed the steps taken by The Royal Tropical Institute, Amsterdam, to develop a leprosy information service which will collect and register and provide information about literature and audio-visual aids available in the leprosy field.
(3) The workshop recommends that all who publish teaching material in leprosy send sample copies to The Royal Tropical Institute, Mauritskade 63, Amsterdam-O, Netherlands.
(4) The workshop recommends that a series of teaching material- resource- and display-centres be established in major endemic areas and in the main leprosy training centres.

5. DISTRIBUTION

(1) The workshop recommends that existing distribution centres make their services more widely known.
(2) The workshop recommends that a far greater priority in budgeting be given to literature, including periodicals, by all the agencies involved in leprosy programmes and that agencies willing to provide funds for literature should make this fact known.

6. PUBLICATION

(1) Authors seeking to produce material for teaching need the help of experts in design and layout.

A workshop was proposed with the object of providing a manual for guidance in this field.

(2) Field trials for the evaluation of materials are recommended.
(3) There is a need for a critical appraisal of the leprosy component within general medical text books.

7. WORKSHOPS

(1) It is recommended that a workshop on educational technology be held at the next Leprosy Congress.
(2) Audiovisual aids were not reviewed and in view of rapid developments in this field this could also be the subject of a workshop.

ANNEX

Roles in leprosy control

Category	Functions
The Public	Accept and support patients Recognize leprosy Seek medical advice
Patients	Recognize leprosy Seek medical advice Take treatment Practice self-care
Health Worker Category I	Teach and treat leprosy patients Recognize complications Recognize leprosy Keep records
Health Worker Category II	Diagnose and classify leprosy and deformity Recognize complications Teach patients self-care Teach the public Teach health worker I Keep records
Health Worker Category III	Diagnose complications Manage complications Teach health worker II Keep records

BOOK ASSESSMENT FORM

TITLE .....
PUBLISHER .....
DATE OF PUBLICATION .....
LANGUAGE—French ( ), Spanish ( ), Portuguese ( ), German ( ), English ( ), Other

TO BE USED BY:
Job Title .....
Educational Background .....
.....

FOR WHAT PURPOSE:
General Introduction .....
Basic Training .....
Advanced Training .....

* Suitable; ** Very suitable; ***Outstanding
— Not Suitable

AUTHOR .....
PRICE (in U.S.$) .....
PAGE SIZE .....
BINDING—PAPER, CLOTH, HARD
EDITION NUMBER .....

METHOD OF USE:
For Self Instruction .....
Part of a Course .....
A Working Manual .....

CONTENT:

General

1. Are the objectives stated?	( ) In each chapter	( ) Elsewhere	( ) Not at all
2. Is it accurate and up-to-date?	( ) Entirely	( ) Mainly	( ) Serious errors
3. Does it contain sufficient real examples for local application?	( ) Yes	( ) Too many	( ) Too few
4. Does it contain sufficient practical instructions?	( ) Yes	( ) Too many	( ) Too few
5. Does it include sufficient accurate summaries?	( ) Yes	( ) Too many	( ) Too few

Specific to user and purpose given above—

6. Does it include sufficient relevant review questions?	( ) Yes	( ) Too many	( ) Too few
7. Is the subject matter relevant?	( ) Completely	( ) Mainly	( ) Partly
8. Is the level of difficulty appropriate?	( ) Yes	( ) Too easy	( ) Too difficult
9. Is the coverage appropriately complete?	( ) Yes	( ) Too much is included	( ) Serious omissions

10. Other comments:

PRESENTATION:

1. Is the type easy to read?	( ) Yes	( ) Too large & spread out	( ) Too small & cramped
2. Is the line length appropriate?	( ) Yes	( ) Too long	( ) Too short
3. Are illustrations relevant?	( ) Yes	( ) Confusing	( ) No
4. Are illustrations annotated?	( ) Yes	( ) Too much	( ) Too little

5. Are illustrations of good quality?	( ) Yes	( ) To some extent	( ) No
6. Language—Vocabulary	( ) Appropriate	( ) Too difficult	( ) Too easy
7. Language—Structure	( ) Appropriate	( ) Too complex	( ) Too simple

Which of the following additional learning aids are used: Abstracts, algorithms, boxed slogans, cartoons, case studies, decision tables, diagrams, exercises, footnotes, graphs, lists, references, sense lines, tables.
Please circle and comment as to quantity, relevance, and quality of the aids used.

OVERALL ASSESSMENT
FOR USE BY:

Category	Purpose	Rating
Public		
Patients		
H. Worker 1		
H. Worker 2		
H. Worker 3		
Specialist		
Physical Th'y		
H. Educator		
Social W.		

Purpose	Introduction	1	Rating	Outstanding	***	H. Worker 1 ≙ Health Worker
	Basic Training	2		Very Suitable	**	H. Worker 2 ≙ Lepr. Auxiliary
	Advanced Training	3		Suitable	*	H. Worker 3 ≙ Doctor

Approximate Equivalents

Applicability	—Useful only in country of origin	( )
	Wide usefulness in original language	( )
	I recommend translation into	
Relative rating	—Nothing else exists in its field	( )
	Better than	
	Not as good as	
Summary	—Fills a gap in the literature	( )
	Needs revision & updating	( )
	Should be replaced by something better	( )
	Define "something better" below	

This book contains sufficient material to enable the reader to:

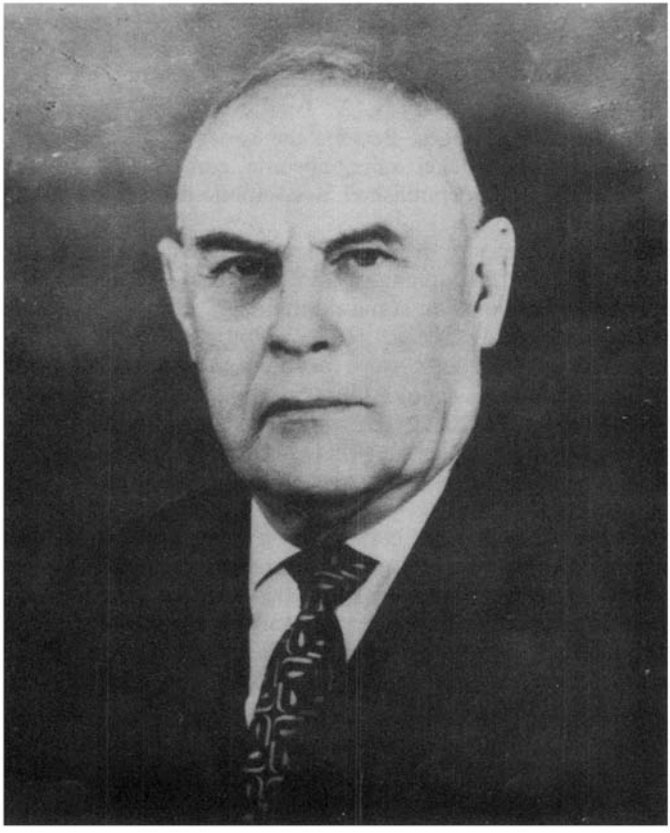
	No	Yes	Notes
1. Accept/Support patients			
2. Recognize leprosy			
3. Give out treatment			
4. Recognize complications			
5. Diagnose leprosy			
6. Classify leprosy*			
7. Grade deformities*			
8. Manage leprosy			
9. Diagnose complications			
10. Manage complications			

* Name system used.

Lepr. Rev. (1979) **50,** 79–82

Obituaries

NICKOLAY ALEXANDROVICH TORSUEV
1902–1978



Professor Nickolay Alexandrovich Torsuev, one of the leading leprologists of the USSR, a member of WHO Expert Committee on Leprosy, died on 6 May 1978.

N. A. Torsuev was born on 13 December 1902, in Gorky (the former Nizhny Novgorod). He graduated in Medicine from Novgorod University in 1925 and first practised as a dermato-venerologist. Since 1932 he became a

teacher at the Department of Skin and Venereal Diseases of the Gorky Medical Institute. Thereafter he headed the Departments of Skin and Venereal Diseases of the Medical Institutes in Simferopol (1937–1944), Rostov-on-Don (1944–1961), Donetsk (1961–1976). Since September 1976, he was appointed a professor-consultant at the Department of Skin and Venereal Diseases of the Donetsk Medical Institute (the Ukraine).

N. A. Torsuev was a prominent clinician — dermatologist and leprologist, experienced teacher and eminent scientist.

His medical and scientific interests were many and varied.

He published over 700 scientific works including 24 monographs and a textbook of skin and venereal diseases for medical students. Under N. A. Torsuev's guidance 70 theses were done.

Early in his scientific activity N. A. Torsuev was much engaged in studies on occupational skin diseases. Besides the series of the articles devoted to dermatoses caused by nickel salts, chrome compounds, sodium cyanide, lubricators and so on, he published a comprehensive bibliography on this subject in 1934.

N. A. Torsuev achieved a deserved success in investigating the problems of innervation of normal and damaged skin. His thesis "The nerves of skin and histiocyte (barrier) response in some dermatoses" (1938) was awarded with a special prize from Moscow Society of Dermatologists.

A lot of Torsuev's articles were devoted to the questions of skin and venereal diseases control, aetiology and pathogenesis of various dermatoses and history of dermatology and venerology.

The first article by N. A. Torsuev on leprology appeared in 1931. Since that, during all his scientific life N. A. Torsuev was constantly investigating different problems of leprosy. In his studies N. A. Torsuev was dealing with epidemiology of leprosy, its classification and differential diagnosis, its treatment and prophylaxis. He studied different aspects of pathogenesis, early manifestations of the disease, interactions between murine and human leprosy. In all he published about 230 articles on leprosy, the most important of which were the following: a guide for medical practitioners *Leprosy* (1951, 1952), monographs *The History of Leprosy Classification* (1956), *Leprosy in the Former Russian Empire* (1958), *Brief Reference-book on Leprosy Control* (1958), *Recognition and Differential Diagnosis of Leprosy* (1971) and various articles on the problems of leprosy treatment, relapses in leprosy, differential diagnosis of leprosy and some tropical diseases.

Thanks to N. A. Torsuev's initiative and energy, in 1947 a clinico-experimental leprosarium was founded in Rostov-on-Don (closed in 1970) which he headed up to 1960. In this role he played a great part in the training of doctors and scientists. During this period under his guidance a great number of scientific researches were performed and 23 collections of the scientific works on leprology and dermatology were published.

Prof. N. A. Torsuev took part in preparing the 4th Report of WHO Expert Committee on Leprosy (1970).

He was an honoured member of 13 Societies of Dermatologists, a member of the International Association of Tropical Diseases and International Leprosy Association, and a member of the editorial boards of many medical

publications including *International Journal of Leprosy, Castellania, Vestnick dermatologii i venerologii* and others.

For his dedicated work in the field of medical sciences and health services. Prof. N. A. Torsuev was awarded with honorary titles "Meritorious Science Worker", "Meritorious Physician" and some Government rewards.

N. A. Torsuev, specialist, scientist and teacher, will always be remembered by his students, friends and colleagues.

A. JUSCENKO, V. SHUBIN and V. LOGINOV

ERNANI AGRICOLA
1887–1978

The world of leprosy has lost one of its best-known and best-loved workers in Dr Ernani Agricola, who died on 14 July 1978 in his ninety-first year.

He was early attracted to leprosy; in fact, the thesis he submitted for his doctorate degree in 1920 concerned the value of lymphatic node puncture in leprosy. His first medical appointments took him away from his Brazilian Alma Mater in Bela Horizonte, out into the vast rural areas in the State of Minas Gerais. His interest in leprosy was stimulated by these wide contacts with the problems of rural health, sanitation and prophylaxis, preparing him in many ways for what was to become his life-work — the investigation and control of leprosy. With undiminished interest in all matters of public health, including malaria, Dr Agricola became in 1931 General Director of Health in the State of Minas Gerais, and in 1941 he was appointed Director of the National Leprosy Service, a position he held for 13 fruitful years. It was during this time that Dr Agricola became a familiar figure on the international leprosy scene, attending the Congresses in Havana, Madrid, Tokyo and Rio de Janeiro, and representing his motherland, Brazil, at many important international gatherings. His profound local experience of leprosy in Brazil and his zeal in enlisting the active sympathy of medical teachers, social workers and politicians, added weight to his public announcements and professional contributions.

He was honoured by numerous bodies, in South America and elsewhere, and was held in high esteem wherever leprosy was taught or studied. He travelled widely, both to extend his own knowledge of leprosy and to give of his advice — terse and always very practical.

He was a member of the International Leprosy Association since 1938, a valued Councillor, Vice-President (1963–1968), and an Honorary Vice-President from 1968 until the time of his death.

We honour the memory of a great Brazilian leprologist, and extend our sympathy to his sorrowing family.

S. G. BROWNE

Lepr. Rev. (1979) **50**, 83–90

Leprosy and the Community

SEMINAR IN MADANG, PAPUA-NEW GUINEA, JULY 1978

Under the joint sponsorship of the Government of Papua-New Guinea and the Damien Foundation (Brussels) and with the cooperation of TLM (Australia), a National Seminar on Leprosy Control was held in Madang, P.N.G., from 24 July till 28 July. It was attended by some 30 participants, most of them Provincial Medical Officers and Health Extension Officers in charge of leprosy. Dr Alan Tarutia, First Secretary General for Health, opened the Seminar. The following topics were covered: diagnosis, bacteriological examination, treatment, organization of control, rehabilitation, the eyes; a number of clinical sessions were organized. Resources persons included personnel from the Ministry of Health, WHO, the University of PNG, Training College in Madang, and two oversea consultants (Dr M. F. Lechat from Belgium and Dr D. Russell from Australia).

INTERNATIONAL WORKSHOP ON LEPROSY IN EUROPE
Rome, 9–10 June 1978

Under the auspices of the Amici dei Lebbrosi, an *ad hoc* group of leprosy specialists met in Rome on 9 and 10 June 1978 to review the leprosy situation in European countries and to make recommendations for the control of the disease.

It is noteworthy that the widespread mediaeval endemic in Europe was on the wane in the west and north-west countries long before specific chemotherapy became available: only 3 patients remain in Norway, for instance, as a relic of the considerable endemic of the mid-19th century. However, leprosy has persisted in the countries bordering the Mediterranean and in the USSR. The estimated total number of leprosy sufferers in Europe is about 50,000. More recently, leprosy has been imported into the industrialized countries of Western Europe by guestworkers and students from southern Europe and particularly from countries of the Third World where leprosy constitutes a disease of public health importance. Despite this recent accession, leprosy has failed to re-establish itself in any of these countries.

The Group studied up-to-date reports from various European countries, and reviewed the social services available to leprosy patients as well as the legislation in force concerning leprosy.

Although not empowered to offer advice officially, this group of experienced leprologists possessing valuable local knowledge drew up a Report and made recommendations that should carry weight with the governments of the various European countries still faced with an endemic leprosy problem.

LEPROSY IN EUROPE — EPIDEMIOLOGY AND RESIDUAL FOCI

Leprosy was probably brought to Europe by the troops of Alexander the Great returning to Greece from the Indian campaign in 327–6 BC. It was heralded as a new disease by the observant Greek physicians. Once established, it spread to the countries bordering the Mediterranean and even further afield. A secondary importation occurred with Pompey's legionaries coming back from Egypt in 62 BC. Known by the Greeks as leontiasis or satyriasis, and thereafter as *elephantiasis Graecorum* and *Lepra arabum*, true leprosy can be recognized in Greek and Latin texts, and from references in Alexandrian records.

The spread of leprosy in Europe is largely a matter of conjecture, apart from a few skeletal remains from the first millenium of our era showing specific erosion of the anterior nasal spine and alveolar process of the maxilla, and references to the foundation of hospitals and hospices for "leprosy sufferers" in Caesarea, Rome and the lands of Western Europe. It is presumed that some Phoenician, Greek and Roman soldiers, sailors, merchants and administrators carried the causative organism with them to the countries comprising the Roman Empire, but the actual dimensions of the leprosy endemic at that time are of course quite unknown. The whole subject is confused by nomenclature, since the Latin transliteration of the Greek *lepra, lepros* was as imprecise and vague as the Hebrew *tsara'ath*.

There are indications that true leprosy spread slowly in mediaeval times westwards and northwards across Europe, becoming generally endemic by the 12th and 13th centuries. The invading armies of Ghengis Khan left pockets of leprosy in central and south Europe, Iran, etc. The number of hospices for leprosy sufferers in European countries indicates a widespread charitable concern for the victims of various chronic skin diseases, or venery, or poverty — rather than a precise representation of the spread of leprosy.

Estimates of the size of the leprosy endemic in southern and western Europe have varied between the widest extremes, but the general consensus now is that at its zenith it attacked no more than about 5 persons per thousand. After the 14th century leprosy began to wane in Europe generally, but it persisted in the countries of Southern Europe, and began to disappear later in those countries that received the invader last, that is Scotland and Scandinavia. The reasons for the decline of leprosy are far from clear, but probably relate to the decrease in domestic overcrowding coupled with the rise in socio-economic levels.

As an endemic disease, leprosy disappeared from the British Isles in 1798, and has all but gone from Norway (Scandinavia) during the past decade, only 3 patients now remaining to represent the widespread endemic of last century. Within the present century, leprosy has gone from the endemic foci in Finland, Denmark, Germany, Switzerland and the Low Countries, and has almost disappeared from France.

Small residual foci, insignificant from the epidemiological standpoint, but interesting nonetheless, remain in Iceland and in France (Nice, Marseilles and Bordeaux, and the *bidonvilles* of Paris housing Algerian immigrants).

Somewhat larger foci persist in parts of USSR to the North West (the old Latvia, Esthonia and Lithuania), but the problem attains the dimensions of an endemic of public health importance in Southern USSR (the Donetz Basin, Astrakhan, Rostov), and in all the countries of Southern Europe bordering the Mediterranean, that is Portugal, Spain, Italy, Greece and Turkey, the islands of Malta and Cyprus, and also Rumania and Yugoslavia.

The prevalence of leprosy in these countries is patchy at present, and to judge from oral tradition and folklore, these foci are local remnants of a former widespread and more uniformly distributed endemic, now perpetuated by some local factor or factors. In the absence of precise figures from the past, it is impossible to delineate the changing dimensions of the leprosy endemic: suffice it to state that the general tendency, as in France and Switzerland, has been for a gradual reduction in the number of victims.

Europe does not differ from other continents in the uncertainty of its total number of leprosy patients. The largest reservoir of undiagnosed and unregistered cases is undoubtedly Turkey (25,000), but USSR (6000), Spain (4000), Portugal (3000) and Greece (1300) also have many leprosy sufferers. More recent figures, and perhaps more accurate figures, will probably be furnished by participants at this Workshop who are provided with more up-to-date information concerning the leprosy situation in their countries.

Until recently, imported leprosy has played little part in the overall European picture, except perhaps in Spain, where a small but constant accession of cases from Algeria (and formerly from Morocco) has left its mark on towns and villages to the south and east of the Iberian peninsula.

In the past 30 years, however, the epidemiological situation in Western Europe has changed, consequent on movements of population from countries where leprosy is endemic to those completely or almost without autochthonous cases. From Southern Europe, workers and in some cases their families have gone to France, Switzerland, West Germany, Belgium, Holland and the United Kingdom. Turkey, Italy, Spain and Portugal have exported their *M. leprae* as well as their guestworkers, not to mention the 70-odd Italians with leprosy in Toronto.

From further afield have come larger accessions — from the Indian subcontinent (India, Bangladesh, Pakistan), from Africa (particularly Nigeria), from Surinam and Indonesia (almost exclusively to Holland), from Algeria, "Indo-China", French West Africa and the Caribbean islands (Saint Pierre and Martinique, Guadeloupe) to France, and from the Philippines and West Indies mainly to Britain.

The countries of southern Europe in which leprosy is endemic have been exporters rather than importers of the bacillus, but the importing countries, although they have been receiving large influxes of populations that include cases of leprosy, have apparently not provided the bacillus with conditions conducive to its transmission. Thus, in Great Britain there has been no indigenously contracted case of leprosy during the past 40 years, despite the presence since 1951 of no fewer than 1054 registered cases. In France and in Holland, the numbers can be counted on the fingers of one hand.

The situation is far otherwise in the southern USSR and in the countries of southern Europe, where the endemic foci persist.

The profoundly practical questions of the disappearance and the persistence of leprosy in Europe may be considered in the light of the extinction of the endemic imported from Scandinavia into Minnesota and Missouri, and of the French focus in Quebec, against the persistence of the French-Spanish importation into the southern States of USA and of the German focus in Venezuela.

Before any effective anti-leprosy therapy became available, leprosy had virtually disappeared from north-western Europe, and in Norway it was the abandonment of the old charitable practice of requiring farmers to entertain leprosy sufferers for 3 months at a time rather than compulsory segregation in hospitals old and new of about a third of the total leprosy population that contributed to the acceleration of a declining incidence. In Japan, to go to the other side of the world, the reduction in total prevalence by two-thirds in 30 years is probably due to humanitarian hospitalization of the majority of sufferers.

In the Europe of today, the epidemiologist has to take into account both the failure of leprosy to install itself in the industrialized West, and its persistence in the countries of southern Europe; the intractable problem of transmission in predominantly rural situations in Italy and southern USSR, and the apparent failure of transmission from imported index cases in the urban West. The ubiquity of tuberculosis and diverse opportunist mycobacteria, especially in an urban environment, may provide group-antigenic stimulation of cell-mediated immunity as well as skin sensitization, and opportunities for repeated and massive exposure to viable leprosy bacilli may be reduced in an urban environment.

The tuberculinization of Europe has been cited as a factor in the reduction of prevalence rates, but the historical data are almost valueless in this regard, and present statistics of prevalence rates of both leprosy and tuberculosis, and the frequency of pulmonary tuberculosis as a major cause of death in old-style leprosaria, together offset the slight protection against leprosy apparently afforded by a clinically transient episode of tuberculosis.

Another possible factor sometimes cited is the selective action of such epidemics as plaque and typhus in causing more deaths among the verminous and dirty and ill-nourished sufferers from leprosy than in the non-leprous population, thus eliminating the carriers of genes of susceptibility to leprosy infection. A pretty theory, impossible of verification.

The role of nutrition in leprosy infection is probably marginal; prolonged undernutrition may be modifying cellular and humoral immunity potential have some effect on susceptibility to leprosy infection, just as such viral diseases as measles may act in the same way.

The importance of these various possibilities cannot be determined in retrospect in explaining the undoubted decline of true leprosy in the countries of north-western Europe since the 15th century to the present day.

A possible modification in the pathogenicity, virulence and invasiveness of the agent has also been suggested to account for the waxing and waning of the leprosy endemic in the world. So far, laboratory limitations have circumscribed any objective demonstration of this possibility,

but with the examples of streptococci and spirochaetes in mind, this factor cannot *a priori* be ruled out. Strains of *M. leprae* from various countries, from different kinds of leprosy, do not apparently differ markedly in pathogenicity or in response to mycobacteriostatic drugs, as judged by inoculation into the mouse footpad.

The imprecision of these suggestions throws us back to the rather unsatisfactory and unscientific explanation of a general reduction in the infective contacts as the likeliest reason for the decline of the leprosy endemic in north-western Europe and its persistence in the south.

The general epidemiological principles for the control and prevention of a specific bacterial infection, which has no necessary intermediate host or vector, should be applied to the countries of Europe still beset by this intractable mycobacterial menace; that is, in the continued absence of specific preventive measures, to reduce rapidly the infectivity of the index cases, and to reduce the occasions of successful passage of the infective agent to susceptible contacts. The practical measures for the application of these principles call for medical expertise and social awareness. With such generally low prevalence rates, and a rising socio-economic level, there appears to be no insuperable medical difficulty in the identification of the index cases and their treatment with a mycobactericidal drug. The social component may well prove more intractable.

The principal reasons for the persistence of the European foci of leprosy, particularly in the countries bordering the Mediterranean will, it is hoped, be revealed in the course of this Workshop; and the importance of the different medical and social components will also become apparent. The medical reasons are: the failure of doctors to recognize the signs of leprosy, especially early leprosy; the lack of confidentiality; poor patient compliance; irregular medication. The social reasons are mainly concerned with prejudice and stigma, and with positive discrimination against leprosy patients.

S. G. BROWNE

WHO/UNDP: THE SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES

Reports of Progress in 1976 and 1977

Following the issue, to all interested applicants, of Volume I (Introduction, The Diseases, the Research and Training Needs; Malaria, Schistosomiasis, Filariasis, Trypanosomiasis, Leishmaniasis and Leprosy), Volume II (Epidemiology, Biomedical Research, Vector Biology, Socio-economic Considerations, Training and Institution Strengthening, Prior Scientific Recommendations, Programme Management), and a separate Inventory of African Research Institutions, a further loose-leaf volume has now been produced, which includes the following:

> Report of the THELEP Screening Committee, Geneva, 14–15 December 1976, Report of the Third IMMLEP Scientific Working Group Meeting, 21–25 February 1977, Report of the First Meeting of the THELEP Scientific Working Group, Geneva, 15–29 April 1977.

A Report of special importance for leprosy is that of the First Meeting of THELEP, where pages 8 and 9 deal with drug regimens to be tested, and Appendix 5.13 and 5.14 with the management of reversal reactions and of erythema nodosum leprosum.

> We continue to draw attention to the development and progress of this momentous Special Programme for obvious reasons, and take this opportunity of reminding readers of *Leprosy Review* that by writing

formally to Hilary Boardman, Secretary, Special Programme for Research and Training in Tropical Diseases, WHO, 1211 Geneva 27, Switzerland, *bona fide* applicants may obtain documentation on the Programme, and also have a regular Newsletter posted to them.

A. C. McDOUGALL

THE 1ST INTERNATIONAL WORKSHOP ON LEPROSY CONTROL IN ASIA, JAKARTA, INDONESIA
28 November–1 December 1977

Published by Sasakawa Memorial Health Foundation, Sabokaikan, 2-7-5 Hirakawa-cho, Chiyoda-ku, Tokyo, 102, Japan, August 1977

In *Leprosy Review* (1978), **49,** 78, we described at some length the corresponding Workshop on Chemotherapy, held in Manila in January 1977. The present Proceedings on Leprosy Control are recorded in a similar format of 249 pages, and the subject matter is divided into reports on (1) leprosy control in Indonesia and other countries (Korea, Nepal, Philippines and Thailand), (2) a report from WHO on policy in leprosy control, (3) ILEP reports from Leprosy Relief Work Emmaus Switzerland, Damien Foundation, German Leprosy Relief Association, Netherlands Leprosy Relief Association, Danish Save the Children Organization, Sasakawa Memorial Health Foundation, The Leprosy Mission, and from ILEP itself (headquarters in France, and Indonesia). As in the previous report on chemotherapy, almost half of this one is devoted to a verbatim account of the discussions arising from papers read, and once again, the views of the various experts taking part make fascinating, if at times slightly perplexing, reading.

The final recommendations on pages 227 to 232 are forthright and clear. They largely support those made by the recent Fifth Expert Committee of WHO, while emphasizing (1) the urgent problems of dapsone resistance, (2) the need to establish mouse footpad testing stations in Indonesia and other Asian countries and (3) the potentially damaging consequences of attempting to integrate leprosy control into primary health care too quickly. Under the heading of Integration, paragraph 3 on page 231 contains the vital sentence: "... the Workshop is of the opinion that leprosy treatment should be entrusted only to adequately trained and adequately supervised primary health care workers". In view of the increasing complexity of treatment and control in this disease, and the demands which are already being made on these workers, it will be interesting to see, during the next few years, how this is to be achieved.

A. C. McDOUGALL

MAKOGAI — IMAGE OF HOPE
A brief history of the care of leprosy patients in Fiji

Sister Mary Stella, Lepers' Trust Board, New Zealand, pp. 186, including index. No price indicated.

This is a well-written story of an island in the South Pacific that for over a half-century epitomized the resignation and despair, and also the hope and

comradeship, associated with the enforced segregation of leprosy sufferers. It is a story of tremendous courage on the part of many of leprosy's victims, and of tremendous devotion and dedication on the part of those who cared for them.

In a way, the book reflects a general and almost universal picture of attitudes over the years — attitudes towards leprosy itself, and attitudes towards those who happen to catch the disease. In 1911, people in Fiji and the other islands in the South Pacific — Tonga, Samoa, Cook, Gilbert and Ellice, the Solomons and the rest — were branded as dangerous criminals, and segregated in a distant island far from family and friends. Despite the tragedy of hopelessness and frustration, and the absence of anything but palliative help for their ulcerating extremities and severe bouts of reaction, many of these condemned and dangerous "lepers" found a new way of life and made the best of a depressing situation.

This book is the result of meticulous researches carried out by the author. She delved into government records as well as into patients' memories; she questioned colleagues and former inmates; and she has told the story in fascinating detail of people and events.

The recurrent use of the banned word "leper" may grate on the ears of many, and the less-than-felicitous references to some aspects of leprosy and its treatment may offend the knowledgeable — but these shortcomings will not detract from the impact the story will make on the general reader, for whom it is intended.

Leprosy has now become a treatable and manageable disease. The coming of the sulphones to Makogai and the great changes they have brought about are told in the vivid language of eye-witnesses and participants. The Missionary Sisters of the Society of Mary emerge with flying colours from the long saga of care and compassion, of sheer courage and determination. So does the Lepers' Trust Board of New Zealand, and its intrepid founder P. J. Twomey. His name is enshrined in the Memorial Hospital just outside Suva, the capital of Fiji, where leprosy patients now receive the best of modern care during the short period they need treatment as inpatients.

When Makogai was abandoned in 1969 as an island that had served its purpose, no fewer than 4185 patients had been welcomed to its hospitable but dreaded shores; 2343 had been discharged, and 518 repatriated. Only 83 remained in December 1969, to continue treatment either at home or in the new hospital at Suva.

Thus Makogai — like many another islands utilized for the same purpose — passes into history, leaving a tale of blended heroism and compassion.

LEPROSY AND TUBERCULOSIS

At the 24th World Conference of the International Union Against Tuberculosis, held in Brussels, 5 to 9 September 1978, a two-hour plenary session was devoted to leprosy. Although a regrettably small proportion of those attending appeared to find the subject of leprosy sufficiently attractive, many doctors from countries of the Third World who are today faced with the

problems of both leprosy and tuberculosis were eager to avail themselves of the expertise provided by such well-known figures as Drs Michel Lechat, H. Sansarricq, S. G. Browne, S. Pattyn, E. Freerksen and R. J. W. Rees.

The various contributions indicated the similarities between the two diseases, and also the differences. In leprosy, the continued lack of a method of culture of the causative organism on artificial media still hampers investigations, as does the apparent impossibility of matching the excellent controlled clinical trials in tuberculosis that have meant so much in the popularization of precise programmes of multi-drug therapy.

With governments examining, or actually adopting policies of combined attack on both these "tropical" scourges, it behoves those concerned primarily with leprosy to renew their efforts to arrest the disease in patients suffering from multibacillary forms of leprosy and prevent the infection of susceptible contacts. The increasing menace of drug resistance, the investigation of which has owed much to the earlier work on tuberculosis, lends point to many of the views on this theme expressed during this interesting session at the Congress.

At a sectional meeting, some of the microbiological aspects of the two diseases were discussed.

Thanks are due to Dr Annik Rouillon, the dynamic Director of Scientific Activities of the World Conference of the International Union against Tuberculosis for her initiative in suggesting these sessions and for her contacts with the Medical Commission of ILEP.

THE TANZANIA LEPROSY ASSOCIATION

Consequent on the break-up of many of the common services in East Africa, the East African Leprosy Association ceased to be, but the members of its Tanzanian Branch refused to accept this coup de grâce. The happy suggestion that the branch should join forces with the National Leprosy Advisory and Co-ordinating Committee of Tanzania resulted in the creation of the Tanzania Leprosy Association.

His Excellency the Minister of Health of Tanzania, Dr Leader Stirling, officially inaugurated the new Association at an enthusiastic and representative meeting on 25 July 1978 at Arusha, and announced that President Julius Nyerere had consented to be the Patron of the Association.

The first activity of the newly formed Association was to organize and sponsor a highly successful scientific meeting at Arusha. Dr H. Sansarricq, the chief of the Leprosy Section of the Division of Communicable Diseases of the World Health Organization was there; Dr Stanley Browne, Secretary of the International Leprosy Association, brought greeting from the old Association to the new one; Dr Harold Wheate, who was formerly Leprosy Advisor to the government of Tanzania, journeyed from Addis Ababa to participate in the Meeting.

Under the dynamic leadership of Professor G. D. Georgiev of the University of Dar-es-Salaam, and Dr K. Balslev, the Tanzania Leprosy Association should fulfill a real need, and, to judge from the highly successful Scientific

Meeting at Arusha, it should exert a salutory influence on the whole policy and programme of leprosy control in Tanzania and beyond.

WHO REGIONAL COMMITTEE FOR EUROPE

At the meeting of the above Committee held in London recently (19–23 September 1978), Dr Stanley Browne was given an opportunity of addressing the delegations from Member States on behalf of The International Leprosy Association. The following summary of his speech appears in the Report of the Meeting:

Dr Browne (International Leprosy Association) recalled that indigenous leprosy remained a sizeable and still virtually uncontrolled problem in a number of European countries, notably countries of Southern Europe and the USSR; that was quite apart from the problem of imported leprosy. Naturally, however, leprosy in Europe was only of very small relative importance when compared with the situation in countries of the Third World. He would accordingly, together with the Director-General of the World Health Organization, plead for greater recognition by the countries of Europe of their medical, social and moral obligations for the health problems of the developing countries. He urged closer links between existing expertise so that resources could be deployed for the benefit of leprosy sufferers, particularly in the realms of microbiology, immunology and therapeutics. As Chairman of the WHO Expert Committee on Leprosy, he had warned governments of the gravity of the problems of drug resistance and persister organisms, and of the urgent need to give more serious attention to the problem of leprosy. He drew attention to the International Leprosy Congress to be held in Mexico City in November of the present year.

S. G. BROWNE

Lepr. Rev. (1979) **50,** 91–94

News and Notes

INTERNATIONAL SEMINAR ON LEPROSY, 22–28 APRIL 1979

US Public Health Service Hospital, Carville, Louisiana, 1978–1979 Seminar Series

PURPOSE

To provide an educational opportunity for professional leprosy workers to become aware of contemporary medical management and control techniques in leprosy. The programme also offers an opportunity for medical missionaries and others planning to work abroad for the first time to become familiar with the management of leprosy.

ELIGIBILITY

Medical, nursing, and allied health personnel now working, or planning to work, in anti-leprosy control programmes in countries other than the United States.

SPONSORSHIP

Seminar is sponsored jointly by the American Leprosy Missions, Inc., Bloomfield, New Jersey and US Public Health Service Hospital, Carville, Louisiana.

PROGRAM

The seminar content will consist of a comprehensive description of the epidemiology, diagnosis, and treatment of leprosy as well as appropriate public health control techniques. Teaching methods include lecture, panel discussion, clinical demonstrations, workshop activities, and self-study activities.

COST

There are no expenses involved in attendance except travel to and from New Orleans International Airport, New Orleans, Louisiana.

CERTIFICATION

Attendance acceptable for credit toward the American Medical Association Physician's Recognition Award in Category 1 on an hour for hour basis.

APPLICATION

Application for attendance should be submitted directly to *American Leprosy Missions, Inc., 1262 Broad Street, Bloomfield, New Jersey 07003,* not later than 1 February 1979.

SCHIEFFELIN LEPROSY RESEARCH & TRAINING CENTRE, KARIGIRL, SOUTH INDIA. SCHEDULE OF TRAINING COURSES FOR THE YEAR 1979

Courses	Qualification	Duration	Commencing date	No. of seats
FOR DOCTORS				
(a) Condensed courses for doctors	MBBS, or equivalent, from any recognized University	1 week	15 January 23 April 10 September	20
(b) Medical students course	Undergraduates	1 week	Pooja Holidays	20
(c) Medical officers' course	Medical personnel engaged in leprosy work	6 weeks	29 January 16 July	16
(d) Ophthalmic aspects in leprosy	Qualified medical personnel (to follow Jan. course)	1 week	12 March	10
(e) Postgraduate qualified specialist practising surgeons	Qualified plastic/orthopaedic surgeons	2 weeks	12 November	6
FOR NON-MEDICAL PERSONNEL				
(a) Non-medical supervisors' course	Fully qualified paramedical workers with a minimum of 5 years experience	4 months	4 June	12
(b) Orientation course in leprosy (personnel not requiring any Government recognized certificates)	For paramedical personnel (nurses, physios, OT & administrators) (1 week doctors' course & 3 weeks inservice training)	1 month	15 January 10 September	6
(c) Paramedical workers' course	SSLC passed, graduates preferred	6 months	9 April 8 October	20
(d) Medical record-keepers' course	2 months inservice by previous arrangement. SSLC with proficiency in typing & good English	2 months	2 April 1 October	6
(e) Physiotherapy technicians' course	SSLC passed, graduates preferred	9 months	13 June	8
(f) Social workers' & medical administrators course	Any other category wishing an orientation, are invited to correspond regarding period of inservice training	1 week	17 September	10
(g) Laboratory technician	SSLC passed, graduates preferred	12 months	6 August	4

INSERVICE TRAINING				
(a) Inservice training in medicine surgery, pathology, control & laboratory technology	For suitably qualified personnel by previous arrangement	9 months	by arrangement	
(b) Prosthetic technicians	SSLC passed, PUC preferred	18 months	July & January	3
(c) Shoe-makers' course	V standard with knowledge of English preferred (by previous arrangement)	6 months	by arrangement	
(d) Smear technicians	SSLC passed qualified lab. technicians (by previous arrangement)	3 months 1 month	by arrangement	

Note

These courses are recognized both by the Government of Tamil Nadu and the Government of India. Candidates will be awarded Government recognized certificates.

Inservice Training for Doctors: In the case of inservice training, medical personnel are expected to carry out routine regular duties in the concerned departments like any other member of staff in that particular department.

All courses for non-medical personnel are open only for sponsored candidates. Private candidates will not be accepted for any of them.

Food and accommodation will be provided either in the Guest House in the case of medical and overseas personnel, or in the Hostel for non-medical personnel. Family accommodation *will not be* provided unless previously arranged, subject to availability.

Please note that in view of the very limited number of rooms available in the Guest House, Guest House accommodation is *not guaranteed*. This is allotted only on a "first come, first served" basis. However, alternative accommodation can be arranged either in one of the lodges in the town Vellore (at approximately Rs. 5/- Rs. 10/- per day) or in the CMCH-Annexe (at Rs 15/- per day) according to preference of candidates. Non-resident trainees can utilize the services of the Staff Bus that leaves the CMC Hospital compound at 7.15 a.m. sharp.

Application forms will not be considered if they are not accompanied by a postal order for Rs. 10/- towards registration fee.

For prescribed forms and other details, please contact: *The Training Officer, SLR & T Centre, SLRS P.O., via. Katpadi 632106, North Arcot Dist., S. India.*

EXCERPTA MEDICA

Leprosy and Related Subjects, Vol. 1, Issue 1, 1979

Price Dfl 180.00, Postage included, for Volume 1, 10 issues

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 will include material on other mycobacterial diseases and related pathology, particularly to the extent that their management, prevention or epidemiology may be relevant to the leprosy problem. Following introductory chapters on the organization of the struggle against leprosy, the distribution of information on this disease, education and training, social hygiene and public health, each issue will contain several chapters on the clinical and therapeutic aspects of leprosy and related mycobacterial diseases, with particular attention to differential diagnosis, chemotherapy, surgery and

rehabilitation. Finally, there will be extensive information in each issue on the bacteriology of the mycobacteria, animal models, the pathogenesis and histopathology of leprosy in man and animals, and the immunological and serological aspects of leprosy and related problems.

In this way, information which is currently found not only in specific leprosy journals but scattered over primary journals in many different disciplines will be concentrated in a single convenient source.

Orders to *Excerpta Medica, PO Box 1126, 1000 BC Amsterdam, The Netherlands.*

ILEP MEETS AT CARVILLE

The Medical Commission of ILEP met at Carville, Louisiana, on 20 November, immediately following the International Leprosy Congress in Mexico City, under the Presidency of Professor Michel Lechat.

Among the important matters discussed were recommendations for the International Year for Disabled Persons (1981) and programmes for combined attacks on leprosy and tuberculosis.

The Commission paid tribute to the dynamic leadership of its President, who relinquished his office after a 3-year term. Dr K. F. Schaller was elected in his place, with Dr J. A. Cap and Dr A. Colin McDougall as Vice-Chairmen.

S. G. BROWNE

EDITORIAL OFFICE CHANGE OF ADDRESS

Please note that the new address for the Editorial Office of *Leprosy Review* is *The Slade Hospital, Headington, Oxford OX3 7JH. Tel. Oxford 64841, ext. 597.*

LEPRA; PRIZE ESSAY COMPETITION, 1979; "THE IMMUNO-PATHOLOGY OF NERVE DAMAGE IN LEPROSY"

Since 1972, first in Oxford, then in Birmingham and Edinburgh, the British Leprosy Relief Association (LEPRA) has annually offered prize money of £100 for essays from medical students on various aspects of the leprosy problem. In 1977 it was decided to extend the offer to all universities with a medical faculty in the United Kingdom. The response in that year, and also in 1978, was encouraging, and the competition is therefore being continued in 1979, with the above title. Posters with full details of the conditions of entry are now being printed and will shortly be issued to universities. The closing date is 31 December 1979.

Lepr. Rev. (1979) **50,** 95–98

Book Reviews

Handbook of Leprosy, 2nd Edition, by W. H. Jopling, 1978. Published by William Heinemann Medical Books Ltd, London. Price £3.75.

Dr Jopling's book, first published in 1971, is an authoritative account of a disease that is no longer confined to endemic areas. There was, at that time, no shortage of literature on the subject but there was no up to date monograph suitable for student, general physician and leprosy paramedical worker to turn to. *Handbook of Leprosy* filled this need and has continued to do so.

Since 1971 there have been great advances in leprosy research and Dr Jopling has again brought those findings of clinical significance together in a revised second edition of his excellent book.

The colour plates have remained essentially unchanged but most have been reproduced with greater magnification and therefore better definition. The illustrations have been indexed and expanded and some have been changed to give better examples of the features described.

There is a new chapter on Immunological aspects of the disease which has, thanks to WHO support and stimulation, been the area of greatest development in the past few years. The chapter is remarkable in that the fundamentals of immunology and their application to leprosy are put across in such a manner as to enable the reader to understand the most dramatic and difficult side of leprosy management; that of reactional states. A new table compliments this chapter but will be of little practical help to the majority of leprosy workers as the tests described are mainly research tools and the significance of results obtained when they are applied is still debated in the literature.

Therapeutic advances and setbacks have emerged and these are documented in an expanded and very thorough chapter on management. Dapsone continues to take its place as the treatment of choice and Dr Jopling devotes much of the chapter to this drug and its various formulations. The emergence of dapsone resistance in lepromatous patients is discussed in detail along with suggestions as to how it can be dealt with.

The use of Thalidomide in the management of Type II reactions is discussed and readers are informed how they can obtain supplies of this drug. By inference, Dr Jopling obviously prefers this drug to Prednisolone for controlling Type II reactions because of the lower incidence of side-effects, but regretfully many doctors are still reluctant, and with good reason, to dispense Thalidomide when they cannot be certain it will not fall into the wrong hands.

With his characteristic attention to detail, Dr Jopling documents details of management of iritis, rhinitis, neuritis and chronic leg ulceration, all of which, if not attended to with competence and vigour, result in great morbidity.

To ensure that cases of leprosy are not missed in these times of human migration and jet travel, this small, inexpensive, well illustrated and extensively referenced book should be read by all doctors. For leprosy field workers, this second edition will, I am certain, be warmly and gratefully received.

D. S. JOLLIFFE

Physical Therapy in Leprosy for Paramedicals, by Ellen Davis Kelly. American Leprosy Missions, 1262 Broad Street, Bloomfield, New Jersey 07003.

The value of physical therapy in the prevention and correction of the crippling effects of leprosy has long been under-emphasized. Now, a new book by Ellen Davis Kelly, Ph.D. will bring this form of treatment to many more leprosy patients.

Entitled *Physical Therapy in Leprosy for Paramedicals,* the 235-page paperback is designed to train paramedical workers in the field of physical therapy as it applies to the leprosy patient.

At the present time, there are very few physical therapists in the countries where leprosy is endemic and of these, only a small number treat leprosy patients. Dr W. Felton Ross, Medical Director of American Leprosy Missions, suggests that "Access to appropriate physical therapy should be an inalienable right for every leprosy patient who needs it. This may seem to be an unattainable goal, but it is a goal which this very practical handbook will bring closer to reality."

The instructional material is organized in three levels. The first is a basic summary of the signs and symptoms of leprosy and, in particular, those effects of the disease which lend themselves to treatment by physical methods. Level II covers the physical therapy techniques used by paramedicals assisting in clinics and hospitals when patients do not need surgery or when no reconstructive surgery is available. It also explores methods for supervising field staff members who should be teaching simple techniques to their patients. Finally, Level III covers pre- and post-operative physical therapy and the anatomy and physiology necessary to understand it.

Eminently qualified to write this outstanding new manual, Dr Kelly has had over forty years of experience in teacher education in health and physical education. Since 1972, she has been deeply involved in leprosy work. She has visited leprosy programmes throughout Asia and has taught paramedical personnel at the Africa Leprosy and Rehabilitation Training Center in Ethiopia and the Schieffelin Leprosy Research and Training Center in India. Furthermore, she has assisted resident staff members, developed teaching materials, and designed courses for doctors, nurses, and rural area supervisors.

American Leprosy Missions, the oldest service agency in the United States aiding the world's leprosy victims, is proud to have taken part in the production of *Physical Therapy in Leprosy for Paramedicals*. Copies of the manual will be available by about 1 October and will be distributed on a restricted basis at no charge. Write to: *American Leprosy Missions, 1262 Broad Street, Bloomfield, New Jersey 07003.*

Pathology of Tropical and Extraordinary Diseases, edited by Chapman H. Binford and Daniel H. Connor, Armed Forces Institute of Pathology, Washington, 1976, pp xxiii + 696. Price Vol. I $15.00, Vol. II $20.00.

These two volumes are intended as the successor to *Pathology of Tropical Diseases — An Atlas*, by Ash and Spitz. They do indeed retain the style and framework of that veteran of 1945, which has become a collector's item. The difference is that the new version is just twice the size of the old one, and against 90 diseases it describes 218. It is interesting that 56 of these have been recorded in man for the first time since 1945. The 44 contributors all write from first hand experience of their subject. Very many are members of the AFIP and they are a tremendous testimony to the strength of that institution and its interest in tropical pathology. In a work of such uniformly high standard as this it would be invidious to single out either authors or chapters, but the most frequent contributors are Dr Daniel H. Connor, Dr Wayne M. Meyers and the parasitologist Mr Ronald C. Neafie.

The subject matter consists of the recognized tropical and parasitic diseases, and the exotica which often receive scant attention in standard text-books. Several are too recent yet to have found their way there. The mycoses, viral diseases and some tumours prevalent in the tropics are all included, but not the diseases such as tuberculosis which are well described in text-books of pathology. The descriptions provide a general and clinical account of each disease and its aetiological agent, besides its pathology. A short bibliography is appended to each chapter. If the aim was to supplement other readily available sources it might be asked whether it would not have been better to break with the tradition of 30 years ago, and devote more space to pathology, since the rest of the subject matter is so well covered in text-books of parasitology and tropical medicine. A work that extended to the full the experience of this team of authors and the unrivalled resources of the AFIP would indeed have been monumental, though the book as conceived will be of more general interest, and it is still immensely informative. It provides in particular the most valuable and authoritative accounts of many recently described or little known diseases with a tropical bias.

What dispels criticism is the wealth of superb illustrations, mainly pathological but also clinical and parasitological. Although the term Atlas has been dropped from the title (or put in small print), the number and the quality of photographs would have amply justified it. From the point of view of clarity, size and colour rendering they are truly excellent, and instructional value

apart, some are beautiful (some of the clinical subject matter is also appallingly ugly). The care with which the text and figures have been assembled to produce a unified work is impressive, and the two editors will have earned the gratitude of the many who will want to buy this book. Its success is certain. It is intended primarily for pathologists but not only for them. It should appeal to almost everyone with a serious concern for tropical diseases.

The two volumes are offered at a bargain price which can only have been made possible through the grants made towards its production. They are bound in semi-stiff plastic, and regrettably the review copy of one had already shed its cover on receipt. The book is destined for a long life and deserves a hard wearing binding. The book may be ordered direct from Armed Forces Institute of Pathology, GPO Sales Office (Room G-134), Washington DC 20306. For those who want to order volumes separately, Volume I covers the diseases of viruses, rickettsiae, bacteria and protozoa; Volume II helminths, fungi, arthropods and miscellaneous conditions.

D. S. RIDLEY

The Medieval Leper and His Northern Heirs, by Peter Richards, 1977. D. S. Brewer Ltd, Cambridge (UK) and Rowman & Littlefield, New Jersey (USA). Price £6.

After approving the exclusion of the obnoxious word "leper" from modern-day usage, the author gives valid reasons for retaining the word when writing about the history of medieval leprosy. The story opens with a description of leprosy in the Aland archipelago (a group of islands lying between Sweden and Finland) and the opening of a leprosy hospital on Gloskär island in 1653; the high death rate and the "utter destitution" which prevailed led to its closure in 1672 and the transfer of the 23 surviving inmates to a larger establishment on the south-west coast of Finland where conditions were only slightly better. Conditions in English leprosy hospitals two centuries or more earlier were favourable in comparison, and the reader is given a good description of many of these hospitals and the life inside them, together with many sidelights such as the story of Nicholas Harris, footpostman of Totnes, Devon, who in 1620 was accused of being a leper and who travelled to the Royal College of Physicians in London to be examined and to obtain a certificate that he was healthy. Did you know that the last case of endemic leprosy in Britain was John Berns, a Shetland Islander admitted to the Royal Infirmary, Edinburgh, in 1798?

The basis for segregating a leper from the community, whether in England or in Scandinavia, was essentially religious, formalized in Levitical law, and the afflicted person was required to cut himself off from society. As very few could afford home isolation, most were forced to seek shelter and support in an institution. Containing infection was not the problem.

Leprosy declined in England in the 15th century, and a century later in Denmark and southern Sweden, but in Finland, Iceland, Norway, northern Sweden, and the eastern shores of the Baltic, the disease persisted well into the 19th century. A census of leprosy in Norway in the mid-19th century showed an incidence of 2 per 1000, but as the disease was almost entirely confined to the west coast, here the incidence in some communities was as high as 20 to 25 per 1000. Between 1861 and 1908 more than 600 cases were notified in Sweden, and in Iceland 236 cases were known in 1896 — an incidence of 3 per 1000. In all these countries new leprosy hospitals were built after the middle of the 19th century and existing ones were enlarged. In Norway at this time, a country very conscious of its leprosy problem and one which possessed the world's leading leprologists, laws were passed making admission to hospital compulsory; yet at the same time the inmates were not segregated from healthy persons. For example, St George's Hospital, Bergen (where Hansen worked), had many visitors, and inmates freely sold their wares in the open market. Readers will puzzle over this apparent paradox: why compel patients to enter hospital and then not to isolate them? The author confirms that it was not fear of infection which was the motive for making admission to hospital compulsory, but tantalizingly does not explain the reason. The prime aim and object was to ensure *sexual segregation*, and Irgens confirms this in *Int. J. Lepr.* (1973), **41,** 189. To enforce sexual segregation in 19th century Norway was rational prior to Hansen's discovery of the leprosy bacillus in 1873 as leprosy was at that time considered to be a hereditary disease, therefore admission to hospital separated husbands from wives and stopped further breeding; there was no objection to casual contact between diseased and healthy persons by day so long as the former were accounted for and locked up at night! One further question arises. Why did the same policy

persist after 1873 when the idea of infection was gaining ground? The reason was the belief (which still dies hard) that prolonged and intimate contact was necessary for the spread of leprosy, hence the objective was to separate diseased persons from their families.

Readers who doubt that those who were labelled lepers in the Middle Ages actually suffered from the disease we know as leprosy will, after reading this book, have their doubts dispelled by the reproductions of drawings made of real-life patients, and by the description of Møller-Christensen's excavations in the 1950's of the burial ground of a medieval leprosy hospital in Naestved, Denmark, which revealed skeletons with indisputable changes of leprosy.

In these pages, profusely illustrated, is a fascinating story of leprosy in Britain and Scandinavia up to the end of the 19th century, and the author is to be congratulated on producing such a well documented literary gem.

W. H. JOPLING

Lepr. Rev. (1979) **50,** 99–106

Abstracts

1. SHEPARD, C. C., WALKER, L. L. & VAN LANDINGHAM, R. M. **Immunity to *Mycobacterium leprae* infections induced in mice by BCG vaccination at different times before or after challenge.** *Infect. Immun.,* Feb. 1978, Vol. 19, No. 2, 391–394.

The authors have previously reported that an intradermal injection of approximately 10^7 viable BCG given to mice about 1 month before challenge into the footpad with 5×10^3 *M. leprae*, results in effective protection. However the mechanism of this protection remained doubtful.

Either the BCG was causing macrophage activation via *BCG-recognizing* lymphocytes, which then non-specifically limited the growth of *M. leprae*, or the BCG was stimulating the development of a population of T-lymphocytes able to recognize antigens shared by the two organisms, which could then interact specifically with the antigens of the subsequently injected leprosy bacilli. Resolution of this dilemma is important, since only the latter antigen-specific mechanism is likely to give the very long-lasting protection which would be a prerequisite for a human vaccine. Thus the non-specific macrophage activation would not be expected to persist after the disappearance of the vaccinating organisms themselves.

In this paper the authors have attempted to clarify this point by varying the time of vaccination, relative to the *M. leprae* challenge. The numbers of organisms in challenged footpads were counted at 4 week intervals up to 300 days after challenge, and growth curves were plotted. There was clear protection whether the BCG was given as early as 168 days before challenge, or as late as 56 days afterwards. Only when vaccination was delayed until 91 days after challenge, was any reduction in protective efficacy seen. The authors noted that the ability of BCG to protect when given 168 days before the *M. leprae* did not, however, prove that the protection was due to the antigen-specific mechanism, since enlargement of the nodes draining the vaccination site persisted for at least 400 days. This implies the persistence of BCG, and, therefore, the possibility of continuing systemic macrophage activation, via the release of mediators from lymphocytes.

It seems likely that both of the mechanisms discussed are relevant to protection from *M. leprae* by BCG, but it is clearly exceedingly difficult to demonstrate the antigen-specific component unequivocally in the mouse model.

G. A. W. Rook

2. RIDLEY, M. J. & RIDLEY, D. S. **Surface markers on lymphocytes and cells of the mononuclear phagocyte series in skin sections in leprosy.** *J. Path.,* 1978, v. 125, 91–98.

The authors have attempted to identify the cells present in cryostat sections of lesions from the various forms of leprosy, and from other granulomatous and mycobacterial diseases. They have used a technique which is more often applied to cells in suspension than to intact tissue sections. It exploits the fact that lymphoid cells of different types can be distinguished by the presence or absence on the cell membrane of receptors for untreated sheep erythrocytes, or for the Fc portion of IgG, or for the third component (C_3).

The reagents used were

(1) untreated sheep erythrocytes, referred to as (E);
(2) erythrocytes which had been pre-incubated in a rabbit anti-sheep erythrocyte serum as a source of IgG. Such erythrocytes can attach to Fc receptors and are referred to as (EA);
(3) erythrocytes which had been preincubated in the same concentration of antiserum, and then in non-lytic mouse complement as a source of C_3. These cells were referred to as EAC. These EAC will have been able to bind to both Fc and C_3 receptors, so that only in sections where the EA *failed* to bind can one argue that adherence of EAC demonstrated the presence of C_3 receptors.

The E, EA, or EAC were allowed to settle onto fresh cryostat sections at room temperature for 1 h. The sections were then gently washed, fixed in paraformaldehyde, and stained in haematoxylin-eosin. The treated or untreated sheep erythrocytes remained attached to the sections in areas rich in the appropriate receptors.

Interpretation of the results in relation to lymphocyte subpopulations is difficult. It is generally accepted that adherence to *untreated* sheep erythrocytes is characteristic of T-lymphocytes, but may occur only if the T-cells are alive. This is in good agreement with the fact that the authors found no adherence of E, EA, or EAC to the lymphocytes found in TT or BT leprosy, or in sarcoid, and concluded that these were T-cells.

In some circumstances T-lymphocytes can carry Fc or C_3 receptors, but these are unlikely to be demonstrable by the technique used. Therefore the authors suggested that lymphocytes binding EA or EAC were B-cells. Here again difficulties arise, because as explained above the EAC used were not specific for Fc receptors. This point is critical, because although it was generally believed that B-cells carry both Fc and C_3 receptors, in which case this lack of specificity would be unimportant, it is becoming clear that peripheral blood B-cells carry C_3 receptors, but *not* Fc receptors. The latter are characteristic of a third heterogeneous group of cells, the majority of which are neither B-cells, nor T-cells, and some of which may be Killer cells. (Ref. Horwitz, D. A. *et al.* (1978), *J. Immun.* **121,** 678–684.)

Thus both EA and EAC bound to the lymphocytes shown to be paradoxically present in BL cases, and also to cells in *M. ulcerans* and atypical mycobacterial lesions. The authors consider these to be B-cells, but as discussed above, the EAC binding must be considered suspect, and EA binding may not indicate B-cells. This raises fascinating questions as to the identity of these cells, which will require further study, particularly in view of the fact that EA and EAC did *not* bind to the few lymphocytes present in LL cases.

Interpretation of the results in relation to the macrophage/epithelioid cell system is easier because giant cells, and the epithelioid cells of TT patients bound EAC strongly, but not EA, suggesting genuine C_3 receptors without Fc receptors.

Macrophages in BB, BL and *M. ulcerans* infection had both Fc and C_3 receptors (though not necessarily on the same cells) whereas epithelioid cells and giant cells in TT, BT, and sarcoid had C_3 receptors only. The foamy macrophages in LL had neither receptor. The functional significance of these changes invites exciting speculation.

In cases of ENL, or BT in reaction, EA and EAC adherence was seen in areas of polymorph infiltration around blood vessels, and in the intercellular spaces. The authors suggest adherence to immune complexes.

Further studies of this type will obviously be immensely rewarding.

G. A. W. Rook

3. **Leprosy: cultivation of the etiologic agent, immunology, and animal models.** Proceedings of the workshop on future problems in the microbiology of *M. leprae*. Scientific Publication No. 342 of the Pan American Health Organization, Washington, D.C. 20037, 1977.

This is a report on the first of three workshops on problems in the microbiology of leprosy, sponsored by the Pan American Health Organization and held at Johns Hopkins University School of Hygiene and Public Health in Baltimore, Maryland, from 12–15 October 1976. In its 74 pages which include 13 Figures and 2 Tables it deals with three major topics.

Topic I is on the problems involved in the cultivation of obligate intracellular mycobacteria, especially on the conditions that must be controlled, such as oxygen tension, oxidation–reduction potential, and temperature. A paper by Dr Lane Barksdale, of New York, questioned the assumption that acid-fast mycobacteria found in leprosy patients are a single organism, namely, *M. leprae*.

Topic II deals with immunology of leprosy, and opens with papers by Dr Quentin Myrvik of Wake Forest University, North Carolina, and by Dr Hubert Sansarricq of WHO, Geneva. Dr Myrvik discusses the role of cell-mediated immunity, interpretation of the lepromin test, the role of BCG as a prophylactic vaccine, and possible approaches to developing a specific vaccine. Dr Sansarricq describes the objectives of the WHO IMMLEP Programme: finding a test for subclinical leprosy, developing an effective vaccine, and methods of immunotherapy.

Topic III is on the subject of animal and rodent models in leprosy research, and contains papers by Dr Jacinto Convit on experience with various species of armadillo, and by Dr Charles Shepard on the role of rodents and armadillos.

The Discussions at the end of each Topic add their quota of stimulating and informative reading. No microbiologist or immunologist will fail to find something of value in this volume, and for all those who are engaged in leprosy work in general, and in leprosy research in particular, it is essential reading.

W. H. Jopling

The abstracts which follow are reprinted from the Tropical Diseases Bulletin, *June 1978, through the courtesy of the Director, Bureau of Hygiene and Tropical Diseases, London. They are classified according to subject.*

1. MICROBIOLOGY

4. RIGHTSEL, W. A., SAWYERS, M. F. & PETERS, J. H. **Comparative effects of sulfones and rifampin on growth of *Mycobacterium lepraemurium* in macrophage diffusion chamber cultures.** *Antimicrob. Agents Chemother.,* 1978, v. 13, No. 3, 509–513.

"A cell-impermeable diffusion chamber technique has been developed that lends itself to growth studies of *Mycobacterium lepraemurium.* This technique, in which the organism grows within macrophage cultures inside the chambers that are maintained on monolayer cultures of macrophages, provides a method for a strict *in vitro* evaluation of antileprosy drugs without the influence of a multiplicity of host factors. This system was used to compare the effect of three sulfone derivatives and rifampin on the growth of *M. lepraemurium* within these diffusion chamber cultures. Two sulfones, 4,4′-diaminodiphenyl sulfone and 4,4′-diacetamidodiphenyl sulfone, as well as rifampin, suppressed the growth of *M. lepraemurium*, but monoacetyl sulfone 4-amino-4′acetamidodiphenyl sulfone had no effect. The results indicate that the diffusion chamber technique can be used to evaluate the inhibitory effect of antileprosy drugs on the growth of *M. lepraemurium.* Also, the method provides for the first time a relatively rapid *in vitro* method for directly comparing the effects of drugs or their analogs when outside the metabolic influence of an animal host. This technique may be a useful tool for chemotherapy studies with other antileprosy compounds."

2. IMMUNOLOGY, PATHOLOGY

5. LEFFORD, M. J. & MACKANESS, G. B. **Suppression of immunity to *Mycobacterium lepraemurium* infection.** *Infection & Immunity,* 1977, v. 18, No. 2, 363–369.

"After injection of 10^8 live *Mycobacterium lepraemurium* (MLM) into the left hind footpad of mice, there is development of local swelling attributable to a granuloma of the cell-mediated immunity type. Concomitant intravenous inoculation of live MLM delays and may even suppress footpad swelling, the effects being proportional to the intravenous dose of organisms. Concomitant footpad infection and intravenous inoculation of 10^9 dead MLM also delays footpad swelling, but over a period of months the feet become excessively swollen. The excessive swelling is due to the local enhancement of infection as evidenced by an increase in the number of MLM per footpad. Attempts were made to prevent such immunosuppression by splenectomy or treatment with BCG. Splenectomy was entirely without effect, but 10^7 live BCG administered intravenously 2 to 4 weeks before dead MLM prevented enhancement of infection. The mediator of the immunosuppressive mechanism that results in enhanced infection remains to be elucidated, but it is unlikely to be antibody or immune complexes."

6. LEFFORD, M. J., PATEL, P. J., POULTER, L. W. & MACKANESS, G. B. **Induction of cell-mediated immunity to *Mycobacterium lepraemurium* in susceptible mice.** *Infection & Immunity,* 1977, v. 18, No. 3, 654–659.

"A mouse strain (CB6) that is highly susceptible to *Mycobacterium lepraemurium* was infected with 10^8 bacilli into the hind footpad. These mice developed cell-mediated immunity to *M. lepraemurium,* as expressed by the development of a granulomatous lesion at the site of inoculation in normal but not in T-lymphocyte-depleted mice, a proliferative response in the paracortical zone of the draining lymph node, delayed-type hypersensitivity to a sonic extract of *M. lepraemurium,* and immunopotentiation of the delayed hypersensitivity response to sheep erythrocytes. Resistance to a second challenge infection with *M. lepraemurium* was not demonstrated."

7. McADAM, K. P. W. J., ANDERS, R. F., AIKEN, G. & TAKITAKI, F. F. **Secondary amyloidosis and the serum amyloid precursor in leprosy: geographical variation and association with leukocytosis.** *Int. J. Lepr.,* 1977, v. 45, No. 2, 150–157.

"The prevalence of the amyloid-related serum component, protein SAA, was investigated in two groups of leprosy patients from different areas of Papua New Guinea. Protein SAA was more prevalent in coastal leprosy patients (49% positive) than in highland patients (21% positive). Paradoxically, many more cases of amyloidosis were diagnosed in the highland group (17 of 199) than in the coastal group (3 of 112).

"In the highland patient group, SAA was found to correlate with the leprosy disease spectrum, being more prevalent in patients toward the lepromatous pole. Borderline and tuberculoid patients who had detectable SAA usually had neurotrophic ulcers. No such relationships were observed in the coastal patient group, probably because other infections, more common on the coast, were also responsible for causing increased concentrations of SAA which is known to behave as an acute phase reactant.

"A correlation was observed between SAA positivity and neutrophil leukocytosis. This suggests that various inflammatory stimuli, such as *erythema nodosum leprosum* reactions, neurotrophic ulcers and intercurrent infections, all contribute to the prevalence of SAA in leprosy patients."

[This is a valuable paper which would repay reading in full.]

M. F. R. Waters

8. ATTA, A. G., FLEURY, R. N., MARINGONI, R. L., TRINDADE, A. S. JR, RUFINO, C. B. F. & FILHO, B. S. **Renal amyloidosis in leprosy. Functional and histopathologic studies.** *Int. J. Lepr.,* 1977, v. 45, No. 2, 158–166.

"Seven cases of renal amyloidosis secondary to lepromatous leprosy are reported. . . . One patient had only mild tubular involvement, three were in a far advanced stage and the other three were moderately affected. Five had a previous history of repeated episodes of *erythema nodosum leprosum* (ENL), three of ENL and plantar ulcers, and one of plantar ulcers without episodes of ENL. None were in active phase of ENL during the renal studies.

"Renal function was evaluated by the clearances of inulin (to measure the glomerular filtration rate), *p*-amino-hippuric acid (to measure the effective renal plasma flow) and by the maximal capacity of the tubules to raise the urine osmolarity after water deprivation.

"The patient with only slight deposits of amyloid in tubules showed excellent functional reserve. The three advanced cases presented serious impairment of the glomerular filtration rate, effective renal plasma flow and tubular capacity to concentrate the urine. The three cases with intermediate type involvement showed an increase of the filtration fraction suggesting a greater vascular involvement or this associated with a deficient capacity of the tubules to transport the dye. . . ."

9. GUPTA, J. C., DIWAKAR, R., SINGH, S., GUPTA, D. K. & PANDA, P. K. **A histopathologic study of renal biopsies in fifty cases of leprosy.** *Int. J. Lepr.,* 1977, v. 45, No. 2, 167–170.

"Renal biopsies from 50 cases of leprosy, including 45 cases of lepromatous and 5 cases of tuberculoid, have been studied in detail histopathologically with special reference to any specific leprosy lesion such as the presence of leproma or granuloma, the presence of acid-fast bacilli and the occurrence of amyloid deposit. Leproma or granuloma, acid-fast bacilli and amyloid deposit could not be detected in any of these cases. Pathologic features of nephritis of various types were seen in only 40% of cases. . . ."

10. BULLOCK, W. E., EVANS, P. E. & FILOMENO, A. R. **Impairment of cell-mediated immune responses by infection with *Mycobacterium lepraemurium*.** *Infection & Immunity,* 1977, v. 18, No. 1, 157–164.

"The effect of chronic infection with *Mycobacterium lepraemurium* upon cell-mediated immune responses was studied in Lewis rats. Rats infected for 40 to 175 days were completely protected from attempted induction of experimental adjuvant disease, and the severity of experimental allergic encephalomyelitis in leprous rats was markedly attenuated. Full manifestations of each autoimmune disease were expressed in littermate control groups. Skin homograft rejection by infected rats was significantly impaired ($P < 0.001$) as was the delayed-type hypersensitivity response to sheep erythrocytes ($P < 0.02$). It is suggested that chronic infection with *M. lepraemurium* exerts a nonspecific inhibitory effect on cell-mediated immunity by perturbation of normal lymphocyte recirculation and by induction of immuno-suppressor cell activity."

11. MELSOM, R., NAAFS, B., HARBOE, M. & CLOSS, O. **Antibody activity against *Mycobacterium leprae* antigen 7 during the first year of DDS treatment in lepromatous (BL-LL) leprosy.** *Lepr. Rev.,* 1978, v. 49, No. 1, 17–29.

"A specific radioimmunoassay was developed for demonstration and quantitation of antibodies against *Mycobacterium leprae* antigen 7 which cross-react extensively with a similar antigen in many species of mycobacteria, including BCG-antigen-60.

"The antibody activity against *M. leprae* antigen 7 showed only a slight tendency to decrease in 15 patients with lepromatous leprosy during their first year of treatment with dapsone associated with marked clinical improvement."

12. McDOUGALL, A. C. **The work of the Leprosy Study Centre in London: a review over 13,000 biopsies.** *Proc. R. Soc. Med.,* 1977, v. 70, No. 10, 731–732.

That leprosy has taken its rightful place in the main stream of medical research is due in no small measure to R. G. Cochrane, whose scientific approach is evident, not only in his writings but in the incomparable collection of histological material matched by clinical records at his consulting rooms in London. It was his dream that this should form the nucleus of an international focal point of leprosy study, and the Leprosy Study Centre is the fulfilment of that dream. Standards of excellence in patient care, in training and in histopathology have given the Centre a high reputation. Biopsy material has been sent from many parts of the world, and now, in magnitude, range and in detailed records the histological collection is unique.

This article, the result of much careful study of the great wealth of material, concentrates more on the results than on the techniques used, already well described by Harman (*Lepr. Rev.,* 1975, v. 46, 125). Unusual aspects of differential diagnosis are mentioned, as is the value of serial sections in indeterminate cases. There is particular reference to microfilariasis [see *Trop. Dis. Bull.,* 1977, v. 74, abstr. 2792] and the contribution of the Centre to elucidating exit routes of leprosy bacilli from the body.

T. F. Davey

3. CLINICAL

13. PALANDE, D. D., DE SEVERY, C. & RAJAGOPALAN, M. S. **Plantar ulcers with osteomyelitis underneath. A bacteriological study.** *Lepr. India,* 1977, v. 49, No. 3, 322–329.

"Thirty-nine consecutive cases of plantar ulcers with underlying chronic osteomyelitis admitted in the Sacred Heart Hospital during 1975/76 were studied for the infecting organisms and their sensitivity to easily available antibiotics. A single organism was isolated in only 10 cases, the infection in the rest being a mixed one. The commonest organisms were *Staphylococcus, Streptococcus* and *Proteus mirabilis.* In a few cases *Pseudomonas* and *E. coli* were also isolated. Chloramphenicol was the most effective antibiotic in general and streptomycin the least. 70% of the staphylococcus strains isolated were found to be resistant to penicillin. Empirical use of ntibiotics especially penicillin and streptomycin is hence deprecated."

14. RAI, V., SINGH, G., SINGH, R. H. & UDUPA, K. N. **Blood histamine and histaminase in leprosy patients — a short communication.** *Indian J. Med. Res.,* 1977, v. 66, No. 6, 978–982.

"In 91 patients of different types of leprosy, blood levels of histamine and histaminase were studied and compared to matched normal controls. The leprosy patients showed markedly raised levels of both histamine and histaminase as compared to controls. This rise was more pronounced in cases of leprosy with a history of longer duration. Patients of leprosy in reaction showed the maximum levels whereas tuberculoid, borderline and lepromatous cases showed moderate levels and others minimum changes."

[See *Trop. Dis. Bull.,* 1975, v. 72, abstr. 511.]

15. HUIKESHOVEN, H. *et al.* **Demonstration of dapsone in urine and serum by ELISA inhibition.** [Correspondence.] *Lancet,* 1978, Feb. 4, 280–281.

The authors produced anti-dapsone antibody in rabbits, and showed that it could be used to detect dapsone by a micro-scale enzyme-linked immunosorbent assay (micro-ELISA). They coated the wells of polystyrene microtitre trays with a dapsone-haemocyanin conjugate, added the anti-dapsone antibody serum so that it reacted with the dapsone, and then detected the antibody by the addition first of anti-rabbit IgG antiserum conjugated to horseradish peroxidase, and then of an amino-salicyclic acid/H_2O_2 solution, whereupon a brown colour developed. When diluted urine or serum containing dapsone was initially added to the coated wells, followed by the anti-dapsone antibody, immunosorption of the latter to the walls of the wells was completely inhibited, so that on completion of the test no brown colour developed (test of inhibition of ELISA (ELISIT) .

From the published results, it is claimed that dapsone solutions containing as little as 0.3 µg/ml could be detected with ELISIT, and that positive and negative solutions could be clearly distinguished when diluted 1/100. Full technical details are available on request to the senior author at the Department of Tropical Hygiene, Royal Tropical Institute, Amsterdam.

[If the authors' results are confirmed, the method will be considerably more sensitive and more specific than the Bratton-Marshall technique. However, although it is claimed that the method is simple enough to be performed in many tropical laboratories, the questions of cost and of the shelf-life of the reagents under tropical conditions are not discussed.]

M. F. R. Waters

16. HUIKESHOVEN, H. & BIJLEVELD, I. **Encouraging results from DDS urine analysis among registered leprosy patients in the Wangas, Kenya: an exception that challenges the rule.** *Lepr. Rev.,* 1978, v. 49, No. 1, 47–52.

"From previous research among the Wangas (Kenya), it appeared to be the standard of medical services, and in particular the leprosy fieldworker's approach, rather than sociocultural factors, which accounts for failure of leprosy control.

"The present investigation adds weight to these findings. Urine samples were taken from 39 patients of one highly reputable leprosy fieldworker, and analysed for DDS/creatinine ratios. Comparison with data from elsewhere demonstrates their scrupulousness in weekly DDS-taking at home."

17. BEDI, T. R., KAUR, S., SINGHAL, P. C., KUMAR, B. & BANERJEE, C. K. **Fatal proliferative glomerulonephritis in lepromatous leprosy.** *Lepr. India,* 1977, v. 49, No. 4, 500–503.

Acute glomerulonephritis is a well known manifestation of ENL reaction in lepromatous leprosy but is usually a transient and self-limiting condition, and this case is reported because of the rarity of a fatal outcome. An Indian male aged 50 years, suffering from lepromatous leprosy, had received irregular treatment with dapsone for 2 years and during this time had experienced a number of ENL reactions which were treated with salicylates and prednisolone. He was admitted to hospital in Chandigarh (Punjab) with signs of renal failure and poorly controlled leprosy, and renal biopsy revealed acute proliferative crescentic glomerulonephritis. He died of uraemia 8 weeks after admission, and post-mortem examination confirmed the biopsy finding. Immunofluorescent studies showed deposition of immune complexes at the glomerular sites.

W. H. Jopling

18. SINHA, S. N., GUPTA, S. C. & BISHT, D. **Serum calcium and magnesium in different types of leprosy.** *Lepr. India,* 1978, v. 50, No. 1, 54–56.

"Serum calcium and magnesium were studied in 200 leprosy patients and 25 apparently healthy individuals. Serum calcium was found to be significantly decreased in all types of leprosy except tuberculoid. The decrease in serum magnesium was highly significant in tuberculoid, lepromatous and borderline lepromatous cases."

19. GANAPATI, R., REVANKAR, C. R., CHRISTINA & ROMANO. **Associated cases in the families of school children with leprosy.** *Lepr. Rev.,* 1978, v. 49, No. 1, 43–46.

"The screening of 190 families in which children suffering from leprosy discovered through school surveys were present, yielded a total of 41 cases. Though the prevalence rate among the contacts was 44 per thousand, only in 14% of the families visited, another associated case could be found, and only in 2 instances out of 27 families, the associated case belonged to **L** type. The school surveys as well as contact examination yielded predominantly cases belonging to non-lepromatous type mostly with single lesions whose contribution to the pool of infection in the community is questionable."

20. MALIK, R., KHANDPUR, R., CHANDRA, K. & SINGH, R. **A clinicopathological study of 244 cases of leprosy with special reference to histoid variety.** *Lepr. India,* 1977, v. 49, No. 3, 400–405.

The authors give brief details of 8 cases of histoid leprosy diagnosed amongst a total of 60 patients with lepromatous leprosy who were studied clinically and histopathologically between 1972 and 1976. Six of the 8 were treated with dapsone and all save 1 patient showed an initial response to the drug, although details of their regimens are not given. Therefore, they conclude that drug resistance is not a significant factor in the pathogenesis of histoid leprosy. However, it is generally agreed that histoid leprosy is usually related to relapse of treated lepromatous leprosy, and this report does not exclude either relapse through failure to take treatment or relapse due to partial (low grade) dapsone resistance.

M. F. R. Waters

21. SINGHAL, P. C., CHUGH, K. S., KAUR, S. & MALIK, A. K. **Acute renal failure in leprosy.** *Int. J. Lepr.,* 1977, v. 45, No. 2, 171–174.

"Three patients having lepromatous leprosy developed acute renal failure. Two patients completely recovered and one was left with a moderate degree of renal insufficiency. Renal tissue obtained by percutaneous biopsy revealed acute tubular necrosis in two and diffuse crescentic glomerulonephritis in the third case."

4. THERAPY

22. SHESKIN, J. **Study with nine thalidomide derivatives in the lepra reaction.** *Int. J. Derm.,* 1978, v. 17, No. 1, 82–84.

"In our studies, 3 out of the 9 thalidomide derivatives used to treat lepra reaction of lepromatous leprosy were effective. All 3 are known to be teratogenic in animal studies. This suggests that the teratogenic and the lepra reaction suppressive properties may be related."

5. EPIDEMIOLOGY

23. WHITE, S. J., STONE, M. M. & HOWLAND, C. **Genetic factors in leprosy: a study of children in Uganda.** *J. Hyg.,* Cambridge, 1978, v. 80, No. 2, 205–216.

"A group of 20,990 children in Uganda was examined for leprosy over a period of 8 years. There was no evidence that the incidence of leprosy varied according to a child's genetic relationship to a leprosy patient, once allowance had been made for the grade of physical contact."

24. DÍAZ ALMEIDA, J., FERNANDEZ BAQUERO, G., MENÉNDEZ GARCIA, V. G., SAGARO DELGADO, B., MUÑOZ, H. & TOLEDO, G. Estudio clinico-epidemiológico de los enfermos ingresados en el hospital "El Rincón". **[Clinicoepidemiological study of (leprosy) patients admitted to the "El Rincón" hospital.]** *Revta Cub. Med. Trop.,* 1976, v. 28, No. 3, 143–155. English summary (5 lines).

Data were collected under the following headings in response to a questionnaire to be completed in respect of 207 leprosy patients: province and area of birth; age-groups; civil status (single, married, etc.); sex distribution, generally and in relation to clinical disease forms [lepromatous (179 cases), tuberculoid (27)]; colour; domicile of relatives (urban or rural); habitual residence of patients; whether working or not and type of employment; time of diagnosis of leprosy (before 1950 to after 1970); bacillary status of patients; Mitsuda test results; previous use of BCG vaccine; previous incidence of pulmonary tuberculosis; results of screening; analysis of initial symptoms; localization of primary symptoms; previous contact with leprosy sufferers; family and other contacts before contracting the disease; and time of contact with a possible source of infection. The survey has been conducted to study clinical symptoms and possibilities of epidemic.

M. de O. Tollemache

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