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LEPROSY REVIEW

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Contents

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Editorial

1. ERRATA IN THE LAST ISSUE OF LEPROSY REVIEW, **37,** 2.

We propose to give a list of these errata and apologise to our readers for them, and explain that they were uncorrected in **37,** 2, though detected at the time, in order to save ultimate time. Through the circumstance that *Leprosy Review* was changing its office at 27 Marylebone Road to 6 Hillcrest Avenue, Pinner, it was clear that much more time would be needed which would eat into the early publication of the Review. It seemed better to publish early and ask the indulgence of the readers for a list of errata in the next issue, **37,** 3, which now follows:—

Errata in **37,** 2.

p. 69, 6th line of right-hand column 'Dr Ross Innes comminuing as Editor' should be 'Dr Ross *continuing* as Editor'

p. 89, 20th line of right-hand column 'and in substituting Hansen's disease for Microbacterial neuropathic dermatosis (M.N.D.)' should be '*Mycobacterial* Neuropathic Dermatosis (M.N.D.) proposed by Ross Innes (1963).

p. 107 in the References No. 6 'planter ulceration' should be '*plantar* ulceration'

p. 125, left hand column 2nd paragraph line 9 should read 30 μ as 30 $m\mu$

2. Leprosy Research continues and we wish to draw attention to 2 very practical advances in information by Dr J. A. Kinnear Brown in Uganda and Dr Dharmendra in India. An abstract of the paper by Dr Kinnear Brown and colleagues appears in *Leprosy Review*, **37,** 2, p. 127, and of Dr Dharmendra and colleagues in **37,** 3, p. 183-184. Their work bears on the protection of children, in one case by BCG and in the other by prophylactic DDS. Each is very encouraging and will be noted with gratitude by all workers who are facing the problem of control of leprosy in endemic countries of the world. The investigation of each type of control is continuing by the authors.

3. OBITUARY NOTICE. We much regret to announce the sad loss of Dr. P. Glyn Griffiths, who died suddenly at Broken Hill, Zambia, on 14 May 1966. He has been a very active leprologist to Zambia and will be greatly missed. We express our sympathy to Zambia in this loss and to his family.

Lep. Rev. (1966) **37**, 3, 141/145

B 663 (Geigy) – Further Observations on its Suspected Anti-Inflammatory Action

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In the course of the first trials of B 663 (Geigy) at a dose level of 300 mg. daily, in a series of 26 patients with lepromatous leprosy in Eastern Nigeria, Browne and Hogerzeil (1962 a.b.) and Browne (1965) found that erythema nodosum leprosum (ENL) developed in only two patients in the course of 12 months; in both cases the condition occurred within the first four weeks of treatment, and was slight and transient. When, however, in these same patients B 663 was subsequently replaced by standard dapsone therapy, 14 of them passed, during the next two years, through episodes of acute exacerbation.

Williams *et al.* (1965) have reported that two patients receiving higher doses of B 663 (600 mg. daily) did not suffer exacerbation while receiving the drug, but did within two weeks of the drug's being suppressed, the signs of exacerbation responding promptly when the drug was readministered at the same dosage. In another patient who was also receiving dapsone throughout, B 663 appeared to exert an anti-inflamatory effect on each occasion it was given.

These findings indicated that further investigations were necessary, not only in order to confirm or refute the supposition that B 663 has an anti-inflammatory action (of indeterminate nature) but also to provide practical data for the use of the drug in treating patients with lepromatous leprosy in persistent exacerbation.

The opportunity to put this suggestion to a severe testing presented itself in Eastern Nigeria: if B 663 proved effective in suppressing persistent exacerbation uncontrollable except by continuous administration of corticosteroids in a series of such patients, then its sphere of usefulness in this regard would be established as far as lepromatous leprosy in Africa is concerned, and trials elsewhere would be indicated.

First Group – Patients with persistent exacerbation

Ten adult patients, all suffering from lepromatous leprosy, with completely negative Mitsuda reactions, volunteered to participate in the trial. They had all been suffering from persistent exacerbation for periods varying from 16 to 36 months, with an average of 24 months. Reaction had begun in these patients at different points of time in the course of treatment: from the 5th to the 9th month in five patients; from the 10th to the 19th in two, and after the 20th month in three.

The anti-leprosy drug that was in use at the onset of the acute exacerbation was in all cases dapsone, the dose of which had been subsequently reduced or suppressed for varying periods; thiambutosine had been substituted in some patients at some time or other. The exacerbation had failed to respond to the usual drug regime: sedation, antimonials, antimalarials, antihistaminics, etc., and recourse in all cases was finally had to the corticosteroids. After numerous unsuccessful attempts at weaning from corticosteroid dependence, it was regretfully concluded that each patient required a maintenance dose of the drug. Resumption of anti-leprosy therapy with small doses of dapsone or thiambutosine, under corticosteroid cover, had in some patients precipitated a return of the acute exacerbation and necessitated either suppression of the anti-leprosy drug or increasing the corticosteroid – or both these courses simultaneously.

The usual practice was then to reduce the maintenance dose of the corticosteroid used until the patient was spared the rigours and risks of severe exacerbation but was still subject to the discomfort of slight manifestations of the hypersensitive state, such as the appearance from time to time of new ENL lesions, the persistence of the more extensive and deep lesions, and the presence of some oedema and erythema and succulence of the lepromatous plaques.

While continuing the maintenance dose of the corticosteroid that had been given for the previous few weeks or months, and after suppressing the dapsone or thiambutosine that had been concurrently administered, we introduced B 663 in doses of 100 mg. daily (three of the patients having a loading dose of 100 mg. three times daily for three weeks), each oral dose being given with 5 ml. of edible vegetable oil to ensure absorption from the intestine.

In the three patients who had had the loading dose of B 663, and in three of the other seven, no more new ENL lesions appeared, and existing signs of exacerbation began to regress. These patients had been experiencing crops of ENL lesions every few days.

In the case of the remaining four patients, in whom the signs of exacerbation remained unaffected for four months while B 663 was given 100 mg. daily, the dose was empirically doubled, 100 mg. being given twice daily. Within two weeks it was apparent that the persistent exacerbation was being controlled: no new lesions appeared, and existing lesions regressed. After six months, the dose of B 663 was reduced to 100 mg. daily. ENL recurred in only one patient; it was controlled within two weeks when the dose of B 663 was doubled, and did not recur when the dose was subsequently reduced to 100 mg. daily and finally suppressed altogether.

When it would seem that all ten patients were no longer subject to acute exacerbation and were all at last showing welcome indications of improvement in their leprosy condition, the maintenance dose of corticosteroids was cautiously and progressively reduced. The rate of reduction varied with the individual patient, as did also the initial dose level. In all ten patients, it has been found possible completely to withdraw corticosteroids, though repeated attempts previously had been unsuccessful.

All ten patients are currently receiving 100 mg. of B 663 daily, in a single dose.

The *bacterial* findings in this group show certain general trends, with noteworthy exceptions. The Morphological Index (M.I.), which represents the average of the percentage of morphologically normal *Myco. leprae* at all eight skin and nasal mucosal sites smeared regularly, has remained at zero during the term of the trial, which is now 17 months. The drug has had no consistent demonstrable effect on the removal of degenerate bacilli from the tissues; in some patients, this function has continued at the same rate as before; in others the rate of removal has increased. Thus, the apparent anti-inflammatory effect in these patients is not related to any obvious factor, such as the precise height of the Bacterial or of the Morphological Index, or in the rate of removal of non-solid bacilli from the tissues.

The incidence of severe lepromatous peripheral neuritis was not high in this group, but the patients who were seriously affected have experienced a substantial and rapid improvement in the pain and tenderness in the nerve trunks.

No cases of reappearance of morphologically normal forms of *Myco. leprae* have been noted. It will be recalled that Browne and Hogerzeil (1962,c) reported that in a series of patients who had received 100 mg. of B 663 three times daily, morphologically normal *Myco. leprae* temporarily reappeared after 12 months in varying proportions at all sites smeared.

The histories of two of these patients may illustrate the therapeutic value of B 663, irrespective of the unidentified precise precipitating causes of the persistent exacerbation and failure to respond to anti-leprosy drugs. Both patients had begun treatment with methimazole (Tapazole, Lilly) (Browne and Hogerzeil 1962,d), and both had received dapsone at various dose levels, and other drugs such as thiambutosine and ditophal (Etisul, I.C.I.). Neither had shown any evidence of clinical progress for a long time. The B.I. in both patients had remained stationary for many months, at about 2.5 for one, and 1.1 for the other (maximum 4.0); but the smears from the first patient still contained nearly 10% of normal bacilli (i.e. after 41 months of treatment), whereas the second had had no normal bacilli for many months.

Both patients had a loading dose of 100 mg. B 663 thrice daily for three weeks, followed by a single daily dose of 100 mg. In the first, this dose was not initially quite sufficient to suppress all tendency to reaction, but the episodes that did occur during the first few weeks were comparatively mild and did not require corticosteroids for their control. He has improved considerably during the 16 months he has been

receiving B 663. The B.I. is falling steadily, being now 1.25. Normal bacilli disappeared finally from smears at all sites after eight months' treatment with B 663, i.e. after a total of 49 months' treatment, and have not reappeared during the ensuing seven months.

The other patient, after being in a clinically stationary condition for many months, has shown progressive improvement under B 663 therapy. Signs of acute exacerbation have disappeared; the B.I. began to fall within a month of his beginning treatment with B 663: now, after 16 months, it is zero. In this case, B 663 appears to have initiated clinical improvement in a man whose condition had been stationary for a long time. Concurrently, degenerate bacilli disappeared from skin and nasal mucosa.

Second group – patients in whom morphologically normal Myco. leprae reappeared.

The second group consists of two patients who have been under treatment for severe lepromatous leprosy for many years, and in whom there suddenly appeared numerous small succulent lesions containing innumerable viable *Myco. leprae* when skin smears had been negative for many months.

The first had had treatment for 15 years, having relapsed twice during that time. On readmission in 1958 his B.I. was 3.5 (maximum 4.0) and the M.I. 100%. By May, 1964, it seemed that the disease was completely arrested: no clinical evidence of leprosy remained, and no bacilli were seen in routine monthly smears from any site. Twelve months later, however, during the 80th month of treatment, while he was receiving 0.05 gr. dapsone twice weekly, numerous small papilliform elevations full of normal bacilli appeared in the skin. Under the impression that these bacilli were probably dapsone-resistant, the patient was given B 663. (In point of fact, it has been conclusively demonstrated by Rees (1966) that on the evidence furnished by mouse foot-pad inoculation, these bacilli are *not* dapsone-resistant).

The patient has responded well to B 663; the small papules are now flattened and level with the skin, and are replaced by striated scar tissue. The B.I. in these lesions has fallen from 2.75 to 0.7. The M.I. which was 65% when treatment started, is now zero, and much of the acid-fast debris is no longer of recognizable bacillary form. B 663 has thus acted well in this patient, who had been erroneously suspected of harbouring dapsone-resistant *Myco. leprae.*

The other patient had been under treatment for leprosy since 1952. Allegedly 'sensitive to sulphones,' she had received thiacetazone (a thiosemicarbazone) for seven years. Successive attempts at desensitization (Browne, 1963), had proved unsuccessful. Minute doses of dapsone seemed to precipitate severe exacerbation within a few hours. While continuing corticosteroid therapy, and not receiving any anti-leprosy treatment, she apparently was able to deal with and to eliminate non-solid mycobacteria and acid-fast debris. In January, 1965, and at every monthly examination subsequently, multiple smears from the skin and nasal mucosa revealed no acid-fast material.

In August, 1965, numerous small papular elevations suddenly appeared scattered over the trunk and limbs. These proved to be teeming with solid-staining *Myco. leprae*, although the intervening skin and the nasal mucosa remained bacteriologically negative. In view of the possibility that prolonged and intermittent very low-dose dapsone therapy might have induced dapsone-resistance, this patient was given B 663, 100 mg. daily. Prednisolone cover was maintained at the same dose as she had been receiving for some months. The lesions responded well, diminishing in size and elevation and eventually leaving a small thin striated scar. The *Myco. leprae* in these acute lesions rapidly showed fragmentation and irregular staining, and diminished in numbers. There has been no recurrence of exacerbation, although the dose of prednisolone given had previously been found to be insufficient to suppress all signs of exacerbation. The *Myco. leprae* inoculated into mouse foot-pads, by kind collaboration of Dr R. J. W. Rees, were shown to be dapsone-sensitive.

Pigmentation

At the dose levels of B 663 given in the 12 patients in these two groups, the red and black pigmentation of the skin was not as intense as in the series reported previously (Browne, 1962) and should not prove a contraindication in patients of similar skin hue.

DISCUSSION

In view of the vast numbers of drugs that have enjoyed but a short-lived vogue in the treatment of acute exacerbation in lepromatous leprosy, the results here recorded should be examined with caution. But because these results are so uniformly consistent, it is suggested that further investigations are indicated, particularly among patients with skin of a lighter hue, who are known to experience prolonged and intractable episodes of exacerbation. In this connection, it should be noted that Jopling (1966) has not observed similar improvement in five patients taking B 663 at dose levels os 50 mg. twice weekly or 100 mg. twice weekly, whereas Williams *et al.* (1965) found consistent ameliorstion when much larger doses (600 mg. daily) were given.

In the present series, 100 mg. daily sufficed in eight patients, but did not in four, in the latter, doubling the dose was followed by suppression of the signs of acute exacerbation.

It would appear that, B 663 in some way exerts its suspected anti-inflammatory action after absorption from the intestine and before being deposited in the tissues. After the administration of such high doses as 600 mg. for some weeks, the tissues are generally stained red with the dye and histological examination confirms that micro-crystals are present. When the drug is temporarily stopped in these patients, however, exacerbation ensues, to be suppressed again when B663 in given.

That its action in this respected is not simple, or simply bacteriocidal or bacteriostatic, is suggested by analysis of the pathological diversity of the patients in this series and the absence of complete concordance between the clinical and the bacteriological findings during the period of treatment with B 663. It will be recalled that all to patients in the larger group were practically stationary clinically because of persistent or recurrent severe exacerbation. Of these, four showed 'solid rods' in the multiple smears after 36, 39, 41, and 44 months' treatment respectively. 'Solid rods' disappeared in all four patients within 6- 12 months of beginning B663, i.e. the M.I. (which was 7%, 1%, 8%, and 12% respectively) fell to zero.

The clearance of the accumulated load of 'non-solid' bacilli proceeded at different speeds, to judge by the rate of fall of the B.I. in the individual patients. In three, all acid-fast material disappeared within 17 months, the B.I. in these patients having remained more or less stationary for many months previous to the beginning of treatment with B 663, with B.I. levels of 1.1, 0.5, and 0.4 (maximum: 4.0, on Dharmendra's notation); in one of these patients rare 'solid rods' had been encountered in the smears at the beginning of this treatment. In three other patients, the B.I. fell during the period of observation (17 months) from 1.1 to 0.2, from 1.0 to 0.5, and from 2.5 to 1.25. In one, it remained stationary.

In spite of these differences in the initial height and in the rate of fall of both B.I. and M.I., clinical progress as judged by the suppression of signs of acute exacerbation and progressive improvement in the patients' condition, was undeniably marked in all cases.

A related group of variables often suspected of playing some part in the initiation or persistence of exacerbation was represented in this small series of patients; that is, the amount of newly-formed antigen surmised to have been derived from degenerating mycobacteria, and either remaining *in situ* or in process of being phagocytosed. To judge from the varying amounts of acid-fast material found in these patients, and the fact that all patients improved when given B 663, the question of the immediate and precipitating cause of acute exacerbation still remains quite open.

The interval elapsing between the beginning of treatment with B 663 and obvious clinical amelioration was variable – from two days to two weeks. When new ENL lesions fail to make their appearance, in a patient who has experienced daily crops, the time-lag is more clearly defined than when the criterion is the diminution in existing signs of exacerbation. This aspect of the difficulty of assessing the value of any anti-inflammatory agent in leprosy, however, is not uniquely confined to the appraisal of B 663. As far as could be ascertained, psychological factors played no part in determining the persistence or the amelioration of the exacerbation in the patients under study. The criteria adopted in assessing improvement were objective.

SUMMARY

B 663 appeared to control persistent exacerbation in all ten patients, who were corticosteroid-

dependent. A dose of 100 mg. daily was sufficient in some patients, but 200 mg. daily was necessary in others. Notwithstanding numerous unsuccessful attempts at weaning from corticosteroids previously, it was found possible in all ten patients gradually to reduce, and eventually to suppress, corticosteroids while continuing to give B 663.

In two other patients, in whom dapsone-sensitive *Myco. leprae* suddenly reappeared in localised lesions in skin that had been bacteriologically negative for months, B 663 was also successful in ensuring both clinical and bacteriological inprovement.

ACKNOWLEDGEMENTS

My sincere thanks are due to Messrs. G. R. Geigy for their generous supplies of their product, B 663; to Drs R. J. W. Rees and M. F. R. Waters, of the Medical Research Council, London, who conducted the dapsone-sensitivity tests; to Dr Norman R. Honey and the laboratory staff of the Leprosy Research Unit, Uzuakoli, for their continued collaboration.

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Leprosy and Blood Groups

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Hsuen, Thomas and Jesudian (1963) described work suggesting an increased incidence of leprosy in blood group O and a decreased incidence in blood group B when compared with controls. The population studied were leprosy patients at the Schieffelin Leprosy Research Sanatorium, Karigiri compared with blood donors from the Christian Medical College, Vellore, about 10 miles away. Since the finding of such a difference between patients and controls was suggestive of genetic factors operating in leprosy, it was decided that a repeat of this work should be included in a general study of leprosy and genetics carried out in the same area in 1964.

Materials and Methods

1085 patients were examined between June and August 1964. All were being treated for leprosy at that time. They included inpatients and outpatients at the Leprosy Research Sanattorium, Karigiri and at the Christian Medical College Hospital, Vellore, together with patients from roadside clinics and leprosy clinics held in local villages. A group of inpatients from Vadathorasalaur hospital, 100 miles away from Vellore, was also included. The overlap of patients with the previous survey did not exceed 2 per cent. All blood donors were first attenders at the Blood Transfusion Centre, Vellore between January and August 1964.

ABO grouping was carried out in India using dried Anti-A and Anti-B sera and wells. Wherever possible leprosy was classified into Lepromatous, Dimorphous, or Tuberculoid patients mostly by leprologists, occasionally by other medical staff. In about 70 patients histology slides were available and these were photomicrographed and later examined at the Leprosy Research Fund, London by Dr Cochrane and Dr Harman. The agreement between clinical and histological diagnoses was good and we feel confident that they represent a uniform classification. Details of sex, age group, and village of origin of patients was also recorded.

In addition to the ABO testing, serum was sent back to England for tests on haptoglobins and transferrins which were carried out by Dr Garlick at University College, London.

Results

The overall blood groups in Leprosy patients and blood donors are shown in Table 1. The blood groups of donors in 1962 are also included (Hsuen et al, 1963) since they are a larger sample and could presumably be pooled with the present donors.

There is no significant increase in the frequency of group O and decrease of group B in leprosy patients compared with Blood donors ($X_1^2 = 1{\cdot}7$; $P > 0{\cdot}1$). In view of the difference between the present results and those of Hsuen, it was decided to examine these populations in more detail.

In the leprosy patients the sex ratio was 2:1, whereas in the blood donors it was 15:1. However no difference in blood group distribution was found in the two sexes. (Table 2).

In view of the fact that the leprosy patients came from a rather wider area than the blood donors, the results obtained in patients coming from within a radius of 30 miles from Vellore were examined. (Table 3). There is no significant difference from the blood donors ($X_1^2 = 2{\cdot}5$; $P > 0{\cdot}1$ for O:B ratio). In view of the previous work this X^2 may lead to some suspicion of non-homogeneity. It was not possible to investigate the blood donors further, but patients were grouped according to origin north or south of the river Polur which lies between Karigiri and Vellore. Karigiri is in the northern area, whereas Vellore is just south

of the river. A significant difference is found between north and south (For O:B $X_1^2=5\cdot1$; $P>0\cdot025$.) (Table 4).

The majority of blood donors were between 18 and 30 years of age whereas the leprosy patients included a much wider range of ages. There is no overall heterogeneity in the blood groups of patients at different ages (Table 5), but in those patients furthest from the age of the donors, i.e. over 44, there is some suggestion of an increase in the frequency of group O ($X_1^2=4\cdot5$; $P>0\cdot05$). It was noticed that the clinics held in villages and on the roadside in the northern area contained 89 people over 44 years old out of a total of 256, compared with 100 out of 689 from other sources.

TABLE 1

Blood group	Leprosy Patients		Donors 1964		Donors 1962	
	No.	%	No.	%	No.	%
A	219	20·5	162	21·4	214	21·4
B	359	33·6	260	34·3	331	33·1
O	440	41·4	282	38·0	397	39·7
AB	46	4·4	51	6·6	58	5·8

TABLE 2

Blood group	Male	Female
A	144	75
B	223	82
O	288	125
AB	26	19
Heterogeneity $X_1^2=3\cdot6$; $P>0\cdot1$		
For O:B Ratio $X_1^2=1\cdot0$; $P>0\cdot1$		

TABLE 3

Blood group	Local leprosy patients	
	No.	%
A	158	18·5
B	263	33·0
O	350	43·5
AB	35	5·0
Total	806	

TABLE 4

Blood group	North		South	
	No.	%	No.	%
A	88	20·4	70	18·7
B	132	30·6	131	34·9
O	201	46·7	149	39·8
AB	10	2·3	25	6·3

TABLE 5

Age group	A	B	O	AB
0–5	1	0	5	0
5–14	34	61	75	10
15–24	47	77	86	16
25–44	90	146	167	12
45+	38	51	93	7

TABLE 6

Blood group	Type of leprosy					
	Lepromatous		Dimorphous		Tuberculoid	
	No.	%	No.	%	No.	%
A	75	19·7	57	22·7	87	20·2
B	129	33·7	85	33·9	145	33·6
O	159	41·7	102	40·6	179	41·4
AB	19	4·9	7	2·8	20	4·6
Total	382	100·0	251	100·0	431	99·8

The distribution of ABO blood groups in the different types of leprosy is shown in Table 6; no difference in distribution is seen. In view of the possible heterogeneity previously shown, lepromatous and tuberculoid patients were paired according to origin north or south of the river and age group (child, adult or over 44). When all the patients in a group could not be paired, those to be discarded were selected by distributing them evenly within the chronological order of grouping. The results are shown in Table 7. No significant difference in distribution is seen ($X_3^2=2$; $P > 0·1$).

TABLE 7

Blood group	Type of leprosy	
	Lepromatous	Tuberculoid
A	44	54
B	77	85
O	113	93
AB	9	11

TABLE 8

Haptoglobin Type	Type of leprosy			Totals
	Lepromatous	Dimorphous	Tuberculoid	
2–2	98	31	75	204
2–1	21	6	13	40
1–1	1	1	2	4
Negative	13	8	12	33
Totals	133	46	102	281

All transferrins tested were of the type C-C, except for one possible type C-D. The haptoglobin frequencies of the leprosy patients are shown in Table 8. The number of negatives is unusually high; ignoring the negatives, calculation of the gene frequencies gives Hp.1. 0·1; Hp.2. 0·9. No difference is seen with different types of leprosy.

DISCUSSION

This study does not support the hypothesis of an association of leprosy with blood group O. In this we are in agreement with most recent work (Beiguelman, 1963/1964; Yankah, 1965; Verma & Dongre, 1965). There is however a suggestion of geographical variation in the blood group distribution in the area studied, with a higher group O near Karigiri than near Vellore. The possible age effect is probably the result of more old people in the clinics of the northern area, or it could be the result of the differential migration of different genetic populations. It was not possible to record the three language groups or the social grades to which patients belonged, so that the primary cause for the differences in the distribution is a matter for speculation. However it seems probable that this geographical variation was the cause of the apparent association of leprosy with group O found by Hsuen working exclusively at Karigiri.

The overall distribution of ABO blood groups does not vary with the type of disease. In this respect the present study is at variance with the

findings of Beiguelman (1963) and Yankah (1965) who have found that group O appears to be increased in tuberculoid leprosy and decreased in lepromatous leprosy. However this association has not been found in other studies (Lowe, 1942; Verma & Dongre, 1965).

The frequencies of transferrins and haptoglobins are in close agreement with previous work on Tamil populations (Steinberg, Lai, Vos, Bhagwan Singh & Linn, 1961). However the high number of negative haptoglobins (11%) have not been satisfactorily explained. Previous studies on Indian populations have shown about 2 per cent negative haptoglobins.

SUMMARY

1. No evidence of a correlation between leprosy and ABO blood groups, transferrins or haptoglobins was found.

2. A high percentage of haptoglobin negatives were found in the population studied.

3. No association was found between particular blood groups and types of leprosy.

4. The apparent association of leprosy with blood group O found by Hsuen (1963) may have been due to difference in area of origin and age between the leprosy patients and the blood donors.

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Management of Lagophthalmos in Leprosy

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Lagophthalmos, or paralysis of the orbicularis orbis muscle, may result from injuries to the facial nerve, non recovery of Bell's Palsy, and leprosy. Syphilis and Poliomyelitis are rare causes. Exposure conjunctivitis, keratitis ectropion and dacrocystitis are common complications. About one quarter of leprosy cases have corneal anaesthesia, and about one in ten show ectropion or lacrymal sac infection. In endemic areas the overwhelming majority of cases, and much consequent eye morbidity, are due to leprosy.

The combination of lagophthalmos with corneal anaesthesia is particularly dangerous, and requires urgent treatment. This is seen most often in long-standing lepromatous patients It is much less common in the tuberculoid and dimorphous forms. In these, lagophthalmos is a special hazard of reaction, particularly in patients with large facial macules.

Leprosy neuritis interrupts conduction in the facial nerve either just distal to the stylomastoid foramen (giving an extensive facial paralysis), or the zygomatic branches are affected where they lie superficially in the cheek. Occasionally enlarged branches may be palpated against the zygoma. The Proprioceptive fibres of the facial muscles travel in the fifth cranial nerve and make multiple connections with motor twigs within the facial muscles. There thus exist anatomical connections between sensory and motor nerves in the face, which may permit *M.leprae* from the sensory nerves to spread into the facial nerve. This may explain the association between large facial macules and lagophthalmos.

Signs and Symptoms

Reduction in the frequency of blinking may be noted. Excessive watering from profuse reflex tear secretion and subclinical ectropion, and burning pain, are prominent symptoms. Very early lag can be detected by gently attempting to open the eye manually against the patient's effort to keep it closed. Degrees of lag in excess of 0.5 mm. are easily seen, and in the fully developed condition even the upward roll of the eye may fail to bring the cornea fully under cover of the upper lid. Lag exceeding 12 mm. is not uncommon. In these conditions exposure changes are likely to be found over the lower one third of the cornea, which becomes dry and vulnerable.

General Management

Many eyes are encountered with minor lagophthalmos, adequate corneal coverage, and freedom from complications. Since most mild cases progress to total paralysis, they should be seen regularly, and be provided with a suitable oil and a mildly antiseptic lotion (see below). Protective spectacles may be required for occupational hazards. Anaesthesia of the hands requires specific use of the eyes for avoidance of injury, and any risk to vision is therefore doubly dangerous.

Many patients suffer from vitamin deficiencies and it is reasonable to give supplements of vitamins A and C. Exposure changes are treated energetically along the usual lines. Ulceration of the cornea is an emergency and must be treated by the method indicated for the particular case. Once complications are controlled, the management becomes that of the uncomplicated case. A mild antiseptic lotion (e.g. ½ oz. zinc in 5% boracic acid lotion, tds.) should be instilled during the day and sterile castor oil drops at night, to prevent drying during sleep. Attention may now be directed to the paralysis.

Management of Paralysis

Lagophthalmos may be 'acute', subtotal, or complete.

'*Acute*' *Lagophthalmos*: This is lagophthalmos of sudden onset, usually associated with reaction. A small proportion of these cases recover when

the reaction subsides: the majority, unfortunately, do not. If the case is seen early, the prospects for recovery can be enhanced by exhibiting steroids. A course commencing with a large dose (e.g. Prednisolone 60 mgm. daily orally) and tapering down to nil within 14–21 days, is useful in practice, and avoids some of the dangers inherent in steroid therapy. These are not inconsiderable, and it is suggested that any who are unfamiliar with these drugs should secure the advice of a physician before prescribing them.

While awaiting the outcome, the general measures noted above are instituted. A severe lag may require support of the lower eyelid by strapping, and very occasionally a temporary tarsorrhaphy is required. After ten days, galvanic stimulation may be started in an effort to minimise atrophy of denervated muscle fibres.

There is no general agreement about how long one should wait before abandoning hope of recovery. A practical rule is to treat partial recoveries as described below, and to advise surgery where no recovery commences within three months.

Subtotal Paralysis: This frequently results from incomplete recovery of an 'acute' lagophthalmos. Residual motor activity is present in the orbicularis, and the lag is insufficient to uncover the cornea. These cases justify a trial of physiotherapy aimed at hypertrophying fibres with intact innervation. The patient practises eye closure many times a day, and courses of faradic stimulation are given. Progress is assessed by periodically measuring the gap between the eyelids. Oil and antiseptic drops are prescribed.

A regular and careful watch must be kept for exposure changes in these cases as well as in those with 'acute' lag. *Sommerset and Sen* (1957) warn about assuming that partial recoveries afford adequate protection for the eye. They advise that 'all cases showing any degree of weakness of the lid movements should, therefore, be carefully watched for involvement of the cornea, and a tarsorrhaphy (lateral or medial) operation performed as a preventative measure in most cases'. In these circumstances, however, it would be functionally and cosmetically more appropriate to perform a temporalis transfer.

Total Paralysis: Total paralysis requires surgery. The presence of corneal anaesthesia is an absolute indication for early operation. The methods at present available are:

1. Tarsorrhaphy
2. Static eyelid slings
3. Sommerset's operation
4. Temporalis transfer

Tarsorrhaphy is a simple procedure, and is reversible. Its main uses are: reaction cases with wide lag where there is hope of recovery, and the highly positive or elderly patient. It does not preclude a later temporalis transfer. The static eyelid sling may be considered for the old or unintelligent patient with lower corneal changes. The orbital fissure is permanently narrowed, though over the long term there may be some recurrence of sagging of the lower lid. Sommerset's operation consists of running a silk or nylon suture round the lid margins. The disadvantage is the risk of infection, and some residual orbicularis action is necessary to effect closure.

The operation of temporalis musculofascial sling, devised by Gillies, has proved to be of immense benefit in lagophthalmos. It is the procedure of choice in the majority of cases, and will be described more fully. The technique is not difficult to master (See *Antia*, 1963: *Andersen* 1961) and deserves to be more widely known.

A modification which avoids reversing muscle polarity has been described by *Johnson* (1962).

Pre-operatively, the conjunctival sac and the lacrymal sac should be free from infection, and patency of the nasolacrymal duct is confirmed by syringing. The scalp is completely shaved and the field is prepared with 1% cetrimide solution.

The operation is carried out under local infiltration anaesthesia (½% xylocaine with 1 : 200,000 adrenaline), or light general anaesthesia. The head is draped leaving the side of the head and the upper face exposed.

Figures 1 to 4 illustrate stages of the operation. Incision A, within the hair line, extends from the upper border of the zygoma to 2 cm. above the superior temporal line. It is deepened to the temporal fascia, which is exposed by retraction of the wound margins. A strip of fascia is outlined by a pair of vertical incisions half an inch apart, starting below at the zygoma and ending in periosteum half an inch above the superior temporal line. The strip is elevated from the subjacent temporalis muscle but is left attached

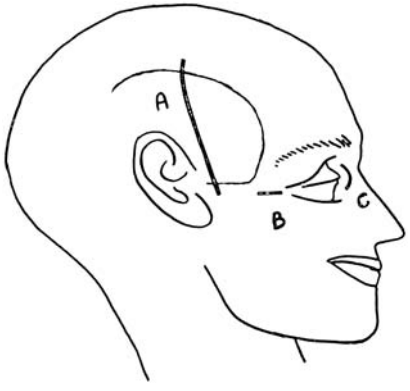

FIG. 1
Incisions

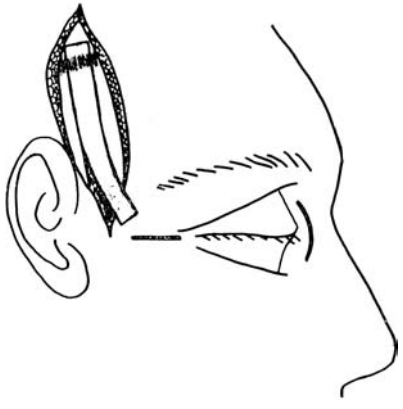

FIG. 2
Fascial strip outlined and elevation commencing

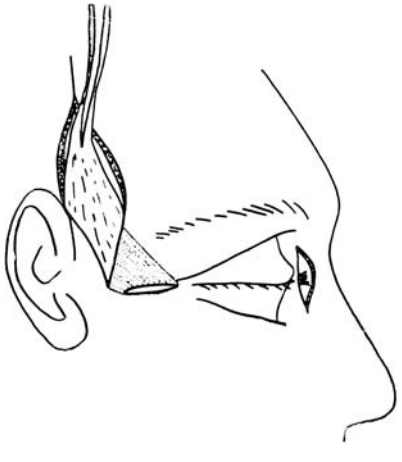

FIG. 3
Single fascial strip divided into two thin slips

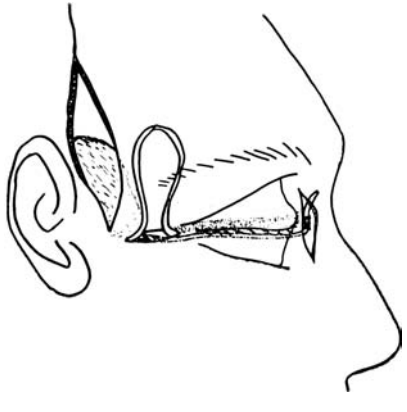

FIG. 4
Eyelids tunnelled, lower eyelid slip in situ, upper eyelid slip ready for passing

above. (Fig. 2). At the lower end the fascia divides into superficial and deep layers inserting into the inner and outer margins of the superior surface of the zygomatic arch. The space between the layers contains vessels; this configuration may occasion a little difficulty in freeing the strip at the lower end, if forgotten. The upper end of the strip is freed by a transverse incision through the periosteum, followed by downward stripping with a periosteal elevator. This process also elevates temporalis muscle from the bone of the superior temporal fossa, and by splitting the fibres on each side a muscle slip is fashioned in continuity with the fascial strip. The muscle is freed sufficiently to allow the fascia to reach to the inner canthus on swinging the slip forwards. Its nerve and vascular supply, entering deeply and below, is not disturbed.

From incision A a subcutaneous tunnel is fashioned to a 1 cm. incision at the outer canthus (incision B). The slip is placed in this bed, so that the musculo-fascial junction lies at the outer canthus. The junction can be reinforced with a single suture if desired. The fascia is delivered through the wound, having been divided longitudinally into two strips (Figs. 3 and 4). A

1 cm. vertical curved incision is made, 5 mm. medial to the inner canthus (incision C), and by careful blunt dissection the medial canthal ligament is defined. Damage to the more deeply placed lacrymal sac must be avoided. The inner and outer incisions are joined by narrow subcutaneous tunnels fashioned by delicate blunt subcutaneous dissection close to the margins of both lids. This is facilitated by previous infiltration with anaesthetic solution: occasionally small horizontal counterincisions at the mid points of the lid margins are helpful. The fascial strips are passed through the tunnels, and then deep to the medial canthal ligament (Fig. 4). With high tension applied to the lower eyelid slip and the slack taken up from the upper slip, the upper eyelid will overlap the lower, and in this position the slips are sutured to each other and to the medial canthal ligament.

After checking haemostasis, the incisions are closed without drainage: a pressure dressing is applied to the temporal wound. A little antibiotic ointment is injected between the eyelids.

Post Operative Management

For 10 days the patient takes fluids only by mouth, and soft diet for a further 10 days. Normal diet is then allowed, and chewing is encouraged. The patient is given a piece of sponge rubber to chew upon. The sutures around the eye are removed at four days, the temporal sutures after a week. Eyelid oedema absorbs in 3 or 4 days. After commencement of chewing exercises full voluntary closure is obtained in 2 to 4 weeks. The patient must be taught to clench his teeth periodically while out in the open to mimic the blink reflex. Later the eye will remain closed during sleep.

Lagophthalmos and Ectropion

The presence of ectropion imparts special difficulties to lagophthalmos repair. Great care must be taken to place slings exactly along the lid margin; failure to do this may aggravate the eversion. It is recommended that a standard ectropion repair be performed first, and that the paralysis be dealt with at a second operation. Otherwise, tarsorrhaphy is a safer procedure. For lag with mild ectropion, lateral tarsorrhaphy at the time of temporalis transfer is advised. The tarsorrhaphy may be released later when the transfer has developed its full power.

Causes of Suboptimum Results

The incidence and causes of suboptimum results are illustrated by analysis of the results of 43 eyes (30 patients) operated under the South Indian Peripheral Surgical Assistance Scheme. The operations to be reported were performed by six different surgeons in seven different hospitals, employing the technique described above.

Material and Methods

One patient could not be traced. Five with a follow up of less than three months are also excluded, although all were graded good or excellent. Thus 37 operations on 24 patients are available for report. Ages varied from 23 to 50 years; length of follow up varied from three months to two years. Pre-operatively, the widths of the orbital fissures (on attempting closure) varied between five and 15 mm. the majority being about 1 cm. No patient in this series had corneal anaesthesia, but in 50% exposure changes, usually mild, were present.

Since there is no accepted standard for grading the results of this operation, a method based upon attainment of effective corneal coverage (the main objective of surgery) was devised. The criteria are:

Excellent	—complete closure on moderate effort
Good	—slight lag present on moderate effort, but no lag present on forced effort
Fair	—lag persists, but the cornea is covered on effort
Poor	—lag persists, and the cornea is not adequately covered on effort.

'Moderate effort' is the degree of effort adopted by a patient when asked to close his eyes. It is usually submaximal.

Results

Thirty eyes were graded good or excellent, and seven fair or poor (81% & 19% respectively).

Particular interest attaches to the 19% of unsatisfactory results, which are detailed in the following table.

	Patient	No. of eyes	Post Operative Complications	Remarks	Follow Up
Poor	V.R.	2	Canthal Sepsis 2 eyes	A beggar: did not co-operate post-operatively. On effort could achieve corneal coverage, but made no effort to use his transfer except when supervised.	6/12
Fair	A	1	Canthal Sepsis	Patient co-operated well, but slings lost tension.	6/12
	V.	1	nil	Previous tarsorrhaphy released at time of transfer: tension probably insufficient ab initio.	6/12
	A.N.	1	Canthal Sepsis	Loss of tension	3/12
	B.	2	Canthal Sepsis	Loss of tension in both eyes. Both improved to 'Fair' by exploring and re-attaching the slips which were found to have pulled back into the eyelid.	1 year

Infection at incision 'C' was the commonest complication. It occurred in six of the seven eyes graded fair and poor, but it also occurred in five other eyes which were graded 'good'. It is therefore not necessarily prejudicial to a satisfactory result (fig. 5), but in three of the patients listed in the table it was the most likely cause of loss of tension and consequent downgrading. In case B, subsequent exploration revealed that the slips had failed to attach to the medial canthal ligament, and had, in fact, pulled back into the eyelids.

Discussion

It will be noted that a 'good' result is permitted 2 or 3 mm. of lag on moderate effort, providing that the cornea is covered. In a number of cases the lag was apparent and persisted from the early weeks, and it must be assumed that the initial tensioning was too low. This may have contributed to the result in patient V. ('Fair'). This emphasises the need for high tensioning at operation: over tensioning is really not possible.

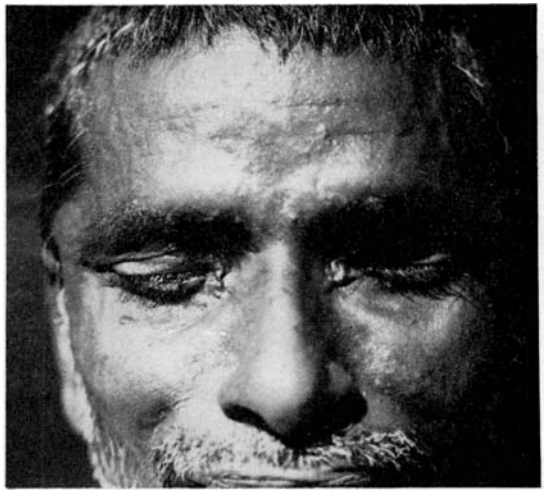

FIG. 5

Canthal sepsis with residual stitch granulomas. Nevertheless Left eye graded **Excellent**. Right eye down graded to **Good** because of 2 mm. lag and trace of eversion of the lower lid. Slings **must** be placed accurately along the margins of the lids

Since canthal sepsis was the commonest complication the placing of incision C well medial to the canthus must be stressed. A small flap of skin and subcutaneous tissue is formed which falls back into place when retraction is released. The canthal skin is very thin; it must be handled with the utmost gentleness, and be sutured meticulously.

The causes of failure in this series may be summarised as follows:

(1) Loss of tension, occasionally following canthal sepsis, but not specifically associated with this complication.

(2) Inadequate tensioning at the time of operation. Failure to obtain sufficient tension at operation resulted in a number of cases being downgraded from 'excellent' to 'good'.

(3) Failure to co-operate in aftercare and physiotherapy. Early chewing might conceivably pull the slips free from the medial canthal ligament.

(4) Error of Selection. Case V.R., a beggar, would have fared better with a tarsorrhaphy (Fig. 6).

Andersen (1961) reports 80% success in a series of 10 eyes with one to three months follow up. Several cases in the present series were graded 'excellent' initially, to be downgraded to 'good' subsequently with the recurrence of a small amount of lag (Fig. 7). Possibly these cases were not tensioned adequately, and it is not unreasonable to wonder if they may require further downgrading at a future date. Because of the possibility of late deterioration, it is reasonable to advise patients to perform specific exercises regularly each day, after discharge.

Summary and Conclusion

A successful temporalis transfer gives support to the paralysed lower lid, and repositions the puncta for draining tears. It provides voluntary power for closing the orbital fissure, and promotes reversal of exposure changes in the eye. It substitutes for the blink reflex, since the eyelids move with every contraction of the temporalis muscle: and resume their wiping and lubricating actions. Effective protection is afforded to the cornea rendered insensitive by leprosy. The cosmetic effect is pleasing; the risks of blindness are minimised.

A series of 37 operations is presented. Infection of the medial canthal wound is the commonest complication. Nevertheless, the operation carries a satisfactory success rate in the hands of non-specialised surgeons, providing the

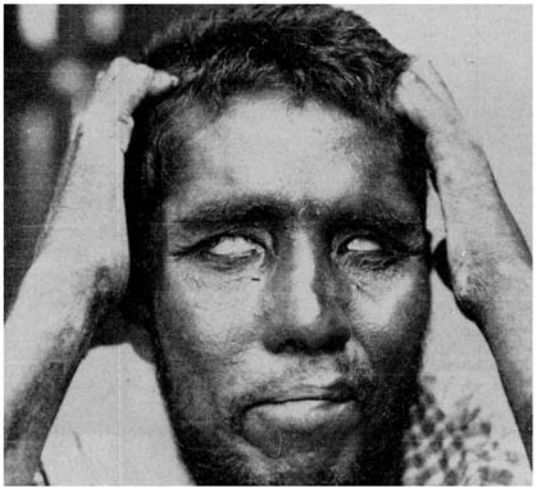

FIG. 6

Case V.R. Maximal effort just covers the corneae, but patient did not achieve this degree of closure unless supervised. Graded **Poor**

FIG. 7

Maximal effort gives full closure. Moderate effort leaves 2 mm. of lag. Graded **Good**. (Left eye)

technique and post-operative regime are carefully followed.

It is the author's hope that the operation will be used more frequently.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge the interest and enthusiasm of all those surgeons who participated in the peripheral surgical project in South India, and who permitted me to examine and comment upon their cases. Much of the follow up data was collected and recorded by John Vinookumar Esq., to whom my special thanks are due.

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A Surgical Programme in Leprosy in Papua-New Guinea

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In February 1965 a surgical unit to deal with the deformities of leprosy was established in the modern General Hospital at Madang, on the north-east coast of New Guinea. Sixty beds and other appropriate accommodation was made available, and at the outset the expatriate staff consisted of the author, a nurse, and a physiotherapist, all of whom received training at Karigiri and Vellore in 1964. Although this unit has been functioning a comparatively short time, it is considered that a report of its development is justified by the social and geographic factors which had to be taken into account.

The Territory of Papua and New Guinea, comprising the eastern half of the island of New Guinea and the Bismarck and other archipelagoes, has a population of two million, half of whom live in the Highlands. With the exception of the sodden wastes of western Papua and the Sepik basin, virtually the whole of the Territory is rugged mountain country. Road systems are fragmentary at present, and for practical purposes all travel on the mainland, apart from patrolling, is done by air.

The estimated incidence of leprosy is 0.77%, and of these one-fifth are lepromatous. The policy of this Department is to isolate infectious cases, and for this purpose there are about a dozen colonies spread over the country. These institutions have also served as homes for many non-infectious patients with various deformities.

It was realised years ago that a great deal could be done to prevent and ameliorate deformity in these patients, but the extension of leprosy services to include surgery was fraught with difficulty. Firstly, although some instances of persecution and murder have been reported, most leprosy patients suffer none of the ostracism which is so common in many other countries, and therefore they do not have the same cosmetic compulsion to co-operate in surgical and para-surgical care.

Secondly, the main centres of institutional leprosy work are far from general hospitals, and few of them offered anything like ideal conditions for surgical work.

Further, many of our patients are unwilling to leave their home ground, and it seemed that only the desperate and hopelessly crippled would be anxious to go to a distant centre for treatment. Even if patients were willing to travel, the high cost of air transport would make it essential that cases were accurately selected. While it is possible for any untrained person to send in a case of footdrop, selection of hand cases can only really be made by the surgeon, and it seemed that if adequate coverage of the Territory was to be achieved, the surgeon must travel, or risk waste of money and disappointment following transfer of unsuitable patients.

The great benefit of taking surgery to the patient has been amply demonstrated by Antia at Kondhwa and by Lennox at various places in South India, and it seemed desirable to develop a surgical service for leprosy in New Guinea on these lines.

The three prerequisites for such a service are good communications, good physiotherapy, and an acceptable minimum standard of operating and nursing facilities. The excellent commercial and mission air network eliminated the first problem, and the upgrading of facilities at a number of leprosaria with grants from The Leprosy Mission, and by various missions already staffing other leprosaria, has taken care of the third.

The second difficulty, the provision of good physiotherapy, was crucial, and more than one surgical service in leprosy has failed for want of it. We considered that adequate work could be done by nurses already working in leprosy, if they were trained in the essentials of the subject, with concentrated practice and supervision in the early stages. Accordingly a course was

designed to teach the relevant anatomy (with cadaver demonstrations where possible), muscle assessment, the care of anaesthetic limbs, the prevention of deformities, the care of ulcers, and the basic physiotherapeutic techniques required for standard operations.

These courses, lasting three weeks, have been conducted in Madang, after which the trainees have gone home to prepare suitable cases for operation, and to apply their other new knowledge.

When all is ready the surgeon and nurse fly to the leprosarium and re-assess the cases with the local worker. We like to operate on about a dozen cases at each visit, and have found that nurses rapidly learn to select and prepare patients properly, so that we now are finding the first day's cases ready when we arrive.

At the conclusion of the visit a general inspection is made, prospective cases for the next session are examined, and old cases are reviewed. Particular problems are discussed with the local worker, and opportunities are taken to explain again and again to the assembled patients that trauma is responsible for ulceration and loss of tissue. We have found that this concept is readily grasped by most people, and the occasional rejection of a surgical candidate because of a blister or an apparently trivial wound emphasizes the importance we attach to limb care.

We have made a practice of re-inforcing the local worker's experience in Madang by sending our physiotherapist to assist with the first cases out of plaster, three weeks after operation. This visit lasts four or five days, and we have found that once is enough to give confidence and ensure reliability. We now have nurses in isolated places managing perfectly with such things as Brand's extensor-flexor many-tailed graft, tibialis posterior transfer, the sublimis operation, opponens replacement and other procedures.

This system has allowed the development of regular surgery at eight places away from Madang, only three of which are staffed by trained physiotherapists.

The benefits of this decentralisation are several. The general improvement in morale (of staff as well as patients) has been confirmed in every case. Frequent visitation enables us to see patients at all stages of their desease, and management of deformities, actual or incipient, can be better supervised than by rare visits. The essential health education principles concerning leprosy can be repeated to all, even though only a few may be operated on. Follow-up work becomes a possibility.

Another great advantage of decentralisation is that it allows many more personnel and patients to take part in the programme. At any one time we have 150 or more patients receiving surgical treatment, which would be quite impossible in any single institution in this country. While the volume of work is a poor single criterion of any medical service's usefulness, we feel that the cost of such extensive travelling demands as high a return as is consistent with proper standards.

We frequently find that other surgical cases turn up during a visit to an outstation, and we are glad to exploit this situation to create a link between the leprosy service and the rest of the Department.

The most obvious hazard faced by an itinerant surgeon is the possibility that septic or other complications will arise in his absence, or for that matter in the absence of any doctor. In practice this has not been a problem so far, and it seems that the more isolated the hospital the rarer is the serious pathogen.

Clinical records have proved rather difficult to maintain when patients are widely scattered. A central set of notes is kept in Madang, and a copy of the relevant operation note and clinical photographs are sent to the peripheral institution to supplement the progress notes of the local worker. At each visit progress notes are made for addition to the Madang records, so that we may have a proper basis for follow-up of patients and procedures in the future.

It cannot be too strangly emphasised that surgery in leprosy stands or falls by the quality of the accompanying physiotherapy, and even then it forms but one facet of patient care. However because the results of operation are visible they command the patient's attention in a special way, and he is all the more ready to hear what we tell him about his disease. We have found that these people, many of whom are primitive by any standard, are most grateful for surgical care, and are in fact coming to hospitals looking for correction of claw hands, even

though they may never have bothered to come with a tuberculoid patch, the nature of which they know.

One of the special problems facing leprosy workers in New Guinea is the severe destruction of feet, seen particularly in the Highlands. While waiting for materials for the construction of the most suitable available pattern of shoe we have been using a variety of plastic sandal donated by The Leprosy Mission, and have found that these are acceptable when the patient understands that walking in bare feet will ruin his feet. Although this side of the work, being preventive in nature, is less spectacular than curative therapy where this is possible, we emphasize preventive care at every opportunity.

However, we belive that it is in the long run rather idle, and cold comfort, to tell a patient how to avoid injuring his limbs if we do nothing to correct muscle imbalance. Patients become weary of footdrop springs and hand exercises. We regard surgery as an essential part of any well-rounded leprosy programme, rather than a luxury. With energy and enthusiasm the cost of correcting a claw hand is at least comparable with repair of a hernia or a broken leg.

While we have relied heavily on mission nurses to do the physiotherapy in this programme, for teaching purposes and to deal with special problems in a large unit a widely experienced and fully equipped physiotherapist is essential. There will always be cases needing transfer to the central institution for more expert attention, but in practice we have found that these cases are remarkably few.

SUMMARY

The development of an itinerant surgical service for leprosy patients in New Guinea is described. Experience has shown that the essential physiotherapeutic techniques can be taught to enthusiastic nurses in a short time, enabling them to maintain high standards of almost every aspect of prevention and care of the deformities seen in this country.

ACKNOWLEDGEMENTS

I am grateful to the World Health Organization for the grant of a fellowship which allowed me to spend 1964 in India, and to The Leprosy Mission for providing the nurse and physiotherapist and for the loan of a second physiotherapist for eight months in 1965. Mr. W. R. McKeown (Secretary for Australia, The Leprosy Mission) first suggested this decentralised service, and Dr Paul Brand and Dr Grace Warren assessed our needs. Dr D. A. Russell, Senior Specialist Leprologist, Department of Public Health, T.P.N.G., has supported the programme from the beginning, and I am indebted to him for help at every stage.

I am grateful to Dr R. F. R. Scragg, Director of Public Health, Territory of Papua and New Guinea, for permission to publish this report.

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Leprosy and Nutrition

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Of the many pathological sections of leprosy the most neglected are the nutritional. It is proposed to devote some attention to them in this paper.

Leprosy and Nutrition from the Epidemiology Point of View

According to Munro and Newman quoted by Rogers and Muir[1] the great prevalence of leprosy in the Middle Ages was based on a feeding system poor in the ingestion of meat and fresh vegetables. Also Keil[2] pointed out in Dutch Surinam the relationship between a diet of salted meat and fish and a predisposition to leprosy. Lampe[3] in Java found strong correlation between dried salted fish eating and leprosy. Varriel[4] noted that the eating of a large quantity of raw vegetables in Syria reduced the incidence and morbidity of leprosy. Hasselmann[5] in the Philippines noted a direct relationship between leprosy and the diet of fermented and dried fish, also in Burma Badger[6] pointed a probable relationship between nutrition and leprosy. Hutchinson[7] asserted all his lifetime leprosy depended on feeding with fish and affirmed that leprosy was a 'fish-eater's gout,' and ascribes the improvement in leprosy in the 16th Century to the increased consumption of green vegetables and the decrease of salty fish and meat. Bergel[8] interprets Hutchinson's theory nowadays as follows:— the ingestion of an excessive quantity of unsaturated fatty acids accompanied by a deficiency of tocopherol causes *in vivo* an increase of the auto-oxidative process which would provide a favourable ground for the growth of *M. leprae*.

Oberdörffer[9] assigns to the ingestion of some vegetables a definite role in the infection of leprosy, such as colacassia and agrostemona, foods which contain sapotoxins which have a deleterious action on the adrenals. Bergel[10] showed the inoculation of *M. leprae* in rats was helped by dietetic changes. These have assisted in other infections as Dubós[11] and Hedgecock[12] have shown the importance of lipids in the development of the experimental tuberculous infection. Scrimshaw, Taylor and Gordon[13] mentioned the nutritional factors as perhaps involved in the formation of antibodies, in the phagocytic activity, non-specific resistance factors, tissue integrity, state of the intestinal flora, balance of endocrines, interference with non-specific protective substances, destruction of bacterial toxins, etc., Niemeyer[14] pointed out that the diet could cause vitamin and proteinic deficiencies, disturbance of the electrolytic balance, anaemia, modify enzyme activity and the correlation between enzymes and cells.

Relationship between Diets and Chemotherapy

The author has used pro-oxidant diets in animal experimentation. Bergel[15], Eisman[16], Moore[17] found that the administration of DDS, the thiosemicarbazones, the isoniazids, and thiambutosine, in various amounts to a pro-oxidant diet (a semi-synthetic diet composed of casein, yeast powder, mineral salts, starch, and cod-

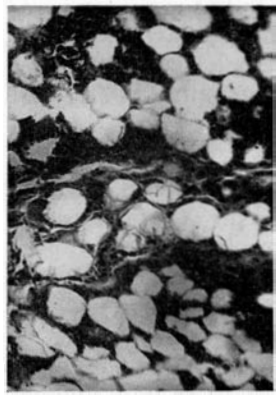

FIG. 1.
Perirenal fat of rat fed 4 months on pro-oxidant diet (Mag. 80 x)

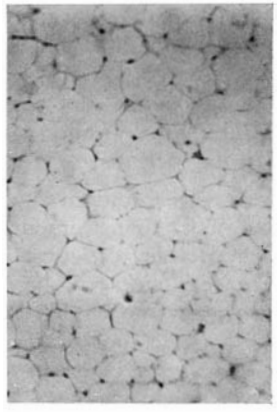

FIG. 2.
Perirenal fat of rat fed 4 months pro-oxidant diet with addition of 4–4[1] DDS at 0.5 per 1,000 (Mag. 80 x)

liver oil) avoids the formation of fuchsinophil ceroid pigment. This means an anti-oxidant biological activity of the anti-mycobacterial chemotherapies. Figs. 1 and 2 show the perirenal fat of a rat fed with a pro-oxidant diet. The therapy has avoided peroxidation of the deposit fat.

Bergel insists that the anti-oxidant diet should have a very low concentration of tocopherols (Vitamin E) and a more or less high quantity of unsaturated fatty acids. *M. leprae* is capable of reproducing itself actively in rats fed with pro-oxidant diets. Bergel verified the effect of a pro-oxidant diet, 10 of which were fed with semi-synthetic diet to which 15% of cod liver oil was added, 10 of which were fed on the same diet, but the 15% oil was rancid industrial coconut oil. The semi synthetic diet was composed of:

industrial casein	23.8 g.
mineral salts	3.0 g.
yeast powder	8.9 g.
corn starch	48.9 g.

The oils were kept under refrigeration and added to the dry mixture in the indicated proportion. Water was administered *ad lib.*

After 20 days under the above diet all the animals were inoculated with .05 ml. of a bacillary suspension prepared from triturated leproma of a young untreated patient. Part of the bacillary material was seeded in Lowenstein-Jensen medium at 37 °C and at room temperature, which did not produce development of bacillary colonies. The animals were maintained on the same diet for 7 months. Some died spontaneously and others were sacrificed at regular periods.

It was found in the experiment that only 1 bacillary development occurred which was a remarkable testicular atrophy in one animal. On the contrary the animals which received pro-oxidant diet did not present bacillary growth in the testes nor testicular atrophy. In previous experiments when pro-oxidant diets had been given in an early age of 20 to 22 days animal, there was a marked testicular atrophy and great bacillary development. In the present group which received coconut oil, there was a noticeable testicular atrophy in all, which presumably can be attributed to lack of Vitamin E.

The following chart (Fig. 3) shows bacillary growth in both groups of animals, the counts being made by the Hanks method.

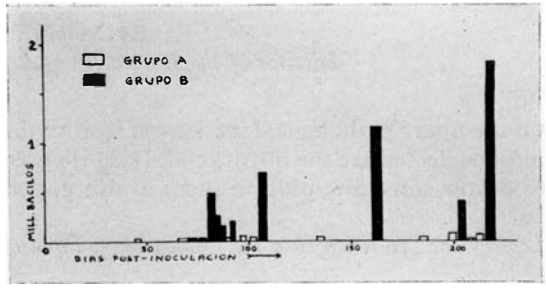

FIG. 3
Chart showing bacillary growth in both animal groups.

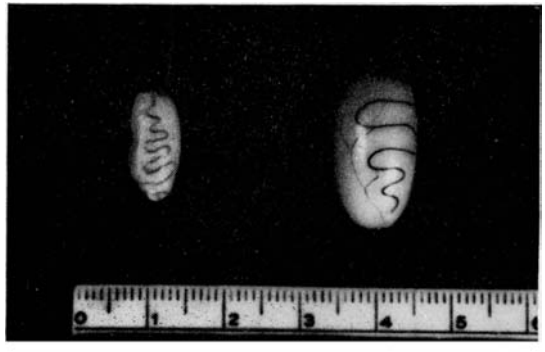

FIG. 4
This fig. shows the comparative size of the testes of both groups of animals.

Figs. 5, 6, 7 and 8 show the histology of some of the testes.

SUMMARY

From experiments with the diet of the experimental animal it appears that diets provoking Vitamin E deficiency and pro-oxidant diets given at an early stage promote the development and growth of *M. leprae* in the animals. It is suggested that the dynamics of anti-leprosy therapy could be partly explained on the basis of its relationship with nutritional factors.

ACKNOWLEDGEMENT

The author records his gratitude to Schering Corporation, Bloomfield, New Jersey, for having

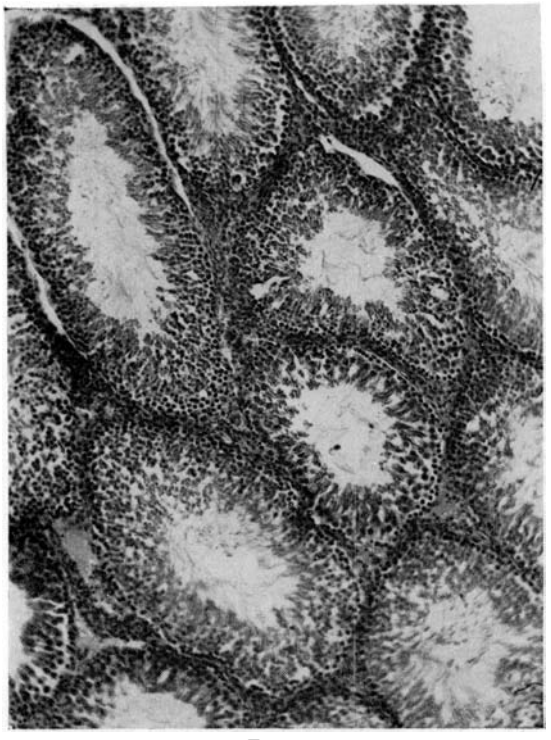

FIG. 5
Testis of 1st group at 210 days of inoculation. Normal structure (x 150).

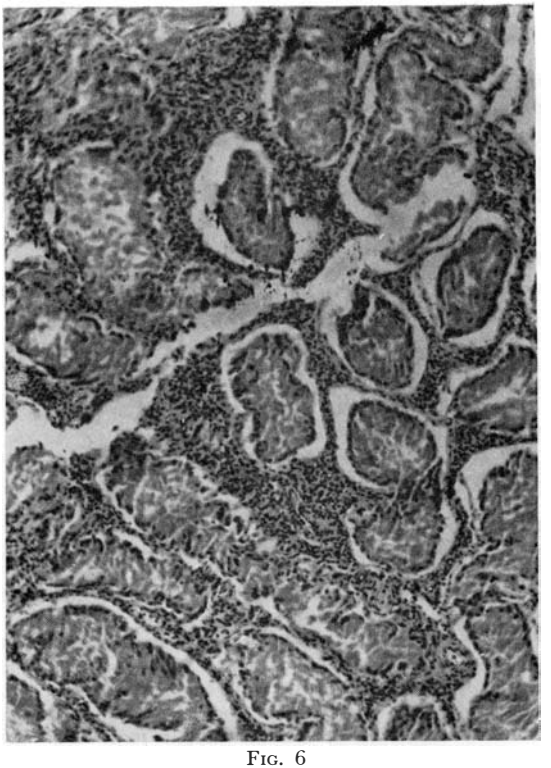

FIG. 6
Testis of 2nd group at 73 days of inoculation, with testicular degeneration and intertubular infiltration. (x 150).

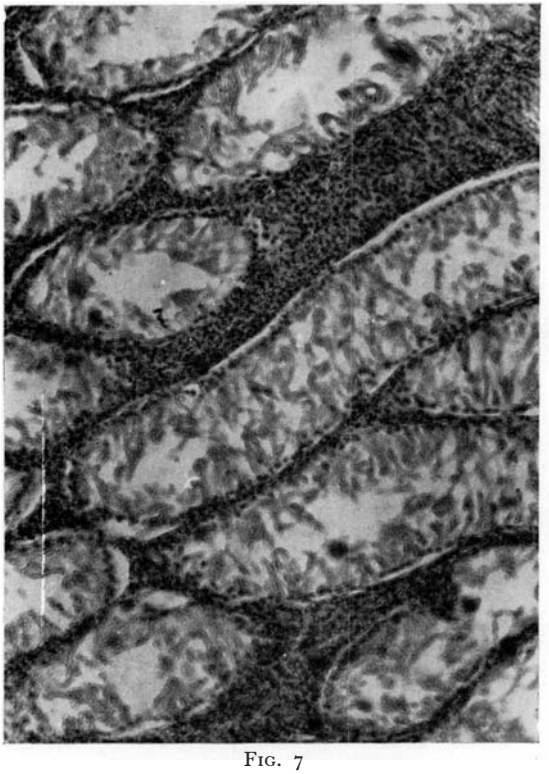

FIG. 7
Testis of 2nd group at 98 days from inoculation. Marked intertubular infiltration (x 150).

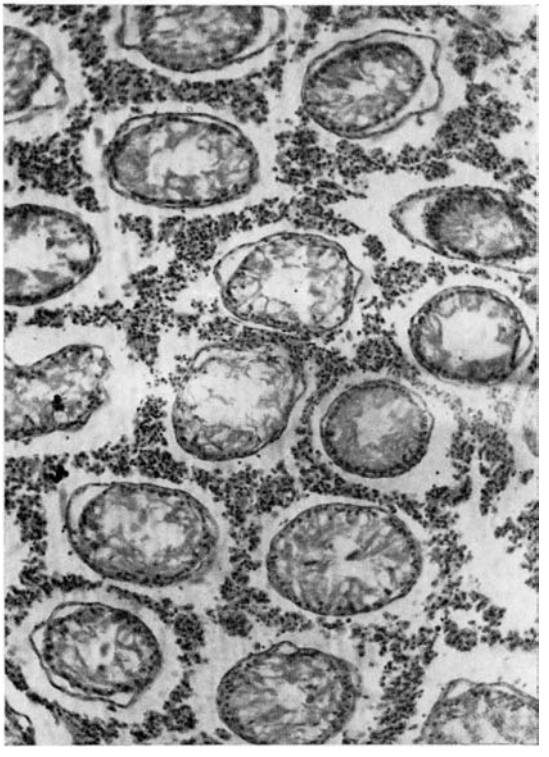

FIG. 8
Testis of 2nd group at 202 days from inoculation. Marked intertubular infiltration and testicular degeneration (x 150)

supplied the diets used in the present experiment, and also to Miss Jeanette Sperling, for her having translated his paper into English, and to Messrs. Remington Rand, Sud Americana for considerable general help.

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Therapeutic Trial Report on Long-Acting Sulphonamide Ro 4-4393 (Fanasil) in the Treatment of Leprosy

M. L. GAIND, C. V. MENOR and RAMAKRISHNA*

INTRODUCTION

The results obtained with sulphadimethoxine,† a long-acting sulphonamide in the treatment of leprosy were encouraging in a large number, so impressive in a few cases, (Gaind and Soli 1964) that we decided to undertake another clinical trial with a newer long-acting Sulphonamide Ro 4-43 93,‡ supplied to us by Roche Products Limited, Bombay. The antibacterial activity of this sulphonamide is equal or superior to that of other sulphonamides and its retention in the human body is markedly more prolonged than any other known sulphonamide (Garcia Herrera, E. 1964, Tschudi Madsen, S. 1964). Because of this property and of our previous encouraging results with Madribon, we felt that the present drug may even be more effective.

Several preliminary reports of clinical improvement in patients with lepromatous and tuberculoid leprosy have been published, bacteriological improvement has been observed by many workers. Recently Opromolla obtained excellent results in 12 out of the 17 cases, (Opromolla *et al.* 1964). Barclay *et al.* (1963) reported good results in 14 patients who completed two years treatment. Ghosh and Chakraborty, (1964) found marked improvement in all the cases of tuberculoid leprosy and marked changes in the morphology of the bacillus and reduction in the bacteriological index in 6 cases of lepromatous leprosy.

The present communication reports a clinical trial in 34 patients of leprosy conducted from March 1963 to December 1964 at the Military Hospital, Poona.

MATERIAL AND METHODS

Thirty-four leprosy patients, 17 lepromatous and 17 tuberculoid, with diagnosis established by clinical, bacteriological and histopathological examinations were selected for this therapeutic trial.

Lepromatous leprosy

17 patients were divided into two groups:

A) those who have had no treatment before the trial (13 patients)

B) those who were having sulphones for a period from 5 months to 2 years and in whom the disease appeared to have become clinically static and were showing no reduction in their bacteriological index (4 patients)

Tuberculoid leprosy

17 patients were divided into two groups.

A) 14 patients who have had no antileprosy treatment before the trial.

B) Three patients who had been having sulphone treatment for a period of 4-6 months and in whom a drug resistance appeared to have developed.

Dosage

A trial dose of half tablet (0·25 g.) was given to the lepromatous patients once a week for two weeks and thereafter gradually and cautiously increased to a maximum of 3 tablets (1·5 g.) a week. At the time of compiling our results, we observed that most of these patients had remained on 2 tablets (1 g.) a week for the major portion of the duration of the treatment. The tuberculoid patients received an initial dose of 1 tablet for the first week. This dose was

*Military Hospital, Wanorie, Poona, 1
†Madribon 'Roche'
‡Fanasil 'Roche'

rapidly increased to a maximum of 3 tablets (1·5 g.) once a week and maintained at this level during the major portion of the treatment period.

RESULTS AND COMMENTS

Lepromatous leprosy

The results are summarised in Table I.

TABLE I

Lepromatous Leprosy

Patient No. 1—with 122 days duration and 24 g. sulphonamide total dose. There was clinical improvement in 6 to 8 weeks in the form of complete disappearance of erythema and infiltration and considerable bacterial improvement in 8 to 10 weeks to negativity.

Patient No. 2—had a duration of 210 days and was given 40 g. sulphonamide. In evolution there was an absence of pigmentation, and infiltration regressed to disappearance of some patches completely. There was favourable bacterial evolution.

Patient No. 3—there was lepra reaction with DDS and sulphonamides.

Patient No. 4—duration was 218 days and 42 g. total dose was given. During evolution most of the hypopigmented patches disappeared; sensation returned in the areas previously anaesthetic. When sulphonamide was stopped bacterial reversal occurred.

Patient No. 5—duration was 244 days and total sulphonamide dose 48 g. In evolution pigmentation appeared in hypopigmented patches and anaesthesia improved in some patches.

Patient No. 6—duration of 358 days and total dose of sulphonamide 65 g. All lepromata flattened markedly, and in certain areas the infiltration completely disappeared to leave wrinkled and atrophic skin. Bacterial reversal when the sulphonamide was stopped.

Patient No. 7—duration was 213 days and total dose 36 g. Infiltration regressed; reaction with 3 tablets, but on 2 tablets a week there was no reaction.

Patient No. 8—the duration was 214 days and the total dose 43 g. There was marked regression in infiltration and flattening of nodules. There was bacterial reversal also when the sulphonamide was stopped.

Patient No. 9—the duration was 126 days and the total dose 41 g. The infiltration regressed greatly.

Patient No. 10—the duration was 188 days and the total dose 39 g. There was partial regression of infiltration.

Patient No. 11—the duration was 183 days and the total dose 36 g. All the infiltrative patches disappeared but there was no effect on the macular patches.

Patient No. 12—the duration was 153 days and the total dose 30 gm. The infiltrative patches on the face disappeared, leaving wrinkled skin behind. There was no effect on macular patches.

Patient No. 13—duration was 109 days and the total dose of sulphonamide 19 g. The patches noticeably flattened and the erythema reduced.

Patient No. 14—the duration was 124 days and the total dose 20 g. There was partial regression of infiltration and return of sensation in some anaesthetic patches. There was bacterial reversal when the sulphonamide was stopped.

Patient No. 15—Duration was 90 days and total dose 15 g. The patient was previously on sulphones for 2 years. Lepra reaction developed after 1 tablet DDS. There was marked flattening of infiltrative patches: nasal blockage and nerve tenderness disappeared.

Patient No. 16—the patient when given sulphetrone or sulphonamide 1 tablet 3 times a week developed lepra reaction but did not on 1 tablet once a week. Some nodular dwellings on the face disappeared completely and there was marked reduction generally. Some of the patches became hyperpigmented.

Patient No. 17—Erythema nodosum leprosum reaction appeared with DDS, Sulphetrone, and sulphonamide.

N.B. Patients 2, 15, 16, & 17 belong to group B.

Group A

Clinically 10 patients showed excellent results. Erythema and infiltration started regressing in 12–16 weeks, nerve tenderness was reduced in 5–6 weeks but the thickening persisted till the end of the trial. In 3 patients the improvement was spectacular (see figures 1 to 9), all infiltrative patches disappeared in $5\frac{1}{2}$ months and became bacteriologically negative in $3\frac{1}{2}$ months and remained negative for 3 months before they were discharged. In one patient lepromata flattened out considerably in most of the areas leaving behind wrinkled skin in 6 months when he became near negative bacteriologically; the condition deteriorated within a month, when Sulphonamide was replaced by Sulphetrone, and he started improving again in 6 weeks after reinstituting Sulphonamide and showed a remarkable clinical improvement in

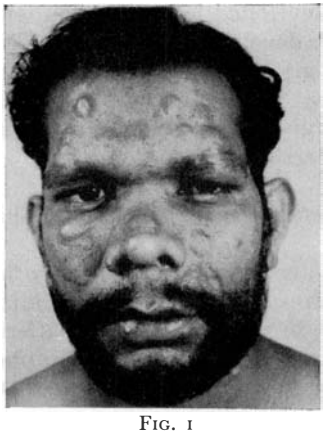

FIG. 1
Leprosy Lepromatous
before treatment.

FIG. 2
Leprosy Lepromatous
before treatment.

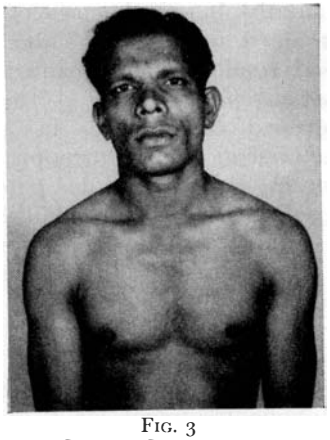

FIG. 3
Leprosy Lepromatous
22 weeks after treatment.

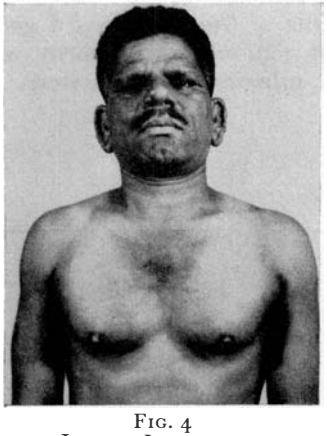

FIG. 4
Leprosy Lepromatous
before treatment

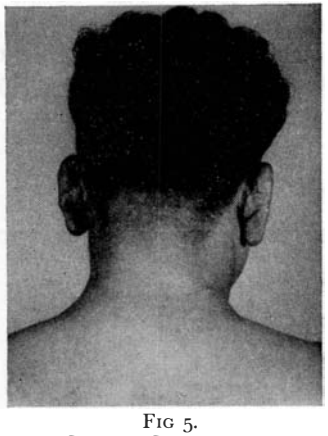

FIG 5.
Leprosy Lepromatous
12 weeks after treatment.

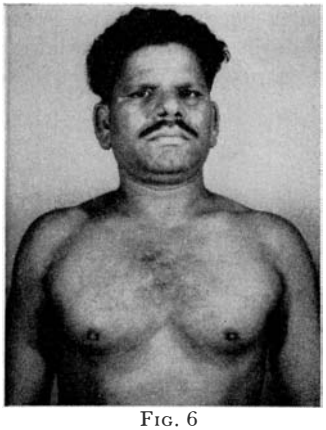

FIG. 6
Leprosy Lepromatous
18 weeks after treatment.

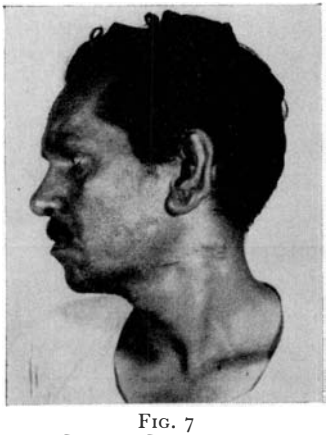

FIG. 7
Leprosy Lepromatous
before treatment.

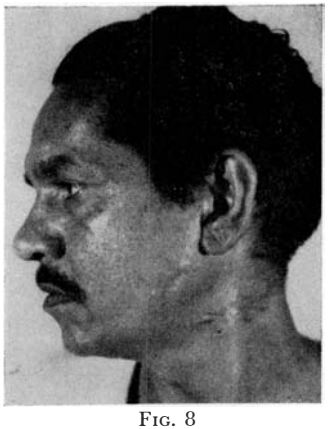

FIG. 8
Leprosy Lepromatous
11 weeks after treatment.

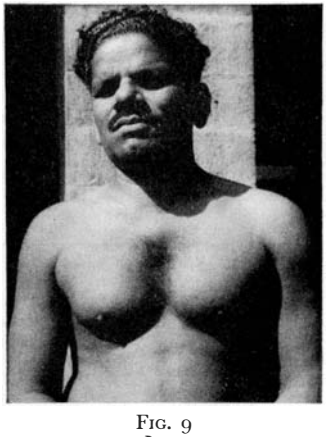

FIG. 9
Leprosy Lepromatous
33 weeks after treatment.

3 months, but the bacteriological improvement remained fluctuating. Three patients showed good results, hypopigmented patches became partially pigmented in 4–6 months, infiltration regressed considerably in 3–5 months and bacteriological modification occurred in 4 months, but the macular patches were not affected. One patient developed a reaction when on a dose of 2 tablets (1 g.) a week; the reaction became persistent and the drug had to be stopped.

Group B

Out of the 4 patients, 2 patients who were on sulphone treatment for 8 months to 2 years started showing appreciable change in infiltrative lesions in 2 months after sulphonamide treatment. Erythema disappeared and the patches became flush with the normal skin in 6 months when bacteriological modification and improvement also became evident. One patient who had developed lepra reaction with $\frac{1}{2}$ cc. of sulphetrone developed a similar reaction with 1 tablet (0·5 g.) of Sulphonamide and the other developed a reaction when 2 tablets (1 g.) a week were given; the treatment in these cases had to be interrupted.

Bacteriological evolution (see Table I). Skin Scrapings

Seven patients became negative in 5–11 months. Considerable improvement with modification of bacilli was found in 7 patients. Three patients who had become negative were put on Sulphetrone $\frac{1}{2}$ cc. bi-weekly but they reverted to positivity after 2–3 months.

Tuberculoid leprosy

The results are summarised in Table II. Clinically 6 patients of *Group A* showed good response; the first sign of improvement was noticeable by the ushering in, as it were, of

TABLE II

Tuberculoid Leprosy

Groups A and B

Patient No.	*Duration of treatment*	*Total dosage*	*Clinical response*
Group A			
1	167 days	32 g.	good
2	120 days	24 g.	good
3	95 days	20 g.	good
4	90 days	15 g.	moderate
5	153 days	30 g.	good
6	30 days	13 g.	moderate
7	120 days	23 g.	moderate
8	45 days	10 g.	poor
9	128 days	24 g.	poor
10	152 days	30 g.	poor
11	190 days	40 g.	poor
12	90 days	18 g.	good
13	160 days	36 g.	good
14	124 days	24 g.	no appreciable improvement (poor)
Group B			
15	153 days	30 g.	good
16	100 days	20 g.	good
17	213 days	23 g.	good

Group A:	Good results	6 patients	*Group B*:	Good results 3 patients
	Moderate	3 patients		
	Poor	5 patients		

pigmentation at the periphery of the hypopigmented patches in 8–10 weeks and the regression of infiltration started in 12–16 weeks when the partial return of superficial sensations in the anaesthetic patches was also detectable. Nerve tenderness started improving in 8–10 weeks and disappeared completely in 5 months, but the thickening persisted till the end of the trial. Return of superficial sensation was not complete, as the residual anaesthesia remained unchanged in the centre of the patches. Three patients showed a moderate response. In these there was a partial and patchy return of pigmentation in some of the patches and there was the regression of infiltration. There was no improvement in the vasomotor discolouration of the hand in two patients and the improvement in anaesthesia was doubtful.

Five patients showed a poor response in 3 months. Their treatment could not be continued beyond this period due to certain administrative difficulty.

Group B

In Group B three patients who had shown no improvement in hypopigmentation, infiltration or erythema, for 4–6 months with sulphones began to show appreciable and impressive changes within 2 months of instituting Ro 4–43 93 and in 5 months the patches flattened out, erythema disappeared and the sensations returned to an appreciable degree and the colour of the patches returned to near normal. This may have been due to the drug substitution.

SIDE EFFECTS

On the whole the drug was well tolerated by the majority of the patients. One patient when on 3 tablets (1·5 g.) developed a generalised rash without affecting the lesions of leprosy; the rash disappeared on stopping the drug for a few days; it did not recur with 2 tablets (1 g.) a week. This rash might have been a drug eruption. Another patient complained of intense itching and burning sensations all over the body which disappeared when the drug was stopped for a few days and did not recur with further treatment. Two patients developed lepra reaction and 2 developed erythema nodosum type of reaction which were under control by chloroquin or chloromycetin. In these patients the drug had to be stopped. In no case was there any adverse effect on blood count or Hb%.

DISCUSSION

The number of cases included in this trial is too small, and the duration of the treatment too short to make a definite and final assessment of the therapeutic efficacy of this drug in leprosy, but in view of the excellent therapeutic results obtained in a large number of cases combined with good tolerance and ease of administration, Ro 4–43 93 (FANASIL 'Roche') should occupy a prominent position among the anti-leprosy drugs available today. Further extensive investigations are required to make a comparative assessment with other anti-leprosy drugs. In some of our patients the results have been superior to those obtained with sulphones and this observation has also been reported by Wilkinson, F. F. *et al* (1961). During the trial we also observed that the drug has a quicker effect on the infiltrative than on the macular lesions of leprosy. Although we have not been able to work out critically the optimum dose schedules, yet we have gained the impression that 2 tablets (1 g.) a week is an adequate dose for clinical and bacteriological improvement and that 3 tablets a week do not produce any accelerated improvement. It may be possible at a later date to increase the interval even more, so as to arrive at a monthly administration regime of the drug.

The mechanism of repigmentation remains obscure but is interesting and is food for thought and further research. It may be possible that the drug in some way brings about some changes in the enzyme system which is connected with the process of pigmentation.

SUMMARY

34 leprosy patients, 17 lepromatous and 17 tuberculoid were subjected to a therepeutic trial with a long-acting Sulphonamide Ro 4–43 93 (FANASIL 'Roche') for a period of 22 months.

Of the 17 lepromatous leprosy patients, 10 patients showed excellent results, of these in 3 patients the improvement was spectacular as seen in the photographs. Two patients with lepra reaction and 2 patients with erythema nodosum type of reaction were encountered.

Three patients showed good results. Of the

17 tuberculoid leprosy patients, 14 had no treatment previously. Out of these 14 patients, 6 patients showed good response, 3 moderate response, and 5 poor response in 3 months of treatment, whereas 3 patients which were previously treated with sulphones and had become static clinically, showed impressive improvement in 2 months after sulphonamide therapy.

Skin eruption was encountered in two patients. However, in both it disappeared after interruption of treatment and did not recur on readministration of the drug.

CONCLUSION

1. Ro 4–43 93 (FANASIL 'Roche') has an indisputable activity in the treatment of leprosy.

2. The drug is well tolerated and easy to administer.

3. Lepra reactions are not frequent with this drug, but all the same it is capable of producing lepra reaction or erythema nodosum type of reaction in those who develop a similar reaction with other anti-leprosy drugs.

4. Two tablets (1 g.) a week appears to be an adequate dose.

ACKNOWLEDGMENT

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Contact Surveys in Leprosy

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1. INTRODUCTION

A number of factors in the epidemiology of leprosy is still shrouded in mystery. Much work is being done on the subject but the conclusions obtained in some cases are as varied as the pattern of the disease. The Division of Epidemiology and Statistics in the Central Leprosy Teaching and Research Institute Chingleput, South India, initiated a series of studies on certain epidemiological aspects of leprosy and the present survey under report is one among them.

An epidemiological leprosy survey (1961) covering a population of more than 200,000 distributed over 381 villages in Chingleput District of Madras State was conducted in a time interval of one year from December 1961 to December 1962, and the results of the survey have already been published (1963).[1] The following were the salient features of the survey.

Population of the area	213,721
Population examined	205,234
Percentage examined	96.0
Total cases confirmed	4,383

All these 4,383 leprosy patients were distributed in 3,666 families and the number of patients per family ranged from 1 to 6. The number of families with more than one patient was 579 and the rest numbering 3087 were single-patient families. There were 14,776 healthy contacts who were living with these patients. All these 4,383 patients and 14,776 healthy contacts form the population under study. With the object of studying the intra-familial incidence of leprosy contact surveys have been launched in this area covering the above said population. This is a continuous type of survey, the period of observation being one year and already two rounds have been completed. Our object in presenting this report is to review the progress made and to present the results obtained.

2. COLLECTION OF DATA: *Materials and Method:*

When the first general survey was carried out the contacts were free from the obvious symptoms of the disease, and the information to be collected was the number of new patients who developed among these healthy contacts during a certain unit of time; and for the sake of calculating the statistical rates this period has been fixed as one year.

All the patients and their contacts were spread throughout an area of 320 square miles. For the administrative convenience and operational facility, the entire area was divided into 20 sectors and a trained paramedical worker posted in each sector. These paramedical workers were primarily meant for the administration of drugs to a certain section of the healthy contacts in the DDS Prophylaxis study which has been going on since 1963 April. All these paramedical workers were trained in the Institute for 6 months in the diagnostic methods of leprosy and they are quite familiar with the local population and in good public relationship with the people under study, which is of vital importance for any survey to be successful. These paramedical workers were utilized in collecting the required information.

The collected information of all the family members is recorded in a family schedule. A copy of the schedule is given in the appendix.[1]

As already mentioned there were 20 paramedical workers and the work load for each paramedical worker ranged from 150 to 200 families.

1963 January is taken as the starting point and the contact population was surveyed to find the number of new patients only after nearly one and half years and the first round of the contact survey was completed in May, 1964 (i.e. after 17 months). From June 1964, exactly after one year, the population was surveyed for the second time in May, 1965. All the new

patients picked up by the paramedical workers were confirmed or rejected by a Senior Medical Officer of the Epidemiology Division who visited all these reported new patients.

At the time of the general survey there were 4,383 confirmed patients and 14,776 healthy contacts living with them. But at the time of starting the first contact survey, there were 4,415 patients and 14,275 healthy contacts. The difference in the number of patients (32) is due to the re-examination subsequently of certain suspected new patients. The decrease in the number of healthy contacts is due to leaving out contacts who were not available for examination. Thus in this population we had 4,415 patients who were considered as the possible sources of infection to their healthy family members. This population is taken up for studying the intrafamilial incidence of leprosy i.e. to know how the disease was spreading in this population who were in contact with the 'source' cases. For this, the population was kept under observation, and the results that are presented here relate to the first contact survey.

3. RESULTS OF THE FIRST CONTACT SURVEY

The First Contact Survey showed that 233 new patients occurred during the 17 months (the period elapsed after the general survey). But for the calculation of the exact period the mid-points of the Survey periods are considered, thus giving us 22 months period during which 233 new patients developed leprosy and for comparing the rates, the results are reduced to a yearly basis.

4. 'SOURCE' SPECIFIC ATTACK RATES

All the patients whom we considered as possible 'source' of infection were not of the same type. With a view to understanding the importance of different types of sources in the spread of the disease, all the contacts and new patients who developed leprosy during the first contact survey period are grouped according to the type of source case. (Here only single patient families are considered since there is no way of separating the contacts of the multiple leprosy patient families, the source patients there being of different types. They are however considered separately and presented.)

There were 3,104 'sources' in single patient families and 1311 in multiple patient families; they have respectively 12,198 and 2,077 healthy contacts. All the sources were broadly classified into lepromatous type (L), non-lepromatous type (N), and intermediate type (N?L). The attack rates according to each type are calculated and given below:

It can be seen that the over-all attack rate irrespective of the type of source is 0.77. The attack rate in the case of lepromatous type of source is 1.75 and 0.49 with intermediate type and 0.69 in the case of non-lepromatous. The attack rate in the case of lepromatous type is statistically significant when compared to the attack rates in the case of the other two types.

The attack rates in the case of non-lepromatous type and intermediate type are not statistically significant from each other suggesting that they are not dangerous to the community to the same extent as far as the spread of infection is concerned.

5. SOURCE-SPECIFIC ATTACK RATES ACCORDING TO BACTERIOLOGICAL INDEX (B.I.)

After noting that the attack rates are different in the case of different types of 'sources', the next thing is to see how the bacteriological status of the source case is important in spreading the infection. For this, all the different types of sources were further classified according to their bacteriological status. Firstly all the types were classified into bacteriological positive, negative, and bacterial index unknown. In the case of non-lepromatous patients only the two classes namely +ve and —ve types are considered and the source patients whose bacteriological index is not known are included in the —ve type. Further all the lepromatous +ve type of sources are classified into different classes according to the degree of the bacteriological index. This helps us to understand whether a high value for bacteriological index has got anything to do with the increased incidence of new patients and thus *ipsofacta* the attack rate. The respective number of contacts and new patients together with the attack rates are shown in the following table:

By looking at the attack rates, we find that there is a good deal of variation. It can be seen from the table that the number of contacts and new patients in certain categories is too few to draw any valid conclusions regarding the type. In the case of lepromatous type, the attack rates

with different value of B.I. are different suggesting that the higher the value of the bacteriological index, the higher the attack rate. When the value of the B.I. of the source patient is 1 to 2 the attack rate is 3·23 which is more than three times the attack rate in the case of sources with B.I. 0–1. But in the case of B.I. 2–3, the attack rate is less than when B.I. was 1–2; it might be due to the small number; and finally in the case of B.I. 3+, the attack rate is very high. Though it is not possible to draw definite conclusions regarding the potentiality of the 'sources' in spreading infection on the basis of 1½ years observation, it gives us some indication that the greater the value of the B.I. the greater the risk of infecting the contacts. Because of the unknown long incubation period, we will have to wait for sometime before we draw any justifiable conclusions.

The attack rate in the case of lepromatous +ve type of source is 2·96 and in the case of +ve intermediate type it is 1·95 the difference being statistically not significant. We are not in a position to say anything regarding non-lepromatous +ve type since we have not observed any new patients during the period under observation in this group. We may be in a position to comment on this in subsequent reports.

The attack rates in the case of —ve types of lepromatous, intermediate and non-lepromatous sources are respectively 0·60, 0·49 and 0·69 which are not statistically different from one another. Thus, broadly we can say that:

(1) among the three types of source patient lepromatous type is more dangerous to the community as far as the spread of the disease is concerned.

(2) when the bacteriological index is considered it is not only lepromatous +ve type but also +ve intermediate type is equally capable of spreading infection.

(3) as far as all —ve source patients are concerned we do not find any difference in the attack rates.

6. ATTACK RATES ACCORDING TO NUMBER OF SOURCES IN THE FAMILY

The next problem is to find out whether multiplicity of source patients in a family has got anything to do with a higher attack rate. For this purpose all the families were classified into 1, 2, 3, and 4 and above source patients families with their respective contacts and new patients, as shown below.

The attack rate in the case of single patient families is 0·77 and in the case of two-patient; families it is 1·57 which is double the former the difference is statistically significant. The attack rate in the case of three-patient families is 1·49 which is sightly less than two patient families-rate, the difference being statistically insignificant. When compared with that of the single patient families, the difference is statistically not significant. The attack rate in the case of 4 patient families is 2·63 which is higher than any one of the above rates but the difference is statistically insignificant. When all the multiple patient families are put together, the attack rate is 1·60 and it is statistically significant when compared to the single source family rate (1·00). This might be due to the small numbers in the 3 case and 4+ case families and also the short period of observation.

7. ATTACK RATES ACCORDING TO THE SOURCE COMBINATION

Leaving aside the single-patient families we have 579 multipe patient families. Out of these 579 multiple patient families 465 are two patient families. The contacts of these source patients were further classified according to the type of source combination. When there are two patients in a family they may be (1) both lepromatous type (LL) (2) both non-lepromatous type (NN) and (3) one lepromatous and another non-lepromatous type (LN). In classifying the contacts under these source combinations, the following rule is observed in the case of contacts having N?L as one or both sources. Whenever it is bacteriologically positive it is taken as lepromatous type and when negative as non-lepromatous type. We are not in error in doing so since the attack rates as already studied is the same for all negative patients. The following table gives the attack rates in the two patient families according to the type of source combination.

It can be seen that the attack rate when both the sources are lepromatous type is 2·02. Though we could expect a much higher attack rate in this case, we cannot be dogmatic without some more data, since by a mere increase of one new patient the attack rate will be doubled.

TABLE 1

Showing the attack rates according to the type of source

Type of Source	No. of sources	No. of contacts	New patients	Attack rate	Attack rate per year
'L'	373	1025	33	3·22	1·75
'N?L'	165	552	5	0·91	0·49
'N'	2566	10621	134	1·25	0·69
Total	3104	12198	172	1·41	0·77

TABLE 2

Showing the attack rates according to the bacteriological index (B.I.) of the source patient

Type and B.I.		No. of sources	No. of contacts	No. of new patients	Attack rate	Attack rate 1 year
N?L	+ve	19	56	2	3·57	1·95
	—ve	105	353	2	0·57	0·31
	B.I. unknown	41	143	1	0·70	0·38
	Total	165	552	5	0·91	0·49
L	+ve 0–1	43	111	2	1·80	0·98
	1–2	51	152	9	5·92	3·23
	2–3	32	71	3	4·23	2·30
	3+	7	16	5	31·25	17·04
L	(All+ve)	133	350	19	5·43	2·96
	—ve	198	544	6	1·10	0·60
	O.B.	4	13	1	7·69	4·20
	B.I. unknown	38	118	7	5·93	3·24
	Total	373	1025	33	3·22	1·76
N	+ve	14	40	0	—	—
	—ve	2552	10581	134	1·27	0·69
	Total	2566	10621	134	1·26	0·69
Grand Total		3104	12198	172	1·41	0·77

TABLE 3

Showing the attack rates according to the No. of sources in the family

No. of sources	No. of contacts	New patients	Attack rate	Attack rate/ year
1 source	12,198	172	1·41	0·77
2 sources	1,665	48	2·88	1·57
3 sources	329	9	2·74	1·49
4+ sources	83	4	4·82	2·63
All multiple sources	2,077	61	2·94	1·60
Total	14,275	233	1·63	0·89

Many of the families are not having contacts at all and their number comes to nearly half. We have to observe these families for some more time before any conclusions are drawn.

When the sources are one lepromatous and one non-lepromatous the attack rate is 3·72 which is higher (3 times) than the attack rate 1·01 when both sources are non-lepromatous type; the difference is highly significant.

These can be further sub-divided according to the bacteriological status of the source patient, but the figures will become still smaller which will vitiate any justifiable conclusion. For this reason, further analysis has not been attempted.

8. SEX AND AGE SPECIFIC ATTACK RATES

Not only the attack rates by type of source is important, the attack rates by sex and age is also important in understanding the factors responsible for the spread of the disease. All the contacts were grouped by three age groups namely children (0–14) adults (15–44) and old people (45 and above) according to sex. The following table gives the attack rates by sex and age in the population.

The table shows that the overall attack rates 1·04 (children), 0·75 (adults) and 0·86 (old people) are not statistically different from one another, thus suggesting that all are equally capable of contracting the disease. In males it can be seen that the attack rate gradually decreases as the age increases, the old people having the minimum attack rate 0·68 when compared to the attack rate of children (1·26) which is almost twice the former. But in the case of females, the picture is different. The attack rate is higher in old people when compared to any other age. But the attack rate in children also is higher than the attack rate in the adults. However the attack rate is lowest in the case of adults (15–44).

When the rates in both the sexes are compared it is seen that the attack rate in adults (1·02) in the case of males is statistically different from the attack rate in adults (0·52) in the case of females. But the attack rates in the case of male children (1·26) and old males (0·68) are not statistically significant when compared to that of female children (0·81) and old females (1·12).

It can be seen that the over-all attack rate in males is 1·08 and that of females is 0·72, the difference being statistically significant suggesting that leprosy attacks males more than females. This difference is mainly reflected in adults since the sex specific attack rates in them are significantly different, while in the old people and children the difference is insignificant.

9. SEX AND SOURCE-CONTACT SPECIFIC ATTACK RATES

All the sources and contacts of the single patient families were further classified into different categories namely (a) Male contacts having male sources, (b) Female contacts having male sources, (c) Male contacts having female sources and (d) Female contacts having female sources. All the new patients classified with respect to the above noted categories along with the attack rates and given below.

The attack rate among the contacts having male sources is 0·85 and that of the contacts having female sources is 0·63 the difference is not statistically significant. The attack rates among the male and female contacts having male and female sources are also not statistically significant from each other. But there is a significant difference between the attack rates of the male contacts having male sources (1·05) and the female contacts having female sources (0·52).

It will further be seen from the previous findings that:

(1) the overall attack rate among female contacts is less compared to the attack rate among male contacts, the difference being statistically significant.

(2) the attack rate among the females is minimum in the age group of 15–44.

(3) the attack rate among the female contacts having female source is least and there is a significant difference when compared to the attack rate among the male contacts having male sources.

These findings suggest some kind of association between the factors governing the transmission of leprosy among the sexes.

To understand clearly the pattern of spread in the population or, in other words, to find whether any particular age group is more vulnerable to the disease, all the contacts were classified into five-year age groups with their

TABLE 4

Showing the attack rates according to the type of source combination

Type of Source	No. of contacts	New patients	Attack rates	Attack rate per year
LL	27	1	3·70	2·02
LN	337	23	6·82	3·72
NN	1301	24	1·84	1·01
Total	1665		2·88	1·57

TABLE 5

Showing the age and sex specific attack rates

Age	*No. of contacts*			*New cases*			*Attack rate/year*		
	M	*F*	*All*	*M*	*F*	*All*	*M*	*F*	*All*
	3111	3047	6158	72	45	117	1·26	0·81	1·04
	2727	3224	5951	51	31	82	1·02	0·52	0·75
	1045	1021	2166	13	21	34	0·68	1·12	0·86
Total	6883	7392	14275	136	97	233	1·08	0·72	0·89

TABLE 6

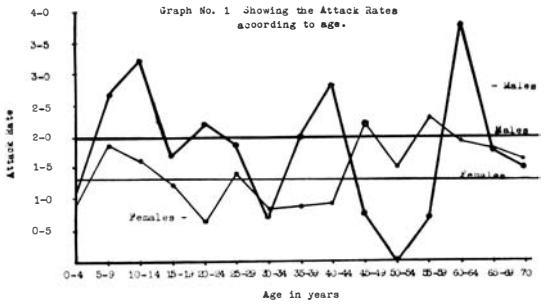
Showing the attack rates of different types of contacts

Type of sources	Type of contacts	No. of contacts	No. of New patients	Attack rate	Attack rate/ year
a. Male	Male	3443	66	1·92	1·05
b. Male	Female	4438	56	1·26	0·69
Total (a + b)		7881	122	1·55	0·85
c. Female	Male	2521	33	1·31	0·71
d. Female	Female	1796	17	0·95	0·52
Total (c + d)		4317	50	1·16	0·63
Total		12198	172	1·41	0·77

respective new patients in both males and females and the attack rates are calculated and shown in the table given above.

It is evident that there is a great deal of variation between the attack rates in different age groups in both between and within sexes. It can also be seen that no particular age is exempt from getting the disease. The age specific attack rates in both the sexes are plotted and shown in the graph overleaf.

The graph show that the attack rate in the case of males steadily increased till the age of 14 and decreased in the next five years. Again in the next five years, it increased to a certain extent and thereafter the increase and decrease occured at intervals of 10 years.



In the case of females, the attack rate increased steadily till the age of 9 years and thereafter gradually decreased till the age of 20 years. In the next five years again the attack rate increased followed by a decrease in the next five years. The attack rate is almost stationary between the ages 30–44 and thereafter the increase and decrease took place at intervals of five years except the last two age groups. As was observed in the previous paragraphs, the attack rates were least and remained stationary between 30 and 44 years. This was seen only in the case of females.

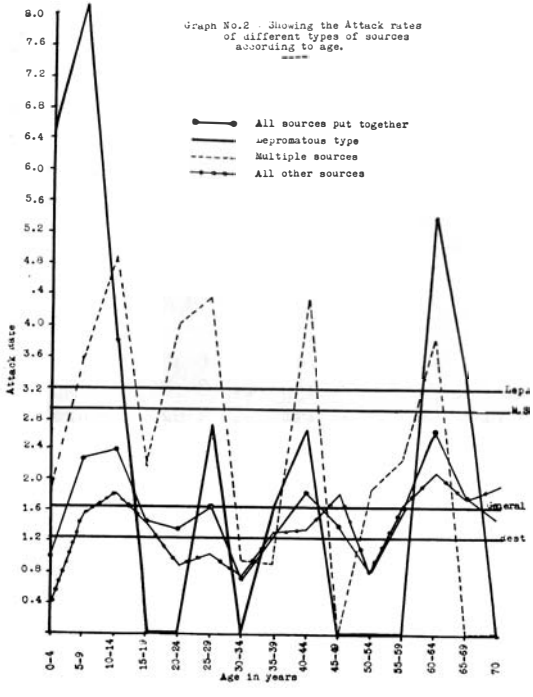
All the contacts for whom the attack rates were calculated are living with different types of 'sources' having different attack rates. The variation which we observed might be due to the different types of sources having different attack rates. To make this point clear all the contacts and new patients were further classified according to the type of source. For this, only three categories were considered, namely, Lepromatous source patients, multiple source patients, and the rest; we have already observed that the attack rates were different in the above categories when compared to the overall attack rates. The following table gives the number of contacts and new patients in the respective age groups according to the type of source patient along with the attack rates.

The age specific attack rates are plotted on a graph in the case of (a) Lepromatous type of source (b) Multiple patient source (c) All the rest, and lastly (d) All sources together. It will be seen that:

(1) The overall attack rate in the case of lepromatous type of source is highest when compared to others.

(2) The attack rate in the case of multiple source patients is also high but slightly less (the difference being statistically not significant(than that of lepromatous type but higher than (c) and (d), the difference being statistically significant.

Even after separating out the different types of sources having different attack rates, still we observe the variation in the age specific attack rates in all the categories namely a, b, c, and d. One interesting fact we observe from the graph is that the variation is systematic in the sense all the peaks and dips in the different patients occurs almost at the same age level in spite of the different sources having different attack rates. Thus it is clear that the variation is not due to the presence of different types of sources having different attack rates but it is due to some other factor which is operating independently of the source. This has to be investigated further before we draw any inference.



Graph: 2.
Showing the attack rates of different types of sources according to age

TABLE 7

Showing the age specific attack rates

Age	*Male contacts*	*N. cases*	*Female contacts*	*New patients*	*Attack rate* M	F
0–4	980	10	970	9	1·02	0·93
5–9	1190	32	1141	21	2·69	1·84
10–14	941	30	936	15	3·19	1·60
15–19	602	10	498	6	1·66	1·20
20–24	632	14	714	4	2·22	0·56
25–29	540	10	699	10	1·85	1·43
30–34	333	2	510	4	0·60	0·78
35–39	301	6	471	4	1·99	0·85
40–44	319	9	332	3	2·82	0·90
45–49	268	2	228	5	0·75	2·19
50–54	224	0	271	4	0·0	1·48
55–59	138	1	173	4	0·72	2·31
60–64	165	6	209	4	3·64	1·91
65–69	115	2	111	2	1·74	1·80
70+	135	2	129	2	1·48	1·55
Total	6883	136	7392	97	1·98	1·31

TABLE 8

Showing the age specific attack rates according to different types of sources

Age	*Lepromatous Type* C	N.C.	A/R	*Multiple sources* C	N.C.	A/R	*All others* C	N.C.	A/R	*Total* C	N.C.	A/R
0–4	108	7	6·48	323	6	1·86	1519	6	0·39	1950	19	0·97
5–9	159	13	8·18	335	12	3·58	1837	28	1·52	2331	53	2·27
10–14	131	5	3·82	267	13	4·87	1479	27	1·83	1877	45	2·40
15–19	64	0	0	184	4	2·17	852	12	1·41	1100	16	1·45
20–24	93	0	0	224	9	4·02	1029	9	0·87	1346	18	1·34
25–29	109	3	2·75	160	7	4·38	970	10	1·03	1239	20	1·61
30–34	62	0	0	106	1	0·94	675	5	0·74	843	6	0·71
35–39	61	1	1·64	107	1	0·93	604	8	1·32	772	10	1·30
40–44	37	1	2·70	92	4	4·35	522	7	1·34	651	12	1·84
45–49	45	0	0	71	0	0	380	7	1·84	496	7	1·41
50–54	36	0	0	54	1	1·85	405	3	0·74	495	4	0·81
55–59	26	0	0	44	1	2·27	241	4	1·66	311	5	1·61
60–64	37	2	5·40	52	2	3·85	285	6	2·10	374	10	2·67
65–69	30	1	3·33	26	0	0	170	3	1·76	226	4	1·77
70+	27	0	0	32	0	0	205	4	1·95	264	4	1·52
Total	1025	33	3·22	2077	61	2·94	11173	139	1·24	14275	233	1·63

SUMMARY AND CONCLUSIONS

1. Of all types of leprosy, the Lepromatous type has the highest attack rate and is hence more infectious.

2. When the bacterial index is considered, it is not only the lepromatous positive type but N?L positive patients also are equally capable of infecting the contacts.

3. When the bacterial index is negative all the three types whether lepromatous, intermediate or non-lepromatous, the rate of infection is the same and it is less than that of the positive cases.

4. Within the positive lepromatous group, (though it is not quite clear because of insufficient data) it appears that the attack rate increases with the value of the bacterial index.

5. The attack rate in the case of two source families is statistically significant (it is almost double) when compared to the single source family.

6. In the two-patient families, the attack rate is highest when the source combination is lepromatous and non-lepromatous and it is statistically significant when compared to the attack rate when both sources are of non-lepromatous type.

7. In the case of males, the attack rate decreases with the age and in the case of females, the attack rate is lowest in the age group 15–44.

8. The difference in the overall attack rates in the case of males and females are statistically significant.

9. The attack rate is least among the female contacts having females as source cases.

10. The attack rate among male contacts having males as sources is higher compared to the attack rate among female contacts with males or females as source cases

11. Age specific attack rates are studied in respect of different types of source patients. The attack rate takes the maximum and minimum values at particular age levels and the variation so observed is rather systematic. No comments are offered on this peculiar phenomenon at present but the matter is being further studied.

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APPENDIX I

Proforma
No. EPID/3/64

Central Leprosy Teaching and Research Institute

Contact Survey Record

Village: House No.: Family No.: Sector No.:

No.	Name	Age & Sex	Relationship	First General Survey	DATE	1st Contact Survey	DATE	2nd Contact Survey	DATE	3rd Contact Survey	DATE	4th Contact Survey	DATE	5th Contact Survey	DATE
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
11															
12															

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Reports

(1). Annual Report, 1964, of Central Leprosy Teaching and Research Institute, Chingleput, Madras State, India.

Dr Dharmendra, M.B.B.S., the Director reports on his staff for the year. Until the end of August, 1964 he had Dr H. Paul who was succeeded by Dr K. Ramanujam on 1 Sept. There were three resident medical officers in the leprosarium. There was one post of medical officer which was vacant and the post of visiting ophthalmic surgeon was vacant, and one visiting dental surgeon was occupied until August 1964. The Research Section was fully occupied with a senior and junior scientific officer and a m.o. in charge of the mobile treatment unit. In the orthopaedic surgery department there was an orthopaedic surgeon and a junior scientific officer, a medical officer (post is vacant) and a physiotherapist. The post of officer in charge of the X-ray department was vacant. In the Ayurvedic Unit there was a junior scientific officer and a research assistant. In the Children's Clinic at Saidapet there was one medical officer in charge, and one medical officer. In the Laboratories Division there were five officers, and in Epidemiology and Statistics three officers. There was one administrative officer and one social welfare officer in Information and Social Welfare.

With this staff there has been good progress in research and special mention should be made of the investigation of the prophylactic value of DDS in healthy contacts of leprosy patients: the results were very encouraging as to this method of prophylaxis, and 700 contacts were studied on a 'double-blind' method with a due use of placebo tablets, after an initial leprosy survey had been made of 213,000 population. In the young contacts of leprosy the DDS prophylaxis group compared with control groups was found definitely protected.

Teaching and training through the year resulted in a yield of 54 paramedical workers, seven physiotherapeutic technicians, 23 health inspectors, 37 pupil health visitors, and one medical officer was trained for one year in reconstructive surgery.

Under the Leprosy Research Workers Co-ordinating Committee of Madras State the Institute held two scientific seminars and the Institute held a third seminar on 'Drug Trials in Leprosy', and the staff of the Institute took an active part in the Conference of the Indian Association of Leprologists, and Dr Dharmendra the Director was in charge of the Committee of Assessment of the Conference.

The Clinical Division conducted the leprosarium both the hospital section and outpatients, clinical and therapeutic research, an orthopaedic surgical section, the mobile treatment unit, and the Silver Jubilee Children's Clinic, Saidapet.

The total of the inpatients was 945 inpatients and 825 ambulatory patients. Patients are kept until stabilisation of their treatments and as soon as possible hospital patients are changed from hospital to out-patient treatment, and 902 inpatients were discharged.

Therapeutic investigations were carried out:

(1) The long-acting sulphonamide RO 4–4393, with the conclusion that it is not very effective;

(2) Alectra parasitica, with the conclusion that it is of little value, and no further trials are indicated;

(3) Therapy with combined DDS and anti-tuberculosis treatment, with the conclusion that it does not produce results better than DDS alone;

(4) Therapy with parenteral DPT showed definitely less incidence of lepra reaction; it does not seem better than DDS, and DDS in the present smaller dose schedule is as effective and produces fewer complications; further studies in comparison with DDS are planned;

(5) Acute leprosy neuritis was investigated by a trial of a vasodilator drug Isoxsuprine for relief of pain in 23 patients and it was concluded that this drug was useful and without permanent harmful effects and the mode of administration

by intraneural injection calls for further investigation before a permanent decision.

Clinical investigations were made into borderline leprosy as to bacteriological status, immune status, and response to treatment.

General immunology in all three types of leprosy was studied, and surgical orthopaedics, physiotherapy, and footwear also studied. The procedures were studied and classified, and steady advances made in various procedures. Special investigations were made in field survey, plantar ulcers, extensively infected feet, dynamic foot-prints, protective appliances, and outpatient management of plantar ulcers. The children's clinic at Saidapet continued its mainly routine work, besides its important share in the investigation of DDS prophylaxis.

The Epidemiology and Statistics section studied genetic factors in leprosy, conjugal leprosy, examination of contacts of known patients, survey and re-survey for leprosy, and certain other aspects. It is interesting that re-survey covered 96% of the available population and detected 0·45 per mille in one year and 1·02 per mille over $2\frac{1}{4}$ years.

The Laboratory was very active in routine work and also carried out several useful investigations. For example it classified the histopathological findings according to Ridley & Jopling (*Leprosy Review*, 1962, **33**, 119–128), and made bacteriological studies per phagocytyzing leucocytes, and drug assays in body fluids etc.

The Welfare section made important work studies in education and occupation, and culture, recreation, and co-operation and rehabilitation.

This fascinating and useful report merits intimate study in the original.

(2). The Gambia Leprosy Control Project, 1965.

Mr Frank Mead, Lepra representative, is stationed at Mansakonko, and reports that this project in 1965 again concentrated on field work and is still handicapped by lack of proper headquarters, a hospital and laboratory facilities, and above all by a medical officer of its own. In July the post of medical officer (leprosy) was abolished so that no patients were issued with discharge certificates during the year. The last leprosy officer was Dr I. A. Susman who left in Jan. 1965. The Leprosy Control Officer, seconded from the British Leprosy Relief Association, has been on duty throughout the year and has carried out the administration of all the field work. There are two of the senior grade of Leprosy Inspector and eight Assistant Leprosy Inspectors. In January two Assistant Clinic Inspectors were recruited and trained and are now working in their stations. In addition there is a clerical assistant and several staff drivers. At the end of 1965 there were 11 landrovers (gifted by UNICEF plus four bicycles, and six landrovers were on weekly treatment circuits in the regions of Lower River Division, MacCarthy I. Division, and Upper River Division. Of the bicyles three are used on weekly circuits and the rest in reserve. There is one motor cycle in Brikama where the circuit is large. Allatento Leprosy Village one mile west of Bansant Hospital remains as the only such village treatment centre and a Leprosy Inspector was posted to the village to give daily supervision and the Leprosy Control Officer
visits. There was a visit of Dr Blanc of WHO to Bansang, Basse, and Mansakonko, Bathurst and other centres, and during 1965, the School Survey was followed up.

A section of statistics reveals that a total of about 5600 leprosy patients were under treatment and nil discharged with certificates. The lepromatous type of leprosy was 8·7% and the tuberculoid 91·3%.

From the report it is clear that (1) the control project needs a head, a medical officer of its own; (2) field work is nobly trying to cover the project but sadly needs a central leprosarium and laboratory.

(3). Annual Report, 1965, Leprosy Research Unit, Uzuakoli, Eastern Nigeria.

This report, the last to come from the pen of Dr S. G. Browne, who has been the Director of the Uzuakoli Leprosy Research Unit since 1959, reviews the problems of control in a country where great progress was registered both just before and immediately after the introduction of mass treatment with the sulphones. The number of new cases diagnosed is now approaching the number of discharges. Early lepromatous leprosy is no longer recognized by the laity. It is

vident that the threshold below which leprosy ases to be a public health menace is not yet nown.

Chemotherapeutic trials have again taken a rominent place in the activities of the Unit, anks to the co-operation of leprosy settlements Eastern Nigeria.

The phenazine dye, B 663 (Geigy) continues hold promise of being a useful product, orthy of investigation on a larger scale. A eries of patients on a lower daily dose (100 mg.) ave shown improvement at the same rate as ose in the previous series of 300 mg. daily. Once again, the virtual absence of episodes of cute exacerbation in patients with lepromatous eprosy has been noteworthy.

A small group of patients who had been ubject to persistent and prolonged exacerba- ion, all improved when given B 663, and aintenance doses of corticosteroids could be educed and eventually completely suppressed.

So far, there have been no examples of sudden eappearance of morphologically normal forms f *Myco. leprae* in these recent series of patients aking B 663.

As regards low-dose dapsone, it is now evident that doses of the order of 50 or 100 mg. weekly are effective, clinically and bacteriologically, in lepromatous leprosy. Resistant strains have not appeared in this régime. Studies are proceeding with low doses of dapsone in other types of leprosy.

Groups of patients with lepromatous leprosy at Uzuakoli and at Oji River are receiving a long-acting sulphonamide (Fanasil, Roche), with good effect. No cutaneous sensitivity has been noticed, and no instance of parallergic sensitization has occurred.

Other investigations have been carried out in the Unit during the year, as evidenced by the 23 publications listed. Dr Browne again travelled widely, presenting papers and giving lectures in four continents.

Since the report was compiled, we learn that Dr A. McKelvie has been appointed to succeed Dr Browne at Uzuakoli. Our best wishes go with him as he assumes the direction of the Uzuakoli Leprosy Research Unit, where John Lowe and Frank Davey did their outstanding work.

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Abstracts

A rational view of world leprosy. S. G. BROWNE, *Without the Camp*, Apr.–Jun. 1966, **278,** p. 32.

The author describes that the world leprosy problem, far from diminishing, is most probably increasing. The world population is increasing, particularly in countries where leprosy is prevalent. Everybody is living longer, including those who suffer from leprosy. Many people travel further afield in search of work. Overcrowding and low standards of hygiene affect more people than ever before, especially in those countries where leprosy is prevalent.

The proportion of leprosy patients under treatment remains low: in the world as a whole, only 1 leprosy patient out of every 5 has any chance of treatment for leprosy. For some years now, enough knowledge to control leprosy has been available, but this knowledge has not been applied. It is quite premature, and grossly misleading, to speak of leprosy as being 'on the way out'. A higher priority must be given to leprosy. There are two new reasons for hope: (1) Dr DHARMENDRA of Chingleput, S. India, has reported that the standard leprosy drug DDS will prevent the signs of leprosy developing in a high proportion of family contacts when given regularly by mouth over long periods. Welcome work is in hand to develop and confirm this finding: (2) KINNEAR BROWN has been studying BCG protection against leprosy in a high proportion of East African children. This work is being continued, as the test must be carried further in time. (Lepra has a leprosy control project just started in Malawi to show that this and other knowledge can be used to control leprosy in a reasonable period of time, and orthopaedic surgery and physiotherapy and rehabilitation have an important role in modern control in leprosy). There is a continuing challenge to constant reappraisal by all workers. Facile optimism is out of place, but hope and hard work are called for because of the recent advances and present trends.

2. **Absorption, Metabolism and Excretion of di-p-aminophenyl Sulphone (Dapsone) and di-p-aminophenyl Sulphoxide in Man,** by G. A. ELLARD, *Brit. J. of Pharmacology and Chemotherapy*, Jan. 1966, **22,** No. 1, p. 212.

The excretion in the urine of leprosy patients of di-p-aminophenyl sulphone (dapsone), di-p-aminophenyl sulphoxide, their acid-labile metabolites, and other diazotizable compounds was measured.

About 41% of the dapsone given is excreted as the free compound plus acid-labile conjugates, and 27% as compounds which are hydrolysed to dapsone-like substances by boiling with dilute acid. The absorption of the sulphoxide appears to be less complete than that of dapsone only about 55% of the dose being excreted in the urine as diazotizable compounds compared with 75% for dapsone. Considerable oxidation of di-p-aminophenyl sulphoxide to dapsone occurs in the human body and about a quarter of free amines excreted in the urine after dosage with the sulphoxide are due to dapsone.

The excellent absorption of dapsone previously reported by other workers is confirmed (75% and may be rather more). The author's findings suggest it is relatively slowly metabolized in man and that its anti-leprotic activity is due to the presence of the unchanged drug in the body. The chromatographic studies of JARDIN (1958) suggest that some of the antileprotic activity of the sulphoxide, but not necessarily all, is due to its conversion in the human body to dapsone.

3. **Recent Bact. Immunolog. and Pathol. Studies on Experimental Human Leprosy in the Mouse Foot Pad.** R. J. W. REES, of the National Institute for Medical Research, Mill Hill, London, N.W.7, Proceedings of LWM—AFIP Conference reported in *Internat. J. Leprosy*, 1965, **33,** 3, pt. 2, 646—655.

The author has demonstrated conclusively that human leprosy can be transmitted to the mouse foot pad. Multiplication of *M. leprae* depends on the size of the inoculum and is confined to the foot pad. So far identical infections have been produced with 35 strains of *M. leprae* obtained from previously intreated patients from different parts of the world; 27 from Malaysia, 6 from Burma, 1 from East Africa, 1 from the West Indies. Lepromatous patients provided 29, borderline 5, and reactional tuberculoid 1. Bacilli from patients treated 12 to 16 months with DDS nearly always failed to multiply in the mouse foot pad. A very high proportion of bacilli from these patients were degenerate and yielded irregular staining with carbol fuchsin. The foot pad infection can be inhibited by DDS, phenazine: B 663, Fanasil, and Madribon, and almost completely with Ciba 1906 and TB1. There is suggestive evidence that some *M. leprae* derived from patients on 2 years or more of treatment with Ciba 1906 are partially resistant to Ciba 1906 and show cross resistance to thiosemicarbazone. There has been definite confirmation that a very few patients with progressive leprosy, even after many years of treatment with DDS, are infected with DDS-resistant strains of *M. leprae.*

Detailed analysis of the histology of infected foot pads has revealed a very high proportion of healthy-looking bacilli are sited within striated muscle fibres, appearing as 'microcolonies'. This may be the main site of multiplication of *M. leprae* within the mouse foot pad. It has been shown that *M. leprae* inoculated into mouse thigh muscle can produce a similar picture of multiplication of the bacilli within striated muscle fibres. Studies with other strains of mycobacteria have shown no predilection for muscle fibres. Attempts have been made to diminish the

immunological response and preliminary findings are of significant enhancement in previously thymectomized mice and irradiated CBA mice. This perhaps may lead to a much more progressive and generalized infection with *M. leprae* in the mouse.

This paper by R. J. W. REES is fascinating for what it finds and the lines it suggests. He gives 25 references which suggest his valuable collaborators in this work, and it is hoped in the future they will continue their collaboration.

4. **Influencia de la Talidomida en la Reacción Leprosa.** (**Influence of Thalidomide in Lepra Reaction**) by Dr J. SHESKIN, of the Dermatological Department of the Hadassah University Hospital and its daughter hospital Jerusalem, Israel, whose Director is Prof. E. Sagher, *Revista Dermatologia Venezolana*, 1965, **4,** Nos. 3 and 4, p. 210—21.

The author gives the symptomatology of lepra reaction as follows:— pyrexia up to 40°C, shivering, sleeplessness, lack of appetite, vomiting, joint pains, muscle pains, bone pains, headache, abdominal pains, oedoma of the limbs and glottis, nephritis and enlargement of liver and spleen, orchitis, rhinitis and/or epistaxis, iritis and iridicyclitis, neuritis or polyneuritis, swelling of the lymphatic glands, skin lesions in the form of reactivation of pre-existing lesions and appearance of lesions similar to nodose erythema and/or multiform erythema, accompanied at times by vesicles and/or necrosis and/or ulceration. He reports 11 patients with lepra reactions who received treatment with thalidomide since 6 months ago. They all had lepromatous leprosy and had been under observation 3 months to 22 years. Thalidomide was given on 19 occasions to these 11 patients and placebo treatment on 10 occasions. There was rapid response in lepra reactions in all patients, both subjectively and objectively, and the improvement began within 8 to 48 hours of exhibition of thalidomide. By contract, placebo treatment was ineffective. Since the thalidomide treatment 7 patients appear to have improved in active lepromatous lesions: in one of these there had been no improvement with 19 months of sulphones. Studies of the lesions which seem to have improved in lepromatous patients will be carried on in bacteriology, histology, and immuno-allergy. The dosage given of Thalidomide was usually 400 mgm. daily. Duration and minimum effective dose will require study of a larger number of patients. Secondary effects of thalidomide were noted in a few patients, but did not necessitate cessation of treatment. The dangers of thalidomide in pregnancy are well known. Care was taken to exclude pregnancy. The author recommends the use of Thalidomide in the treatment of lepra reactions. (See 'Further Observation with Thalidomide,' by J. SHESKIN, *Leprosy Review*, Oct. 1965, **4,** p. 183 and comments p. 186—187.)

5. **Prophylactic value of DDS against leprosy – an interim report,** by DHARMENDRA, P. MAHAMEDALI, S. K. NORDEEN, and K. RAMANUJAM, *Leprosy in India*, Oct. 1965, **38,** No. 4.

The prophylactic value of DDS among intra-familial child contacts exposed to lepromatous and bacilliferous non-lepromatous cases is being investigated at the Central Leprosy Teaching and Research Institute, Chingleput, India, which is situated in the midst of a large belt of high endemicity of leprosy.

To begin with, a preliminary house to house survey was done in an area adjoining the Institute, covering a total population of a little over 213,000. This took about 1 year. A prevalance rate of 21 per thousand, and a lepromatous rate of a little over 14% was found. The total number of 'source' cases was 362, including 330 lepromatous cases and 32 bacilliferous non-lepromatous cases. A little over 700 healthy intra-familial child contacts (below 15 years of age) of these cases were recorded.

The healthy child contacts were divided into two comparable groups – the 'prophylaxis' and the 'control' groups.

The prophylaxis group has been receiving DDS in scheduled doses, and the control group, similar looking placebo tablets. The study has been conducted by the 'double blind method'.

All the 'source' cases have also been treated with therapeutic doses of DDS.

The study proper (after the survey which took a year to complete, and after some preparatory work) has now (August, 1965) been in progress for 2½ years, during which all the contacts of both the groups have been examined periodically and regularly.

During the course of study there had been certain deletions and additions in the number of contacts. The number of healthy contacts at the start of the study was 689. Of these, (291 belonging to the prophylaxis group, and 294 to the control group) had been treated for the full period of observation. The present report is based on an analysis of the findings in these 585 contacts.

During the period of observation, 43 patients with leprosy have been recorded in the 585 contacts. Of these cases, 14 have been in the 291 contacts in the prophylaxis group, giving an incidence of 4.81%; and 29 in the 294 contacts in the control group, giving an incidence of 9.86%. This difference is found to be statistically significant at 2% level.

It is therefore tentatively concluded that, under the conditions of the present investigations, administration of DDS to healthy child contacts of leprosy patients has been found to have a protective value against the disease.

The protective value is, however, apparent only after 9 months of the prophylactic treatment; during the first 9 months there was no difference between the prophylaxis and the control groups regarding the incidence of the disease.

Further, there appears to be a relationship between the protective value of DDS and the age of the contact at which the prophylaxis treatment is first started. In the study under report, the prophylactic treatment was found to be of definite value in the contacts up to 10 years of age, but it had no value in contacts above that age. This would emphasise the need for starting prophylaxis treatment soon after exposure to infection; in intra-familial contacts it would mean starting the treatment at as early an age as possible.

There is some evidence to suggest that in the contacts developing the disease, the prognosis may be better in those under DDS prophylaxis than in others.

DDS prophylaxis was also found to be more effective among males. The reason for this observed difference is not clear and no inference can be drawn from this particular finding.

It is proposed to continue the present study for a little longer, and then to analyse the findings from the various aspects before coming to a final conclusion.

Once the effectiveness of prophylactic treatment with DDS is finally established, further studies will have to be planned to get information on various practical points regarding its general application in the control of the disease, and regarding other related matters.

Since the 2¼ years the findings of an additional period of 28 to 30 months have become available and the results strengthen the finding of the value of prophylactic DD in contacts.

This paper is of great value and its intimate study is recommended. There are 10 informative tables and 3 maps and one table in the addendum which extends the period of observation by 28–30 months.

6. **Antigenic Studies of Other Fungi and Mycobacterium Leprae,** by R. J. W. REES, K. R. CHATTERJEE, J. PEPYS, and ROSEMARY D. TEE, *Amer. Review of Respirat Diseases*, Dec. 1965, **92**, Part 2, pp. 139—149.

This report has 9 illustrative figures, 1 table, and 1 diagram. The present studies of the authors indicate the special types of problem which arise during the investigation of the immunological aspects of an infection such as leprosy, in which the causal organism cannot be cultured *in vitro*. Nevertheless it has been possible to use a whole-bacillus antigen, isolated from infected tissues, and also possible, by absorption tests, to distinguish the mycobacterial constituents from the contaminating tissue antigen constituents. Their present studies on leprosy patients were confined to serological tests with culture filtrates, in which it has been shown that circulating precipitating antibodies can be detected, and that these antibodies are predominantly anti-polysaccharide. In future it will be possible to test these sera against disintegrated *M. leprae*, and also investigate whether antigens are produced by protein constituents of mycobacteria.

The serological studies on *M. lepraemurium* multiplying in cell culture have shown for the first time that intracellular mycobacteria release a soluble mycobacterial antigen, polysaccharide in nature, which can readily escape from the host cells into the culture medium. The sera used in these present studies were provided by Dr M. F. R. WATERS from his patients at the Sungei Buloh Leprosy Research Unit, Malaysia.

7. **Observations on the Inoculation of M. leprae in the Foot Pad of the White Rat,** G. R. F. HILSON, M.D., St George's Hospital Medical School, London, S.W.1., L.W.M.—A.F.I.P. Conference, *Internat. J. of Leprosy*, 1965, **33**, No. 3, pt. 2, p. 662..

The author used the Shepard technique and inoculated the foot pads of white rats with human bacilli from two different human sources of leprosy. Methods of microbial enumeration showed that limited multiplication of the acid fast mycobacteria occurred in the two cases, generally similar to mouse foot pads and the histopathology was also similar. Also carried out were two further serial passages of the isolates.

8. **Studies on M. lepraemurium and M. leprae in Tissue Culture,** ELIZABETH W. GARBUTT, M.S., National Institute for Medical Research, Mill Hill, London N.W.7., present address, Dept. of Biochemistry, University of Alberta, Edmonton, Alberta, Canada, L.W.M.—A.F.I.P. Conference, *Internat. J. of Leprosy*, 1965, **33**, No. 3, pt. 2, p. 578.

The author's studies showed that continuous multiplication of *M. lepraemurium* can occur in rat fibroblasts that are subcultured regularly, and there is also some evidence that *M. leprae* will grow in such regularly subcultured cells, both human and rat, provided the cultures are kept a sufficiently long time to overcome an apparent bacillary lag phase of between two and four months.

The cell type used for growing rat leprosy bacilli may be important, for the author found that multiplication did not occur in mouse monocytes, mouse fibroblasts (L strain), HeLa cells, nor monkey kidney cells. Growth of *M. lepraemurium* was achieved only in cells derived from animal species susceptible to the infection. The medium is also of importance in growth requirements, for bacilli were destroyed in cultures of 14pf cells in cell serum and peptone while bacilli in 14pf grown in cord serum and Hank's solution ($CS_{50}H_{50}$) are capable of continuous multiplication.

With *M. leprae* some multiplication has been obtained in rat fibroblasts and human diploid cells, and tissue culture-grown bacilli from the fibroblasts have been passaged successfully in mouse foot pads. The common denominator in these experiments has been a human element, either human cells grown in medium containing non-human serum, or rat cells grown in human cord serum. This raises the possibility that growth of *M. lepraemurium* might be obtained in cells other than these from rats or mice. Grown in tissue culture *M. lepraemurium* has shown all the characteristics of its parent organism and it is suggested that tissue-culture *M. leprae* would do the same.

Letter to the Editor

Dear Sir,

With some hesitation, I enter the arena where two doughty opponents, Dr R. G. Cochrane (*Lep. Rev.* **36**, 196) and Dr Harry L. Arnold (Letter to the Editor, *Lep. Rev.* **37**, 129) are already engaged in a wordy battle concerning the value of nasal smears in leprosy

'There is no "never" and no "always" in medicine.' (Of course it is not the *taking* of the smear, but the results of the microscopical examination of the suitably stained material obtained by this procedure, that is important in this context). I have records of a patient in whom the pre-lepromatous macules were bacteriologically negative at a time when the nasal smears were teeming with *Myco. leprae*, many of which were in typical globi (*Lep. Rev.* 1959, **30**, 174).

As for the "danger" of the procedure, I have yet to see any harm resulting from some thousands of examinations carefully performed under my supervision.

As I indicate in an article shortly to appear in the International Journal of Leprosy, bacterioscopic examination of the septal mucosa of patients with lepromatous leprosy may be of real but limited value. In the broad-nosed Bantu, with wide nares and exposed mucosa, nasel smears may provide valuable data. They frequently show both a higher Bacterial Index and a higher Morphological Index than smears from the ear lobes or the skin lesions. Globi, too, may be more numerous there than elsewhere. Not only globi, but morphologically normal and degenerate forms may persist in the nasal mucosa after they have disappeared from other sites smeared.

Thus, while we all really agree that the microscopical examination of material obtained by nasal smearing is almost never necessary to establish a diagnosis of leprosy, it is not infrequently valuable in certain circumstances in regard to both therapy and epidemiology.

S. G. Browne
The Leprosy Study Centre,
57a Wimpole Street,
London, W.1.
27th May, 1966

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Book Reviews

Proceedings of a Conference on Research Problems in Leprosy, Washington, May 1965, sponsored by the Leonard Wood Memorial and the Armed Forces Institute of Pathology, were published as Part 2, **333** of the *International Journal of Leprosy.*

This valuable record of the conference occupies 794 pages, and uses the double-column style of printing for the first time in the International Journal of Leprosy, which is very clear and easy to read. The illustrations are numerous and clear and very attractive. This valuable book calls for intimate perusal and the records of discussions should be noted. There were 8 sessions in this conference at Washington, and the list of authors and subjects will stir great interest and stimulate the gratitude of all:—

BROWNE, S. G., The Variegated Clinical Pattern of Leprosy, p. 400; COCHRANE, R. G., The Need for Bringing Leprosy Research into Universities, p. 403; FELDMAN, W. H., Gerhard Henrik Armauer Hansen. What did he see and when? p. 412; GOLDMAN, D. S., Intracellular Mechanism for the Control of Respiration and Biosynthesis in Mycobacteria, p. 417; KALLIO, R. E., Physiologic Implications of Hydrocarbons and Lipids in Mycobacteria and Related Forms, p. 441; FASAL, P., Differential Diagnosis of Leprosy, p. 454; NICKERSON, W. J., Environmental Control of Microbial Growth and Morphogenesis, p. 466; ULRICH, J. A., Observations of Fungal Growth *in vitro* and *in vivo*, p. 477; JANSSENS, P. G., Leprosy Teaching and Research in Institutes of Tropical Medicine, p. 488; MOULDER, J. W., Metabolic Capabilities and Deficiences in the Rickettsiae and the Psittocasis Group, p. 494; HART, P. D'ARCY, Further Analysis of the Growth (Elongation) Phenomenon of *Mycobacterium lepraemurium in vitro* and Relevant Studies with *Mycobacterium leprae*, p. 504; REICH, C. V., Approaches to Cultivation of *M. leprae* in a New Laboratory, p. 527; JOB, C. K., An Outline of the Pathology of Leprosy, p. 533; SHEPARD, C. C., Stability of *Mycobacterium leprae in vitro* and Temperature Optimum for Growth, p. 541; CHATTERJEE, B. R., Growth Habits of *M. leprae.* Their Implications, p. 551; HANKS, J. H., The Cultivation of *Mycobacterium leprae.* Search for a Rational Approach, p. 563; TOLENTINO, J. G., Acute Manifestations of Leprosy, p. 570; GARBUTT, E. W., Studies of *M. Lepraemurium* and *M. leprae* in Tissue Culture, p. 578; CHANG, Y. T. and NEIKIRK, R. L., *Mycobacterium lepraemurium* and *Mycobacterium leprae* in Cultures of Mouse Peritoneal Macrophages (Preliminary Results), p. 586; MØLLER-CHRISTENSEN, V., New Knowledge of Leprosy Through Paleopathology, p. 603; PATTYN, S. R., Use of the Mouse Foot Pad in Studying Thermo-resistance of *M. leprae*, p. 611; WIERSEMA, J. P., BINFORD, C. H., and CHANG, Y. T., Nerve Involvement. Comparison of Experimental Infections by *M. leprae* and *M. lepraemurium*, p. 617; IYER, C. G. S., Predilection of *M. leprae* for Nerves. Neurohistopathologic Observations, p. 634; REES, R. J. W., Recent Bacteriologic, Immunologic and Pathologic Studies on Experimental Human Leprosy in the Mouse Foot Pad, p. 646; SHEPARD, C. C., Considerations of the Applications of the Foot Pad Technic in Leprosy Research, p. 657; HILSON, G. R. F., Observations on the Inoculation of *M. leprae* in the Foot Pad of the White Rat, p. 662; BINFORD, C. H., The Inoculation of Human Leprosy in the chimpanzee. Initiation of a Long-term Project, p. 666; IMAEDA, T., Electronmicroscopy. Approach to Leprosy Research, p. 669; BAYNE-JONES, S., Leprosy Research. An International Problem, p. 689; CONNOR, D. H. and LUNN, H. F., *Mycobacterium ulcerans* Infection. (With Comments on Pathogenesis), p. 698; HUERTA, R., Some considerations of the Adequacy and Validity of Data on Leprosy in the Americas, p. 710; TAYLOR, C. E., ELLISTON, E. P. and GIDEON, H., Asymptomatic Infections in Leprosy, p. 716; GUINTO, R. S., Problems Requiring Solution Through Field Studies, p. 732; BLUMBERG, B. S., Leprosy Research Through Genetics, p. 739; LECHAT, M. F., Methodology of Genetics. Study in the Epidemiology of Leprosy, p. 744; DHARMENDRA, Leprosy Research in India, p. 752; BROWNE, S. G., Some Clinical Problems Awaiting Solution by Research, p. 759; TOLENTINO, J. G., Approach to Clinical Research, p. 763; WILLIAMS, T. W. *et al.*, Leprosy Research at the National Institutes of Health. Experience with B. 663 in the Treatment of Leprosy, p. 767; LONG, E. R., Summation of Conference, p. 778

'Insensitive Feet' by PAUL W. BRAND, C.B.E., F.R.C.S., F.A.C.S., 2/6. The Leprosy Mission, 7 Bloomsbury Sq., London, W.C.1, is a pocket booklet of 86 pages, with 45 drawn illustrations, a useful bibliography and 4 Appendices on practical matters, such as Appendix 3, which describes steps in making a moulded-insole clog from a last.

This booklet is timely for it will be gratefully received by all physiotherapists and surgeons who seek to share this great leprosy revolution. The combination of exposition of principles and practical measures will make this booklet a necessary possession, and it is a genuine pocket-book. The contents begin with a clear description of the normal foot and at once go on to discussion of the foot in leprosy, and a study of trophic ulceration of the foot. Damage to the tarsal bones is given similar careful study of causal principles and preventive and curative measures. Footwear is next studied and its great role outlined in the preventive and curative attack on ulcers in extremities in leprosy. For fitting new footwear the value is described of pressure footprints. The necessary amputations are described with the warning that to amputate a limb is a failure but not to amputate may be worse. This booklet is a 'must'.

'Watch Those Eyes'. Eye Complications in Leprosy. by MARGARET BRAND M.B.B.S. price 1/6. The Leprosy Mission 7 Bloomsbury Sq. London W.C.1

This booklet of 31 pages is written by Mrs Brand and is a welcome concomitant to her husband's book 'Insensitive Feet' as it draws attention to the neglect of the eyes in leprosy and points out how much can be done for them in prevention and care. It also should receive a great welcome and join the other in the pocket as it is a pocket size.

'Danger and Safety in Leprosy' by M. ITOH, M.D. and PAUL W. BRAND, C.B.E., F.R.C.S., a cartoon booklet, price 2/- The Leprosy Mission, 7 Bloomsbury Sq., London, W.C.1.

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