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PRINCIPAL CONTENTS

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LEPROSY REVIEW

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Contents

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Editorial

We have been informed by the Gandhi Memorial Leprosy Foundation, Wardha, Maharashtra, India, that it has decided to start refresher courses for general medical practitioners to make them leprosy-conscious so that they may detect leprosy and treat it in the course of their general work. The Foundation is also planning to hold a Leprosy Health Education Training Course for paramedical workers for 2 months from 1 April, 1968. The course will cover the main activities of the paramedical worker, the education of society, contacts with general practitioners, general help to patients and surveys to detect early leprosy patients. Under these headings a very comprehensive programme has been prepared and every aspect of the activities considered.

The plans of the Gandhi Memorial Leprosy Foundation and the article by Bhola Nath in the Journal of the Indian Medical Association abstracted on page 91 are encouraging signs that doctors are taking an interest in helping leprosy in the right way. This is very important action from India and it is hoped that doctors throughout the world will follow suit.

OBITUARY. As we go to press we learn that Stanley Stein, Founder-editor of *The Star*, passed away at Carville on 18 December, 1967. We wish to take this opportunity to pay tribute to one who worked so unceasingly for the good of leprosy patients.

Ninth International Leprosy Congress
LONDON

SEPTEMBER 16-21, 1968

Plans are well advanced for the Congress, despite the inevitable setbacks and difficulties.

ABSTRACTS are pouring in—but many authors have sent one copy (instead of four) and have failed to respect the limit of 200 words, or the deadline (31 March).

AUTHORS of papers will have been notified whether their papers have been accepted for reading in full or reading by title only.

DISCUSSANTS will be chosen by the respective Chairmen of sessions from among authors of proffered papers and from the floor.

STANLEY G. BROWNE, M.D.
Secretary-General.

Lep. Rev. (1968) **39**, 2, 61-66

A Preliminary Report on the Use of B663 in the Treatment of Chinese Leprosy Patients with Chronic Reaction

A. GRACE WARREN, M.B., B.S., D.T.M. & H. (SYD.)
Hay Ling Chau Leprosarium, Hong Kong

One of the gravest problems in the treatment of the patient with leprosy is the severe reactions which may occur while under therapy. This type of reaction resulting in permanent deformity, blindness, scars and disability is more prone to occur in the lepromatous patient.

A number of methods of treatment of reaction exist at the present time, none of which is completely satisfactory. Corticosteroids have often been resorted to, but though they may produce dramatic improvement in the acutely ill they increase the problems of therapy in the long term chronic reaction patient.

It has been apparent that some anti-leprosy drugs themselves can precipitate or accentuate the reaction and so it has become the practice to reduce the anti-leprosy drug in patients with a reaction. This presents a serious problem in patients with active disease.

During the past 10 years increasing attention has been given to a phenazine derivative known as G 30-320 GEIGY (B663) 3-(p-chloranilino)-10-(p-chlorphenyl)-2, 10-dihydro-2-(isopropylimino)-phenazine which was noted to have some effect against *M. tuberculosis* in laboratory animals. This action was not of importance in man but it now appears that B663 may be very effective against other Mycobacterial diseases, including leprosy.

In 1965 several articles suggested that B663 could prevent reactions and also suppress them when fully developed. The drug also had a beneficial therapeutic effect in eliminating the bacillus. However, the drug did tend to produce a pigmentation of the skin.

In November, 1966, a small supply of the drug was received and a patient was selected for trial.

Patient 1 (M.W. F/25)—Diagnosed as borderline leprosy in 1955, her lesions subsided rapidly and after about 2 years' therapy the treatment was discontinued. By 1961 she was an obviously lepromtous type patient with a B.I. of 5.2. On admission here she improved fairly rapidly for 9 months with a B.I. fall from 5.2 to 4.3 and then reaction started and continued relentlessly. B.I. fall was from 4.3 in June, 1963, to 3.8 in November, 1966, and most of 1966 she spent in bed with bouts of ulceration, iritis, neuritis, bone pain and high fever.
When B663 commenced, with 300 mgm. weekly, her B.I. was 3.8, M.I. 0%. Within 3 months the B.I. had fallen to 3.0 and she had only occasional ENL, no pain, no ulceration, no fever and no iritis. She was lightly pigmented but not obviously so. She returned to light work and later (after 6 months on B663) to full work. By the end of 6 months her B.I. was 2.5 and she was obviously pigmented but generally very well except for mild crops of ENL without pain or fever, occurring about once a month.

Requests were received from other patients who wished to have B663. Obviously the pigmentation was no real barrier to the patients with chronic reaction who wished to get better. The success with this patient, and the requests by other patients, prompted a trial on a larger scale.

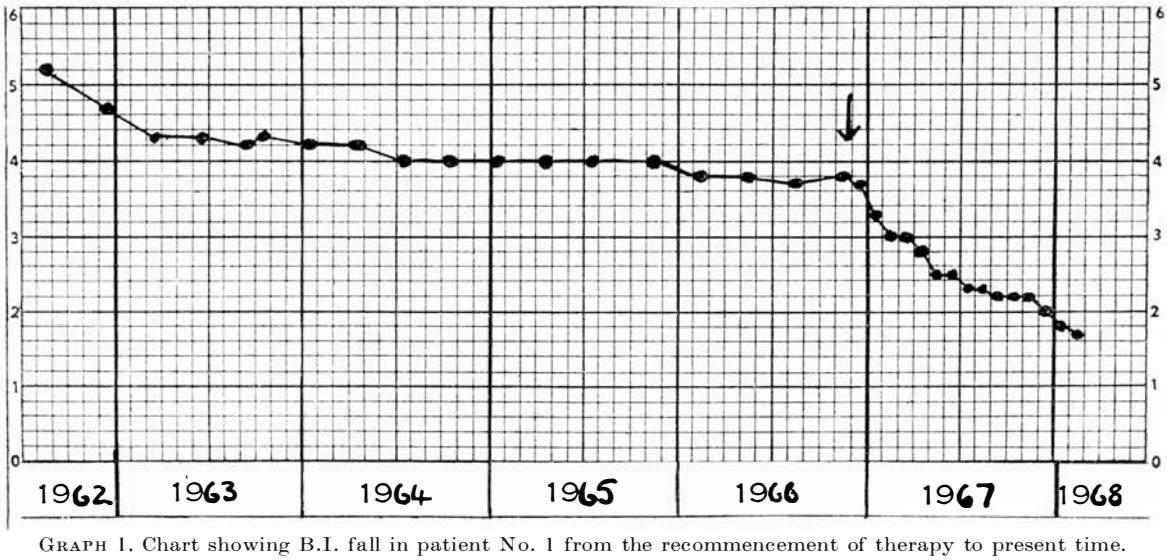
AIM OF THE TRIAL

It was decided that this suppressive effect should be further examined and also that, if possible, the minimum dosage that will control reaction should be ascertained. With this in mind, supplies of B663 were applied for and patients selected.

SELECTION OF PATIENTS

All patients under in-patient care were examined, taking into consideration:

(1) Reaction type, severity and frequency.
(2) Progress so far under treatment—especially rate of fall of B.I.
(3) Drugs used previously for leprosy therapy.



GRAPH 1. Chart showing B.I. fall in patient No. 1 from the recommencement of therapy to present time. Arrow indicates commencement of B663 at dose of 300 mgm. per week.

A total of 30 patients were selected as suitable. All had been under in-patient treatment for at least 2 years with reaction, so their previous responses and reaction pictures were well known. All had M.I. of 0% solid rods, except one patient who had recently relapsed.

They were all basically lepromatous though some had atypical features. None had a definite positive lepromin test.

Five had previously had treatment with good results and then ceased therapy against advice and relapsed, becoming highly positive.

Four were on prednisolone at the beginning of the trial.

Four patients had had leprosy for at least 20 years—the longest for 25 years with intermittent therapy.

Eight had pulmonary tuberculosis though all of these were now controlled; 3 were not receiving TB drugs any longer and the other 5 were still receiving INAH and PAS.

Ten patients had previous episodes of gastritis or frank gastric ulceration. One had had a gastrectomy for duodenal ulceration.

Two were diabetics, being controlled on Diabinase, in whom reaction was associated with diabetic instability.

PROCEDURE

All other anti-leprosy drugs were stopped when B663 was started. At about the time B663 was commenced colour photographs were taken, under controlled conditions, of each patient to record colour change.

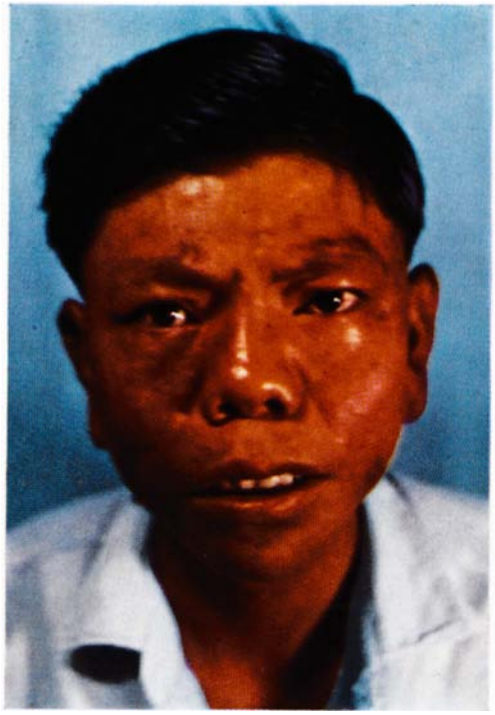
During the trial, skin smears were taken each month by the same experienced technician and a report given on Bacillary Index (Ridley reading) and Morphological Index. Haemoglobin and urine tests done each month; full blood counts, E.S.R. serum proteins, electrophoresis, and liver function tests were done each 3 months.

Most patients commenced therapy with 300 mgm. B663 per week. The more severely reacting patients, including some on Prednisolone, commenced on 600 mgm. B663 per week.

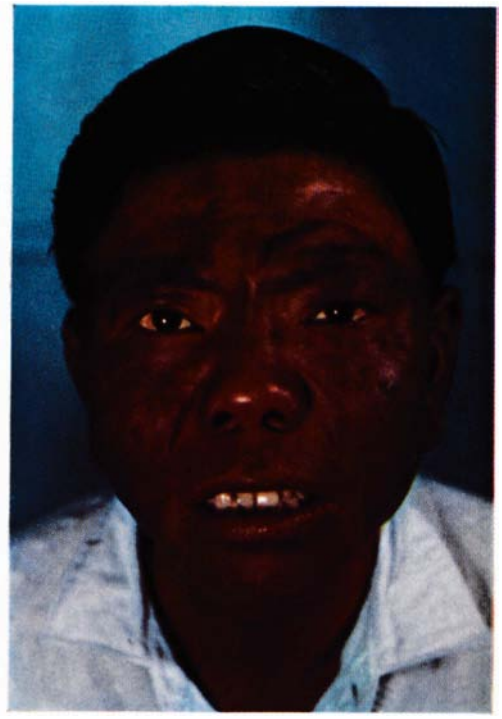
No change was made in other drugs given for preventing or reducing reaction. A careful check was kept on all patients in the trial and if reaction continued the dosage of B663 was increased until the level was found where reaction was no longer present, and then the other anti-reaction drugs were reduced and once the patient had been reaction free for one month at least the B663 was gradually reduced.

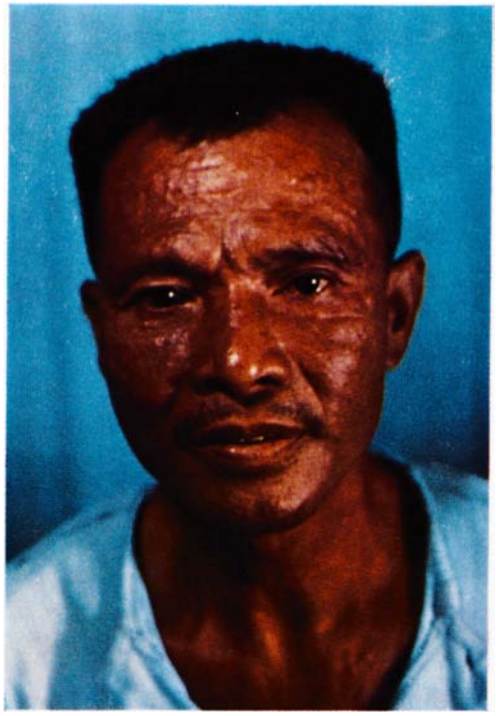
It was found that most patients became reaction free on 600-900 mgm. per week, a few requiring 1,200 mgm. per week, while a number of patients did very well on 300 mgm. per week.

Patient 11
Pre-B663 therapy.



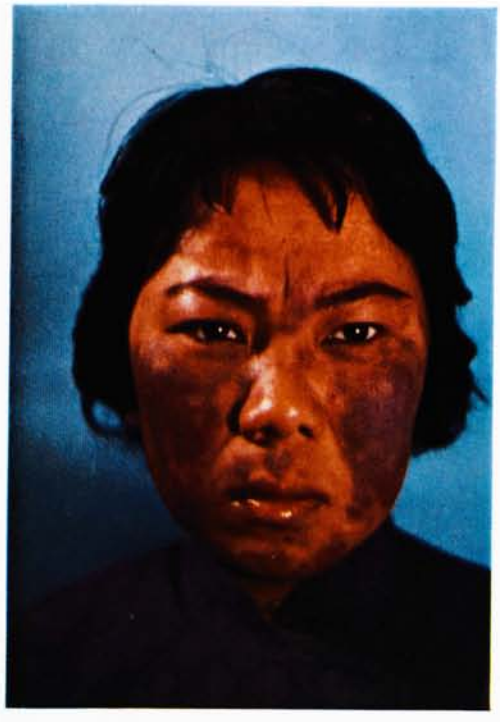
Patient 11
After 6 months B663 therapy, showing very dark pigmentation.



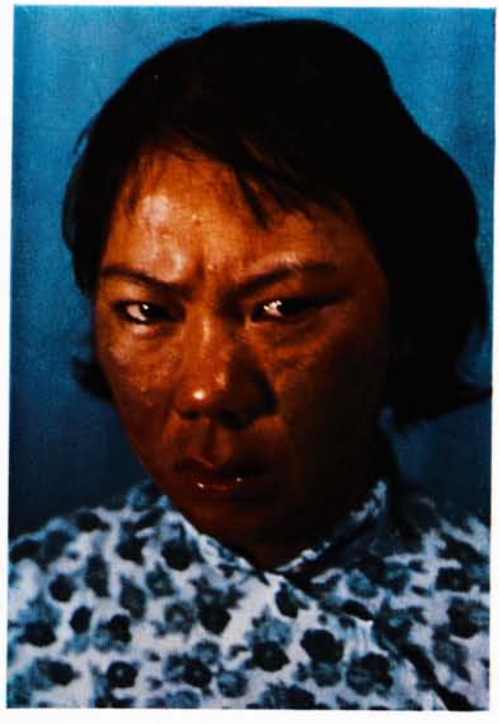


Patient 13
Pre-B663 therapy, showing nodules on face.

Patient 13
After 6 months B663 therapy, showing marked clearing of the skin, and light to medium pigmentation.



Patient
Pre-B663 therapy.



Patient 15
After 6 months on B663, showing marked variation in pigmentation of the skin.

GROUPS

The 30 patients selected fit into 5 main groups.

A. Four patients on prednisolone.

B. Sixteen patients with generalised chronic reaction (excluding mainly neuritis)—skin lesions, ENL and generalised reaction, iritis, bone pain and fever. Some of these were also receiving drugs for treatment of tuberculosis.

C. Seven patients whose reaction was mainly neuritis—chronic pain and tenderness, with or without paralysis.

D. Two patients with diabetes as a pre-precipitating cause of reaction—placed in separate group because of interlink of reaction and uncontrolled diabetes.

E. One case of relapse—new lesions, rising skin smear with return of normal morphology.

RESULTS AFTER 6 MONTHS OF B663 THERAPY

Group A

Four patients on prednisolone, 3 female and one male. Average weight 99 lbs. Three out of 4 patients were easily weaned off prednisolone within 4 months once adequate B663 was given to control reaction.

All 4 patients are obviously much better clinically and in all there has been some improvement in B.I. but this has not been marked.

Patient 1 (F/30)—On prednisolone 10 weeks only but had previously had several courses—B.I. fall 3.3 to 3.2, clinically better, ulcers healed and less pain when on B663, 1,200 mgm. per week.

Patient 2 (F/46)—On prednisolone from September, 1966, requiring 15 mgm. daily to control reaction and prevent ulceration. Received 900 mgm. B663 weekly as maximum. Now off prednisolone for 2 months and reaction free—B.I. fall 2.0 to 1.7.

Patient 3 (M/35)—Many courses of prednisolone over last 10 years—was on 5-10 mgm. daily from November, 1965, to October, 1967. Received 900 mgm. B663 weekly and now off prednisolone and reaction free—B.I. fall 2.2 to 1.7.

Patient 4 (F/35)—Long history of irregular therapy and courses of corticosteriods. On prednisolone from June, 1966, till now—up to 20 mgm. daily at times. Severe reaction on October, 1967, was complicated by infected ulcers and B663 increased to 1,200 mgm. weekly in November, 1967. Mild reaction continued till December. Prednisolone is now reduced to 5 mgm. daily and no reaction. B.I. fall 2.8 to 2.5 in 6 months is above average for this patient, whose physical condition is much better than it has been for the last 18 months.

Group B

This group comprised 16 patients. These were: 4 females aged 28-40 years and weight average 96 lbs., and 12 males with ages 21-53 years and weight average 114 lbs.

The group is divided into sub-groups according to the amount of B663 needed to control the reaction.

(*a*) Those patients requiring 300 mgm. B663 per week:—There were 3 patients (2/F, 1/M) who required only 300 mgm. of B663 per week. The B.I. fall was excellent in each patient, 3.7 to 3.0, 2.7 to 1.7 and 1.5 to 0.5. None of these patients became deeply pigmented. One who had previously tended to have ulcers and pain constantly rapidly improved and has not had ulceration or pain for the past 5 months.

(*b*) Those patients requiring 600 mgm. B663 per week:—There were 9 patients in this group (3/F, 6/M). The B.I. fall also very good, averaging 0.9 over 6 months, with a maximum fall of 3.3 to 1.5 in the 6 months. In some of this group the pigmentation was very obvious though in others it did not appear to be unnatural.

(*c*) Those patients requiring 900 mgm. B663 per week:—There were 3 patients in this group, each of whom had severe lepromatous leprosy of long standing. All showed good clinical improvement and decreasing reaction and pain once the higher dosage was reached. The B.I. fall was 2.5 to 2.3, 3.0 to 2.0 and 3.7 to 2.8. The third patient had previously shown a B.I. fall of only 4.8 to 3.7 in 27 months while constantly suffering reactions, pain, iritis and neuritis. He is now reaction free.

(*d*) One patient who required 1,200 mgm. B663 per week:—
A patient who had stopped his therapy in 1960, when he was previously progressing well. After 18 months without treatment he returned because of reaction and a high B.I. He spent the next 5 years in and out of reaction, with fever, pain, ulceration and neuritis—frequently very depressed and uncooperative. Since starting B663 his general condition has been improving and since he took 1,200 mgm. weekly he has been reaction and pain free and has become co-operative and cheerful: in short a changed personality.

This group included a number of patients receiving therapy for pulmonary tuberculosis who are still taking INAH and PAS. There is no obvious difference in their response to that of the others in the trial.

TABLE 1 **Progress of Patients in Group B**

Patient No.	Sex/Age	Minimum Duration of Leprosy years	Duration of Regular Therapy years	Duration of Reaction years	Maximum Dose of B663 mgm.	At Commencement Weight lbs.	At Commencement B.I.	B.I. at 3 months	At 6 months Weight lbs.	At 6 months B.I.
6	M/50	13	3	3	300	105	2.7	2.0	123	1.7
7	F/35	23	5	5	300	92	1.5	1.0	102	0.5
8	F/60	16	3	3	300	88	3.7	3.2	98	3.0
9	F/43	5	3.25	3.5	600	105	2.7	2.2	112	1.8
10	M/21	7	4	4	600	108	3.3	2.3	122	1.5
11	M/27	8.5	4	3	600	109	2.0	1.8	118	1.5
12	M/35	6	4.25	5	600	106	3.5	3.2	107	2.8
13	M/49	7	5	5.5	600	125	1.5	1.2	132	0.8
14	M/44	6	5	5	600	1 11	2.5	2.0	124	1.3
15	F/28	9	3.25	3.5	600	95	3.5	3.0	106	2.5
16	F/55	5	4	5	600	108	1.2	0.8	107	0.5
17	F/49	6	4	3.5	600	130 (oedema)	4.0	3.8	111	3.5
18	M/53	30	2.25	4	900	130	3.7	3.0	154	2.8
19	M/31	12	5	4	900	118	2.5	2.3	120	2.3
20	M/38	13	11	5	900	120	3.0	2.3	126	2.0
21	M/38	10	4	4	1,200	88	3.0	2.7	98	2.2

TABLE 2 **Progress of Patients in Group C**

Patient No.	Sex/Age	Minimum Duration of Leprosy years	Duration of Regular Therapy years	Duration of Reaction years	Maximum Dose of B663 mgm.	At Commencement Weight lbs.	At Commencement B.I.	B.I. at 3 months	At 6 months Weight lbs.	At 6 months B.I.
22	M/41	11	2.5	4	600	114	2.5	2.0	126	1.5
23	M/41	25	5	5	600	109	2.3	2.0	116	1.7
24	M/33	12	6	6	600	106 (oedema)	2.3	1.8	104	1.7
25	F/36	8	6.5	6	900	96	1.5	1.0	110	0.5
26	M/40	4	3.5	4	900	105	2.0	1.8	103	1.7
27	M/26	9	3	5	900	102	3.5	3.2	104	3.0
28	M/37	15	3	3	1,200	108	4.2	3.5	106	3.0

Group C

Mainly neuritis.

This group comprised 7 patients (6 male and one female) in whom the main form of reaction was neuritis and in whom the B.I. fall was slow.

(*a*) Those patients requiring 600 mgm. B663 per week:— There were 3 patients in this group and their B.I. fall was better than usual—average fall 0.7 in 6 months.

(*b*) Those patients requiring 900 mgm. B663 per week:— There were 3 in this group and the B.I. fall averaged 0.6 in the 6 months. All became free of neuritis.

(*c*) One patient who required 1,200 mgm. B663 per week:—
This dose was not given in the first 3 months, and it is difficult to assess if he really needed to receive such a high dose as he has an unstable personality. His B.I. fall has been dramatic, from 4.2 to 3.0 in 6 months, whereas previously the fall was from 4.5 in 1964 to 4.2 in 1967.

In all these patients there has been no increase in obvious muscle weakness or loss since commencement with B663. One of these patients with a bad history of irregular therapy required 900 mgm. to control neuritis. He stopped his own B663 therapy in December for 2 weeks and neuritis returned. It required a further 4 weeks to eliminate pain again and a few weeks later, when pain returned, it was discovered he was only taking 100 mgm. daily instead of 200 mgm. as ordered. Since resuming the higher dose pain has again disappeared.

Group D

Two diabetics, both men.

Mr. G, aged 65, weight 166 lbs.

Mr. K., aged 46, weight 106 lbs.

Mr. G. had received intermittent therapy for over 20 years. On admission even small doses of routine drugs aggravated reaction, except Vadrine. B.I. fall from 5.0 to 4.3 over 3 years with M.I. fall of 25% to 0%. On B663 the B.I. fall was from 4.3 to 3.8. The patient's diabetes is stable, and he is obviously better and says so; he has had no real reaction since he commenced B663 and urine has remained sugar free. However, nodulation of his hands has returned over the last 3 months since Streptomycin was stopped.

Mr. K. has diabetes (controlled by Diabinase), pulmonary tuberculosis and a gastric ulcer and has also had chronic reaction with ulceration and iritis since 1965. B.I. has fallen 3.3 to 3.0 on B663 at 600 mgm. weekly but the patient generally feels very well and no problems with diabetes or gastric ulcer.

Group E

Male patient aged 35.

He commenced therapy in 1962 but was always reactive and had early attacks of neuritis and acute paralysis. Smear came down gradually between 1962 and 1967 and then became stationary at B.I. 1.8 in spite of continued drug therapy. In July, 1967, new lesions appeared with an increase in B.I. from 1.8 to 4.0 and return of over 10% normal form bacilli. 900 mgm. B663 weekly resulted first in a M.I. fall from 10% to 0% in 12 weeks and then a B.I. fall from 4.0 to 3.7. Clinically he is well, with no return of neuritis or reaction.

SIDE EFFECTS

Apart from the skin pigmentation no undesirable complication has occurred. Only one patient complained of gastric discomfort, but this eased when he took B663 with his meals instead of 'on an empty stomach'.

No appreciable difference in response has been noticed in patients under treatment for tuberculosis or other intercurrent disease.

Some patients complained of marking of their clothes. Reddening of the urine was not constant and only occurred in patients on high dosage, but some women stated that while washing their hair the water became red.

DISCUSSION

All patients selected had set patterns of neuritis and generalised reaction which had persisted for at least 2 years prior to the commencement of this study, and which had not responded to routine methods of therapy. In 6 months on B663 the progress of these patients has been extraordinary. Some of them rapidly became reaction free and remained so. A few developed reaction in the first few weeks and some continued with mild reaction until the dosage was raised and an adequate dosage was given. Only one patient had had a bad reaction and this reaction was less severe than previous reactions that she had experienced.

The E.S.R. for many of the patients showed a dramatic fall, e.g., 94 mm. to 30 mm., 108 mm. to 20 mm., and 120 mm. to 33 mm., but in some patients the E.S.R. did not change significantly.

Initially many patients showed abnormal Albumin-Globulin ratios and changes in the proportions of serum proteins, but this ratio tended to correct itself and the serum proteins resumed their normal proportions.

Most patients showed increase in appetite and increase in body weight.

As the change from anti-leprosy drug to B663 was the only common factor, it would appear that B663 is, in fact, effective in reducing and controlling reaction and at the same time it appears to encourage a more rapid rate of clearance of the acid-fast debris as shown by the increased rate of fall of the B.I. in so many patients. It has previously been shown that the B.I. fall in Chinese lepromatous patients can be expected to average 1.0 per annum in the B.I. range 6.0 to 1.0. Hence a fall of greater than 0.5 in the 6 months under review exceeds the estimated average.

Subjectively the patients are much improved, they seem happier, more cheerful and more inclined to activity. This is mirrored particularly by the better attendance at physiotherapy and general co-operation.

DOSAGE LEVEL

It was found that 9 patients required 900 mgm. weekly, 13 patients required 600 mgm. weekly and 3 patients required only 300 mgm. weekly to control reaction. There were only 4 patients who required 1,200 mgm. weekly and of these 4 there were 2 who had received prednisolone for a long time. The one patient who received 1,800 mgm. weekly was a very chronic patient of heavy weight and on an mgm./lb. basis his dosage correlates well with the others. Hence it would appear that the average Chinese patient

of about 90-120 lbs. weight can be controlled on 600-900 mgm. weekly depending on the severity of the reaction. It has also been noted that once reaction is controlled it is sometimes possible to reduce the dosage level of B663, though if the dose is reduced very quickly reaction will reappear, but can again be controlled by increasing the dosage of B663 again.

CONCLUSIONS

Chronic lepra reaction in typical and atypical lepromatous leprosy in Chinese patients can be controlled by the use of B663.

Patients previously on corticosteroids can be weaned off them while on B663.

The patients' general physical condition improves, they look better, eat better, sleep better and even say they are better.

The dosage appears to be between 600 and 900 mgm. per week in patients of average weight (90-120 lbs.) to control reaction, but that once reaction is controlled the dosage may be reduced and the patient will continue to progress well.

The Bacillary Index falls rapidly suggesting that B663 assists in the clearance of the acid-fast debris, but the rate of fall differs in different patients.

There is a correlation between the weekly dosage of B663 and the severity of the skin discolouration. Ths patients on low dosage showed less discolouration and patients who had showed deep pigmentation showed some fading of the pigmentation when the dosage was reduced. It has been reported (Ahrens) that the pigmentation, considered one of the main disadvantages, is reversible and so is not a contra-indication to the use of this drug. Certainly skin discolouration is not a disadvantage in an institution, or to patients who know of the complications and disappointments of other therapeutic drugs and who wish to recover their health as soon as possible.

There certainly seems to be a place for the regular use of B663 in the treatment of chronic reaction patients and investigations and trials should be continued to clarify the situation and the optimum dosage.

SUMMARY

A study of the effects of B663 in a group of 30 Chinese leprosy patients with chronic reaction has been commenced. Over a period of 6 months it appears that B663 is of definite value in this type of patient and that skin discolouration is not a major problem.

ACKNOWLEDGEMENTS

Special thanks go to Messrs. J. R. Geigy S.A. for generous supplies of B663 and for much helpful advice, and to Dr. S. G. Browne who assisted with the selection of patients and other details. Also to the patients and staff who have co-operated in this trial.

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Presence of *M. leprae* in the Nipple Secretion and Lumina of the Hypertrophied Mammary Gland

IN A CASE OF GYNAECOMASTIA ASSOCIATED WITH ACTIVE AND UNTREATED LEPROMATOUS LEPROSY

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A few weeks after the discovery of *M. leprae* in human breast milk which was described in a previous paper[1], a man with very active and untreated lepromatous leprosy associated with a moderate degree of gynaecomastia, presented himself at my clinic. Being on the look-out for further ways of confirming the presence of *M. leprae* in the breast milk of a lactating woman suffering from untreated lepromatous leprosy, it occurred to me that if 2 lines of investigation in this man proved to be positive, they could provide such confirmation, or at any rate, relative information of a highly suggestive nature. These 2 lines of investigation were:—

1. To search for the presence of *M. leprae* in the secretion which it might be possible to express from this man's very enlarged and elongated right nipple. If bacilli were found in the secretion, then
2. Sectioning of this man's hypertrophied mammary gland would probably result in being able to demonstrate the presence of *M. leprae* INSIDE THE LUMINA of the mammary ducts.

Both these investigations were made and both proved to be positive.

Relevant extracts of my clinical notes and a description of how these 2 investigations were made now follow.

Right Breast: The nipple is much enlarged and stands out from the areola almost 2 cm.; nearer its summit the diameter is about 8-10 mm. and where it joins the areola its diameter is quite 15 mm.; the areola is deeply pigmented and its area is increased. Adjoining the nipple, a nodule approximately 3.5 cm. in diameter is palpable beneath the skin.

Left Breast: This nipple, too, is enlarged to about half the size of the right but it is not connected with an underlying palpable nodule.

(See Figs. 1 and 2. *Note:* The picture is a little confused by the fact that he was also suffering from Von Recklinghausen's disease.)

Skin Slit Scrapings from 6 sites revealed: B.I. 2.8; M.I. 65%.

Nasal mucous smear revealed: B.I. 3; M.I. 90%.

Smear of secretion from right nipple: The nipple and surrounding skin were first thoroughly cleansed with several sterile swabs soaked in ether, the idea being to remove possible surface bacilli. Firm manipulation of the nipple resulted in the emergence on the summit of a bead of serum-like secretion about the size of 1½ office pinheads. This was taken up by application of a glass slide, forming a smear of almost 1 cm. in diameter. Result of systemic search of approximately 400 fields revealed 20 well stained acid-fast bacilli, all of which were in good solid rod form.

BIOPSY

The right nipple and all the underlying breast nodule were removed and fixed in Formol-Zenker's solution for 40 hours before transfer to commercial spirit.

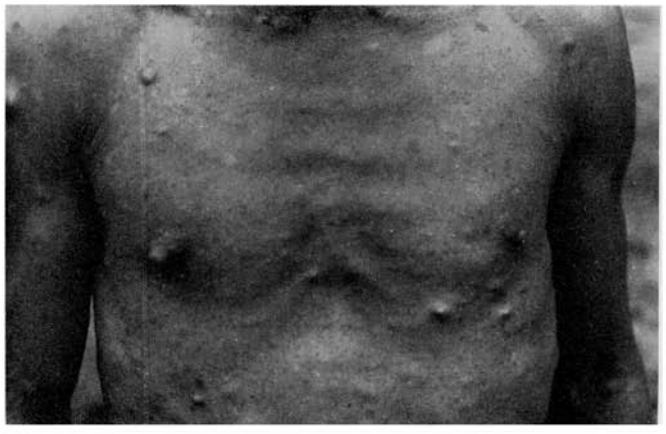

FIG. 1
Showing enlargement of the nipples, especially the right.

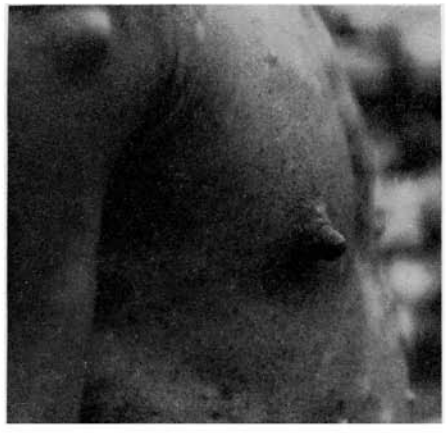

FIG. 2
Showing only the right enlarged nipple.

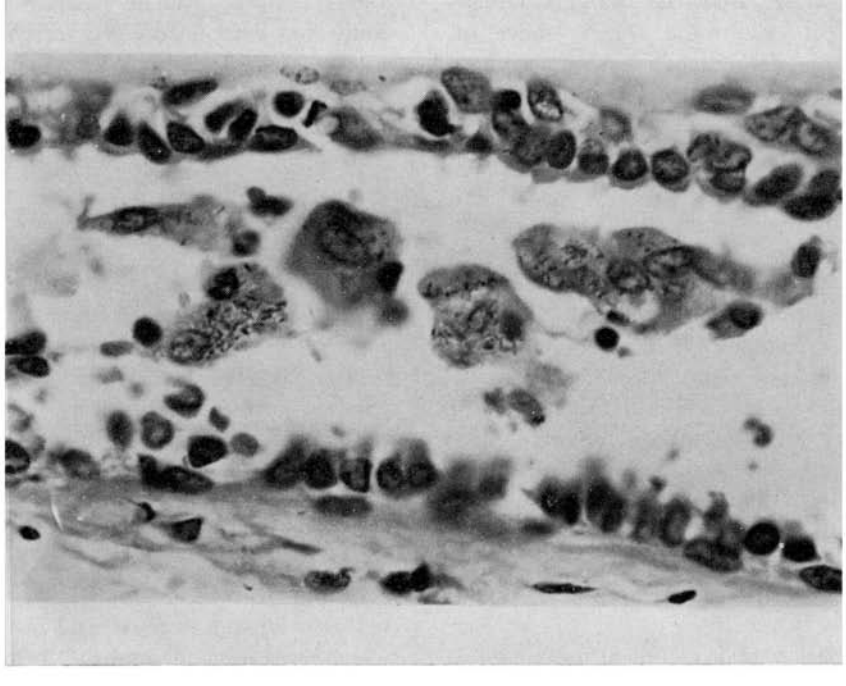

FIG. 3
Longitudinal section of a milk duct in the nipple showing *M. leprae* in and amongst the cells of the duct wall and in cells shed into the lumen.

HISTOPATHOLOGICAL REPORT

I am indebted to Dr. Douglas Harman of the Leprosy Study Centre in London for the following report on the breast tissue (and also for the accompanying microphotograph, Fig. 3):—

Triff Stain

This is a longitudinal section of nipple with some of the underlying mammary gland tissue from a male with gynaecomastia. There is a fairly generalized cellular infiltration of the nipple tissue and of the skin—that is, of the more superficially placed tissues—but in the lobular part of the gland the infiltrate is much less and is confined to the neurovascular bundles.

The infiltrating cells are histiocytes with a considerable number of lymphocytes and plasma cells. There is no particular arrangement of these cells and no appreciable cytoplasmic change in the histiocytes. Fairly numerous acid-fast bacilli are seen in all the nerves and in some of the blood vessels throughout the section, and in the histiocytes in the infiltrated areas. Some bacilli are also present in the smooth muscle of the nipple and scattered throughout the nipple stroma.

An occasional organism is to be found in the cells lining the ducts in the lobular part of the gland or in cells shed into the lumen. In the infiltrated part of the nipple, however, bacilli are seen in much greater numbers in a few of the nipple ducts. They are between and apparently in some of the cells lining the ducts and also in cells and cellular debris shed into the lumen of the ducts.

A large proportion of the bacilli throughout the tissue would appear to be in solid staining form. Many of them are in clusters or in small globus formations.

There is very slight cellular infiltration of the nerves.

Diagnosis and Comment

This is a biopsy of a nipple with a portion of the underlying mammary gland tissue from a patient with active leprosy and gynaecomastia. It is lepromatous with some atypical features. There is no evidence of any effect of therapy. There is infection of some of the ducts of the mammary gland, particularly in the nipple area, with the extrusion of *M. leprae* into the breast secretion, presumably either naturally by the disintegration or shedding of the duct epithelial cells or by trauma.

DISCUSSION

The presence of *M. leprae* in the nipple secretion and in the lumina of the hypertrophied mammary gland of a man suffering from highly active and untreated lepromatous leprosy is highly suggestive that the same histopathological picture would obtain in the mammary gland of a lactating mother suffering from lepromatous leprosy.

For the help of others who may desire to check these findings I would like to stress the following points:—

1. The secretion from the male nipple may be so little that it could be easily missed.
2. It may require quite firm manipulation to express it.
3. The most favourable circumstances in which to confirm these findings is in a patient who is suffering from *highly active and untreated* lepromatous leprosy.
4. Quite a number of sections of a biopsy may have to be cut before finding one which demonstrates the bacilli IN THE LUMINA.

SUMMARY

The finding of *M. leprae* in the secretion expressed from the enlarged nipple of a man with gynaecomastia and highly active and untreated lepromatous leprosy led to the removal of his hypertrophied mammary gland and the demonstration of the presence of *M. leprae* in the lumina of the gland ducts. It is suggested that the same histopathological picture would obtain in the mammary gland of a lactating woman suffering from lepromatous leprosy. Some suggestions designed to help those desiring to check these findings are given.

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Lep. Rev. (1968) **39**, 2, 71-74

Bacterial Density in the Skin in Lepromatous Leprosy as Related to Temperature

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INTRODUCTION

For many years observers[1 2 3 4 5 6 7 11 12] have noted that the tissues most heavily involved in lepromatous leprosy are those expected to be relatively cool, whereas warmer areas of the body are relatively spared. Heavily involved areas include the anterior eye, upper respiratory mucosa, external ear—particularly the earlobes, and the extensor extremities, while the posterior eye, lower respiratory mucosa, internal ear, and flexor aspects of the extremities are relatively or completely spared from clinical involvement. The so-called 'immune areas' for lepromatous involvement, namely, the midline of the lumbar back, upper eyelids, perineum, axillae, and, to some extent, the antecubital and popliteal fossae are all areas in which skin temperature would be expected to be warm.

The present paper deals with an effort to demonstrate that at least one of the 'immune areas' in lepromatous leprosy is indeed warmer and furthermore contains fewer bacilli than a more heavily involved area.

MATERIAL AND METHODS

Five patients with diffuse lepromatous leprosy, as nearly 'pure' lepromatous, or LL in type[9], as could be determined by clinical, bacteriological and histopathological examination, were selected for study. Each was newly admitted to the U.S. Public Health Service Hospital, Carville, Louisiana, and had been on no anti-leprosy treatment for at least 4 years prior to admission.

Each patient was exposed to an ambient temperature of 19.5°C (67.1°F) for a period of 30 minutes, following which 3 thermographs (Model M-1A, Barnes Engineering Co., Stamford, Conn.*) were taken of his lumbar back. The exact skin temperature of each of 4 sites in the lumbar back was further determined with a hand-held radiometer (Medical thermometer Model MT-3, Barnes Engineering Co., Stamford, Conn.*) as an average of 3 readings. The 4 sites measured were determined as follows and marked with ink: the 2 lateral back locations were 5 cm. (2 inches) above the iliac crests, and 10 cm. (4 inches) from the midline. The midline locations were directly over the lumbar spine, 5 cm. (2 inches) and 15 cm. (6 inches) above a line joining the iliac crests.

Following the temperature measurements, the

* Manufacturer's name is for the purpose of identification only and is not meant to imply endorsement by the U.S. Public Health Service.

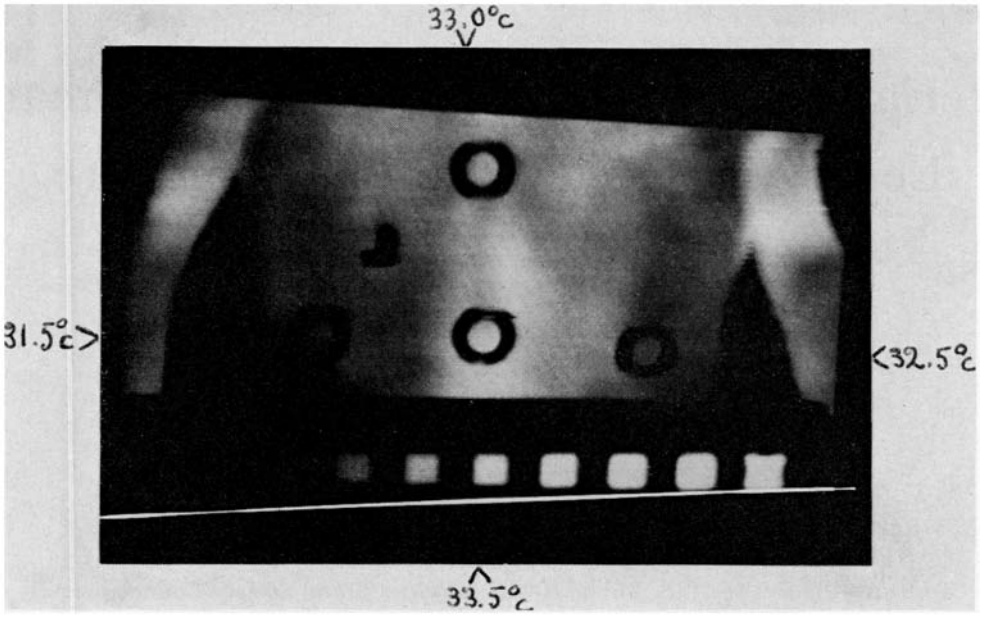

FIG. 1
Patient 2802 — B—77.5 S—17.0
14th April, 1967
20.0°C 69-62

ink-marked sites were biopsied using 3 to 5 millimetre punch biopsies, taking care that each biopsy was taken perpendicular to the skin surface and extending well into the subcutaneous fat, insuring as far as possible that a full thickness of dermis was submitted.

Each specimen was routinely processed and submitted blindly to the pathologist (Dr. Mansfield) and read as to the (*a*) absolute thickness of the dermis in millimetres, (*b*) percentage of the dermis involved in lepromatous infiltrate, (*c*) bacterial index (B.I.), in terms of the Ridley logarithmic scale[8], that is, 6+ equals to greater than 1,000 acid-fast bacilli per oil-immersion field; 5+ equals to 100 to 999 acid-fast bacilli per oil-immersion field; 4+ equals to 10 to 99 acid-fast bacilli per oil-immersion field; 3+ equals to 1 to 9 acid-fast bacilli per oil-immersion field; 2+ equals to 1 to 9 acid-fast bacilli per 10 oil-immersion fields; 1+ equals to 1 to 9 acid-fast bacilli per 100 oil-immersion fields; 0 equals no acid-fast bacilli per 100 oil-immersion fields; and (*d*) morphological index (M.I.)[13,14], or the percentage of bacilli which stain uniformly on routine acid-fast staining. From this data a biopsy index[8] was calculated for each biopsy as a product of the percent dermis involved and the bacterial index.

Results were analysed for significance by means of the t-test for paired measurements.

RESULTS

A characteristic thermograph was obtained in the lumbar back in each case, one of which is shown in Figure 1. The lighter coloured areas are warm, and the darker areas cool.

The exact skin temperature obtained for each of the 4 sites is given in Table 1.

The results of skin biopsies taken from each of the 4 sites are given in Table 2.

TABLE 1

Skin Temperature

Left Lateral	*Lower Midline*
31.33°C	33.83°C
31.66	33.33
31.50	34.41
32.08	32.75
33.50	33.00
Mean 32.01°C (89.62°F)	Mean 33.46°C (92.23°F)
Right Lateral	*Upper Midline*
31.66°C	34.00°C
32.16	33.16
32.41	33.75
31.50	32.83
32.66	33.50
Mean 32.08°C (89.74°F)	Mean 33.45°C (92.21°F)
Mean of Left and Right Lateral Sites combined 32.05°C (89.69°F)	*Mean of Upper and Lower Midline combined* 33.46°C (92.22°F)

DISCUSSION

The lumbar back was chosen for the present study because of the observed differences in clinical involvement between the midline and lateral aspects; and because this area represents a more or less uniform skin area, subject to similar degrees of protection by clothing, similar exposure to trauma, similar anatomical and physiological characteristics, etc. The sites selected were above the belt line to minimize any effect of habitually worn clothing.

The skin biopsies revealed a similar thickness of dermis in all sites; therefore the biopsy index[8] is proportional to the actual number of *M. leprae* organisms present in each area. The outstanding difference in the sites is the warmer temperature of the midline sites (mean of 33.46°C.) compared with the lateral sites (mean of 32.05°C.). This difference is statistically significant with a p value of less than 0.01. As measures by the biopsy index[8] the midline sites (mean of 0.88) have significantly fewer bacilli

TABLE 2

Results of Skin Biopsies

	M.I.†	*Thickness of Dermis*	*% Dermis Involved*	*B.I.*‡	*Biopsy Index*		*M.I.*†	*Thickness of Dermis*	*% Dermis Involved*	*B.I.*‡	*Biopsy Index*
			Left Lateral						*Lower Midline*		
	0.6%	1.40 mm*	30%	4.5+	1.35		0.3%	1.79 mm	11%	4.0+	0.44
	0.4	4.16	42	5.0	2.10		0.5	2.19	9	4.5	0.41
	2.0	2.89	33	5.0	1.65		1.0	2.10	8.5	4.0	0.34
	5.0	4.81	50	4.8	2.40		3.0	3.11	30	4.6	1.38
	1.5	4.97	37	5.0	1.85		1.0	4.73	25	4.8	1.20
Mean	1.9%	3.65 mm	38.4%	4.86+	1.87		1.16%	2.78 mm	16.7%	4.38+	0.75
			Right Lateral						*Upper Midline*		
	0.4%	1.31 mm*	33%	5.0+	1.65		0.4%	2.41 mm	23%	4.0+	0.92
	0.8	2.36	33	5.0	1.65		1.0	2.92	15	4.8	0.72
	1.5	2.54	36	5.0	1.80		0.8	2.80	13.5	4.5	0.61
	2.5	3.54	65	5.0	3.25		1.3	3.37	40	4.5	1.80
	1.5	4.29	35	4.5	1.58		2.0	4.46	22	4.5	0.99
Mean	1.34%	2.81 mm	40.4%	4.9+	1.99		1.1 %	3.19 mm	22.7%	4.46+	1.01
			Means of combined Lateral Sites						*Means of combined Upper and Lower Midline Sites*		
	1.62%	3.23 mm	39.4%	4.88+	1.93		1.13%	2.99 mm	19.7%	4.42+	0.88

* Incomplete thickness of dermis submitted † Morphological index ‡ Bacterial index

than the lateral sites (mean of 1.93) with a p value of less than 0.01. This demonstrates that at least one of the clinically 'immune' areas of the body in lepromatous leprosy actually is warmer and contains quantitatively fewer bacilli than an adjacent 'non-immune' area. These observations correlate reasonably well with Shepard's finding for the optimum temperature for the growth of *M. leprae* in mouse foot pads of from 27 to 30°C.[10] and his observations on the areas most heavily involved clinically[11].

The present findings seem to offer additional support for the concept that in lepromatous leprosy, in which there is presumably little if any ability to localize the infection, at least one of the major factors determining the distribution of the disease process in any given patient is the optimum temperature for the growth and multiplication of the bacilli.

SUMMARY

Five untreated patients with 'pure' lepromatous leprosy were studied by determining the skin temperature at 4 sites on the lumbar back, 2 in the midline and 2 laterally, followed by a skin biopsy in each area. The midline sites were significantly warmer and contained significantly fewer organisms than the cooler, more heavily infected lateral sites. It would appear that the clinically 'immune' areas in lepromatous leprosy represent warmer skin areas in which *M. leprae* would prefer not to grow.

ACKNOWLEDGEMENTS

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Lep. Rev. (1968) **39**, 2, 75-78

Preventive Rehabilitation in Leprosy

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PART III
PRINCIPLES OF PRACTICAL APPLICATION

The overall strategy of approach to the problem of leprosy has changed drastically during the past decade. The era when sanatoria, care homes or leprosy settlements seemed to be the mainstay has given way to survey, examination and domiciliary treatment and leprosy control programmes.

To get a patient to the stage where the disease is 'arrested' and to reduce the reservoir of infection in the community and thus reduce the incidence of the disease in the next generation is basically a right approach to any infectious disease. Yet often the pendulum seems to have swung too far. In the planning of such programmes and the facilities offered therein, the care of the individual patient is often ignored.

The approach to the problem of individual patient care and care of his disabilities in such a leprosy treatment and control programme is vastly different from the one that is adopted in sanatoria with long-term patients. This approach is largely untried and is not provided for in the majority of such programmes.

We have already stated that preventive rehabilitation should be our first aim. Returning to his home and his usual occupation with a knowledge and discipline to preserve his anaesthetic limbs, is not only a practical solution in the developing countries, but also ideal for a leprosy patient whose special need includes social acceptance and the need to retain his family ties.

At the Schieffelin Leprosy Research Sanatorium in the domiciliary treatment and leprosy control programme a method of individual patient care has been planned and evolved during the past 3 years with great success. The domiciliary treatment programme undertaken by the institution in the Gudiyatham Taluk covers an area of 481 square miles with an estimated mid-year population in 1967 of 410,000. Of these, 90,000 are in urban areas. We have so far covered the rural area in terms of census and survey and examination of over 90% of the rural population. So far 7,100 patients have been registered and treated at 41 peripheral clinics in the villages throughout the taluk. The attendance rate is now at 75%. The main hospital caters for short-term patient care for conditions needing intensive medical and surgical care.

There are 2 distinct aspects to the carrying out of a comprehensive programme of preventive rehabilitation and re-education for resettlement. First is the principle and methodology adopted in dealing successfully with the problem of each patient with either early or severe disability.

Second is the problem of practical application of such methods to serve patients in a domiciliary treatment programme, where a large number of patients are scattered over a wide area and have only short periods of contact with hospital personnel.

INDIVIDUAL CARE

'Living with anaesthetic limbs' is the chief disability in leprosy. The life-long discipline and constant vigilance needed to live with anaesthetic limbs requires, firstly, the patient's

intelligent understanding of the problem. Thus group and individual education plays a prominent role. The second requirement includes both practice and discipline that is necessary to translate this knowledge into daily activities.

The problem of communication where the majority of patients are mostly illiterate needs special study. Simple audio-visual aids and practical demonstrations repeated over and over again, each time varying the theme and method of approach to break the monotony are important. Practical illustrations using an injured limb or a 're-educated' patient as a live subject often has quite an impact. When such education is combined with intensive care of even minimal injury or trophic ulceration of anaesthetic limbs, the large majority of patients respond eagerly and acquire sound knowledge and understanding of the problem of anaesthesia.

The problem of application of this knowledge in the day-to-day activities is the most important step in rehabilitation. In our experience, we have found that quite a large majority of patients need a period of intensive practical training with individual supervision to teach them to work with their anaesthetic limbs without further injury. Such a period of training has given excellent results and the majority of patients do not need more than one such training period.

The organisation of such a programme, with individual and group education, followed by intensive, individual, practical training courses to cover the large number of widely scattered patients in a typical leprosy control programme needs a new approach. Analysis of disability among the patients in control programmes has given figures varying from 20% to 25%. In a typical domiciliary treatment clinic most of the patients get the medications once in 3 months. It is then possible to group the disabled patients to attend the clinic on a special 'rehabilitation day' when a little less than a quarter of the patient-load of the clinic will be invited to attend. To this clinic should be sent a team consisting of a social worker, physiotherapy technician, and a cobbler. They can examine the limbs, apply plaster immobilisation when needed, issue footwear, use audio-visual aids and practical demonstrations and supply adapted implements suitable for routine work and activities of daily living. Careful recording of disabilities and injuries sustained and the patients' occupational status is important to enable intelligent organisation and planning of such a programme.

Those who are found to be sustaining repeated injuries and those who are either underemployed or unemployed due to their disabilities need to be brought to the main hospital for intensive practical training courses.

The programme at the main hospital needs to be carefully planned and organised to maintain maximum efficiency and to use minimum time. It is important that a leprosy hospital is planned to cater for anaesthetic limbs both in its construction and in its daily routine and discipline. Whereas such planning is universally accepted for other groups of disabled patients such as paraplegics or spastics, this is still a new approach in leprosy where anaesthetic limbs are such a devastating disability to patients.

It is thus important for example that in a leprosy hospital no patient with anaesthetic feet is ever seen without suitable microcellular rubber footwear at any time. Daily morning inspection of hands and feet and daily oil massage for dry skin should be a part of the daily routine. Every patient should learn suitable first aid methods to deal with fresh injuries, blisters or fissures. Every patient should be encouraged during meal time to use protected utensils and a spoon.

In addition to these routine activities in hospital, practical classes in the activities of daily living, like cooking, washing and cleaning need to be conducted for small groups of patients. In our experience we have found that at least 8 to 10 such classes are essential for each patient. Vocational re-training demands a lot of time and patience from the rehabilitation team. But once a patient is 'broken in' and gets the idea and gets accustomed to the use of adaptations, one has the gratifying prospect of having solved a life-long problem. Effective vocational re-training, in our experience, needs

about a month of regular work under daily supervision. A farmer, for instance, needs to carry out the entire range of activities involved in tending his farm, using the same methods and implements that he is likely to use when he returns home.

In dealing with anaesthetic limbs, the emphasis has often been on adaptations and modifications of handles and tools. *It has been our experience that important as these are and often essential for a significant number of patients, by far the most important requirement is the patient's understanding of the problem of anaesthesia and a period of intensive practical training under supervision.* Large numbers of these patients have returned to full employment with no further incidence of trophic ulceration. What is significant is that a large number of them do not use the adaptations and modifications recommended and supplied to them once they leave the hospital and go to their usual places of work. Often a simple device like a piece of cloth was used and found adequate to protect the hand against injury by heat or pressure. We have thus found it important to shift our main emphasis from adaptations and modifications of the tools to the education and training of the patient.

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I would like to thank my colleagues, particularly those in the Physiotherapy and Occupational Therapy Departments for conscientious and devoted service, which has enabled us to study these problems and find some of the answers.

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Leprosy and Tuberculosis in Kenya

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DISTRIBUTION OF LEPROSY

Leprosy is endemic in most, if not all, parts of Kenya. The prevalence of the disease, however, varies considerably. Ross Innes (1948) found in surveys in West Kenya prevalence rates of more than 3%, in Coastal Areas 0.7% and in parts of Central Kenya only 0.1%-0.4%. Harden Smith (1957) found marked differences in prevalence rates in surveys in the western parts of the country. The numbers of patients registered in treatment centres near Lake Nyanza and near the Uganda border are high; the numbers are low in East Kakamega, in the Nandi territory and in the Kipsigis area. No patients are registered in Kisii.

It appears that there is a rather well defined border between areas of high and of low prevalence of leprosy. This border runs approximately from Mount Elgon southwards to Kisii. In the south this border coincides with the division between the Nilotic Jaluo and the Bantu Kisii, and this suggests a tribal factor. In the north, however, the border line divides the Abaluhia territory showing that possible tribal factor is of secondary importance.

PREVIOUS STUDIES ABOUT THE RELATIONSHIP BETWEEN LEPROSY AND TUBERCULOSIS

Grounds (1960) has compared the numbers of leprosy patients on registers in treatment centres in South Nyanza with the numbers of registered tuberculosis paitents. He found that where numbers of registered leprosy patients were high, the numbers of registered tuberculosis patients were low and *vice versa*. The differences were highly significant statistically.

It seems that the differences in prevalence of leprosy in West Kenya can be adequately explained by differences in prevalence of tuberculosis.

Most leprologists agree that there is an epidemiological relationship between leprosy and tuberculosis but about the nature of this relationship much uncertainty still exists. The hypothesis of a simple antagonism between the 2 diseases seldom fits the facts. In New Guinea (Leiker, 1960) a significant correlation was found between the prevalence of tuberculosis and of leprosy. The differences in prevalence rates, however, were correlated with differences in type and age distribution. Such differences are not conspicuous in West Kenya. Secondly, it is not certain that numbers of leprosy patients and tuberculosis patients registered in treatment centres truly represent the prevalence rates of the 2 diseases. It was found that the staff of treatment centres is insufficiently trained in the diagnosis of leprosy with the result that among the registered patients several were found who did not have leprosy. It was also found in surveys that many patients do not attend treatment centres. Obviously the diagnostic facilities in regard to tuberculosis are limited in many of the rural treatment centres. Early, subclinical, closed cases of tuberculosis can easily be missed. Further studies of the situation are therefore indicated.

LEPROSY SAMPLE SURVEYS

It is already 10 years since the last leprosy

surveys in Abaluhia territory were carried out. Two new sample surveys were carried out in order to verify that the well defined border between areas of high and low prevalence of leprosy still exists.

The population surveys were preceded by a house to house census. The first survey was carried out at Mukweya, North Wanga location, Kakamega district. In 1957 Harden Smith found a prevalence of leprosy of 1.2%. About 450 patients are registered in the local treatment centre. In the present survey 1,089 people were examined and a total of 19 patients were found, giving a prevalence of 1.7%.

The second survey was carried out at Musena, Isukha location, Kakamega district, only about 30 miles east of the previous survey. In 1957 Harden Smith *et al.* found only a few patients with leprosy. Very few patients are registered in the local treatment centre.

In the present survey 650 people were examined and only one was found to have leprosy, a prevalence of 0.15%. It is concluded that the situation has not changed essentially since 1957.

Special skin clinics were held in various Health Centres and dispensaries in Southern Nyanza. In the Jaluo territory many leprosy patients, including many new ones, were seen. In the Health Centre at Kisii no leprosy patients were seen and the local attendant claimed that there is no endemic leprosy in Kisii.

The findings confirm the existence of a well defined border between areas of high and of low prevalence of leprosy in West Kenya.

FURTHER CORRELATION STUDIES OF LEPROSY AND TUBERCULOSIS

Large scale intensive leprosy surveys have not been carried out recently in West Kenya. No attempt was therefore made to base this study on absolute prevalence rates. The numbers of registered patients in treatment centres and the results of previous sample surveys, however, permit the division of the area into parts with a definitely high prevalence of leprosy, an intermediate prevalence and a definitely low prevalence of this disease.

In regard to the prevalence of tuberculosis, instead of basing this study on numbers of registered tuberculosis patients, an analysis was made of the large number of tuberculin tests in school children carried out by teams of the Tuberculosis Unit.

The tests were carried out with 5 T.U. P.P.D., according to the Mantoux technique. Size frequency distribution histograms were made. The histograms of tests in individuals of various age groups and from various areas were bimodal. From the size distribution of the reactions it was concluded that most reactions of less than 10 mm. are non specific and that most reactions of 10 mm. or more are caused by tuberculosis infection. The results are summarized in Table 1.

In 6,340 Jaluo children of 5-14 years, living in an area with a definitely very high prevalence of leprosy the tuberculin index is 14%.

In 12,819 children of the same age group, living in Kakemega district in areas where the prevalence of leprosy is much lower, the tuberculin index is 11%.

In 2,231 children of the same age group, living in Kisii where the prevalence of leprosy is definitely very low or the disease is not endemic, the tuberculin index is only 8%.

The findings do not show a clear correlation between the prevalence of leprosy and of tuberculosis. The tuberculin index is even somewhat higher in the area with the highest prevalence of leprosy.

The findings do not exclude the possibility that tuberculosis has influenced the leprosy situation. The effect of tuberculosis may well be obscured by other factors influencing the epidemilogy of leprosy. It is, however, concluded that the distribution of tuberculosis alone does not offer a satisfactory explanation for the distribution of leprosy in West Kenya.

Assessment of the influence of tuberculosis in Kenya is difficult because it cannot be based on prevalence rates of leprosy only. Information about the type distribution of leprosy is needed and such data are not available. Studies in New Guinea (Leiker, 1960) suggest that mild, high resistant tuberculoid leprosy may be

TABLE 1

Prevalence of leprosy and reactions to 5 T.U. P.P.D. in children in West Kenya

Area	*Prevalence of Leprosy* %	*Reactions to Tuberculosis*								
		5-9 *years*			10-14 *years*			15-19 *years*		
		Nr. tested	*Nr. pos.*	% *pos.*	*Nr. tested*	*Nr. pos.*	% *pos.*	*Nr. tested*	*Nr. pos.*	% *pos.*
Kabras Tiriki ..	0.01—0.02	202	15	7.4	498	67	13.9	172	42	24.2
Kisii	0.01—0.02	924	39	4.2	1,309	133	10.2	298	36	12.5
Kisa, Idakho, Isukha, Bunyore, Maragoli, Marama	0.1—0.2	4,695	271	5.8	7,424	1,015	13.7	2,222	555	25.0
Wanga, Butsotse ..	1.0—2.0	263	14	5.3	530	71	13.4	237	59	24.9
Busia	2.0—5.0	2,890	254	8.8	3,942	641	16.3	1,224	327	26.7
S. Nyanza (Jaluo) ..	2.0—5.0	2,106	182	8.6	4,234	727	17.2	1,103	374	33.9
Total low prevalence areas	0.01—0.2	6,084	339	5.6	9,761	1,286	13.2	2,930	692	23.1
Total high prevalence areas	1.0—5.0	4,996	436	8.7	8,171	1,386	16.8	2,327	701	30.6

prevented by previous tuberculosis infection and that progressive forms of leprosy are not prevented. In Kenya the proportion of high resistant tuberculoid patients is lower than in parts of West Africa with a lower tuberculin index, and much lower than in New Guinea in areas with a very low tuberculin index.

A high proportion of the tuberculoid patients in Kenya are low resistant tuberculoid. It is likely that many mild tuberculoid patients were prevented by tuberculosis infection.

In the last decades there have been marked changes in the age distribution of the population of West Kenya. Due to a decrease in the death rate the proportion of children in the community has become very high. Children are, on the average, more susceptible to a mild tuberculoid form of leprosy than adults. There is no evidence of a greater susceptibility to progressive forms of leprosy. One would expect an epidemic of mild tuberculoid leprosy in children. The incidence of leprosy in children is high, but a large proportion of the patients are low resistant tuberculoid or more progressive forms of leprosy. Probably many mild tuberculoid patients were prevented by tuberculosis infection.

OTHER FACTORS

The possibility that the distribution of leprosy is related to the history of the disease has to be considered. It is often assumed that leprosy is a very old disease in Kenya but there is no proof that this is true.

Doubtless, leprosy has been introduced fairly long ago into Coastal areas, possibly by invaders from across the sea or from the North. Bodily contact between invaders and members of tribes living more towards the interior has been limited. It is likely that the disease has spread only slowly, mainly along trade routes. It is rather significant that, for example, the prevalence of leprosy is higher in Taveta which is an old caravan station than in the surrounding area (Ross Innes, 1948). The best explanation for foci of leprosy in Central Kenya, e.g., in the Wakamba area and near Mount Kenya, is more intensive and prolonged contact with the Coast.

The history of leprosy in West Kenya may be considerably shorter and here the disease may not have been introduced from the Coast. It is more likely that leprosy was introduced by people who have migrated from the direction of the Nile Valley via Uganda to the present sites

in Kenya occupied by the Jaluo and the Abalukia. The Kisii are of a different origin. In the past, the conditions for a rapid spread of leprosy were not favourable. The density of the population was low. The people did not live in villages but in small scattered clusters of houses. Due to hostility, contact between members of different tribes, even of different clans was rather limited.

Even at present, inter-marriage between members of different tribes is still uncommon. Marriage within the clan or with closely related clans is often preferred to other marriages. Villages are still virtually absent.

It is possible that leprosy has been introduced from the North-West and West, has slowly spread towards the East and is still spreading in this direction. This would explain the sharp border between areas with a high and those with a low prevalence of the disease in Abaluhia territory. It would also explain the recent increase of prevalence from 1.2% to 1.7% in this area, and the absence of leprosy in Kisii in a population of different origin.

Tuberculosis spreads more easily than leprosy. Therefore a more even distribution of tuberculosis may be expected. The higher prevalence of tuberculosis in the Jaluo and Abaluhia as compared with the Kisii can be explained by more contact of the former with urban centres. Only relatively few Kisii leave their area to sojourn in the urban centres.

The distribution of leprosy in the whole of Africa is probably closely related to the history of population migrations. It is often assumed that leprosy has originated in Africa. Arguments for this assumption are that recent findings of human fossils strongly suggest that man has originated in Central Africa.

Furthermore, the highest prevalence of leprosy is found in the Central part of the continent. The prevalence becomes gradually less towards the South and is relatively low in North Africa.

A high prevalence of leprosy, however, is not an argument for a long history of the disease. More often a very high prevalence of leprosy points to a rather short history of the disease. In the Pacific (Leiker, 1960) very high prevalence rates were found in particular in area with a definitely short history of the disease.

The epidemiological picture of leprosy in several parts of Central Africa with a very high prevalence of the disease has much in common with that of the Pacific.

It is also significant that some of the oldest populations of Africa, e.g., Bushmen and Hottentots, do not show a high prevalence of leprosy and do not show evidence of a long history of the disease. The pattern of leprosy in the Pygmies of the Congo suggest a short history.

A more likely explanation for the distribution of leprosy in Africa, compatible with the main direction of migrations, is that leprosy was introduced in the North and has spread southwards. The disease declined in the oldest foci in North Africa as it has in Europe. Leprosy has lingered or was introduced later in some of the more isolated parts, e.g., the Ethiopian Plateau. The disease may still be increasing or may have reached a peak in Central Africa and is probably still on the increase in parts of the Southern half of Africa. It is significant that the highest prevalence rates are found in populations who have been or still are rather isolated. This may be due to local conditions favouring the spread of the disease, but also to a later introduction of leprosy and of tuberculosis.

Accurate, detailed sample surveys, study of the history of leprosy and the history of population migrations are needed for a better understanding of the epidemiology of leprosy in Africa and re-surveys of the sample areas are needed for assessment of the trend of the disease.

SUMMARY

Regional differences in prevalence of leprosy in Kenya, varying from 0.1% to more than 3%, have previously been explained by differences in prevalence of tuberculosis. The validity of these studies, based on numbers of registered tuberculosis and of leprosy patients is doubted.

In this study the tuberculin reactions in large numbers of children in areas with a definitely high prevalence of leprosy are compared with those in areas with a definitely low prevalence

of the disease. No correlation was found between leprosy index and tuberculosis index.

It is concluded that in West Kenya the distribution of tuberculosis alone does not offer a satisfactory explanation for the distribution of leprosy. It is likely that tuberculosis has had some influence on the epidemiology of leprosy but the effect is obscured by other factors. The distribution of leprosy may be related to the history of the disease, in Africa and in the country itself. Leprosy probably did not originate in Africa but was first introduced in North Africa. The main direction of spreading has been from North to South. In West Kenya leprosy was probably introduced by people who migrated from the Nile Valley via Uganda into West Kenya. The disease is still spreading from West to East.

ACKNOWLEDGEMENTS

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Effect of BCG Vaccination on Leprosy in Kenya

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In 1962 Dr. C. M. Ross had started a pilot leprosy control project in Samia district and he intended to study the effect of BCG vaccination on leprosy. The work of this devoted and conscientious leprologist was broken off by his death in 1964. The data of his surveys mentioned in this article are derived from his original notes.

In 1962 Ross examined 177 children in schools at Buholo, Central Nyanza. He found 28 children with leprosy, a prevalence of 16%. All patients were non-lepromatous.

In 1964 the schoolchildren in this area were vaccinated with BCG. In 1966 we have carried out a re-survey in the same schools. In 320 children examined only one tuberculoid patient was found, a prevalence of 0.3%.

In 1962 Ross also examined 60 children in schools at Sio Port. He found 8 non-lepromatous patients, a prevalence of 13.3%. In 1964 BCG was given to the children. In 1966 we re-surveyed the schools. In 276 children examined only one tuberculoid patient was found, a prevalence of 0.4%. This patient was one of the few children who were absent when the schoolchildren were vaccinated. He developed leprosy in 1965.

Of the 37 patients registered by Dr. Ross in 1962, 15 children were re-examined in 1966. In these children the lesions had completely resolved, in many of them without treatment. Obviously the patients seen by Dr. Ross, and classified as indeterminate or tuberculoid, had a very mild self-healing type of leprosy.

DISCUSSION

It is unlikely that in the 4 years between the surveys major changes in the leprosy and in the tuberculosis situation have occurred. The decline in incidence of leprosy in the schoolchildren is probably to the greatest extent due to the BCG vaccination. The findings correspond with those of a recent BCG trial in Uganda (Kinnear Brown *et al.*, 1966). BCG vaccination confers substantial protection against some forms of leprosy. In Kenya, as in Uganda, the incidence of lepromatous leprosy in children is low. No conclusions can therefore be drawn as to the protective value of BCG vaccination against more progressive forms of leprosy. For several reasons such an effect does not seem to be probable.

Leiker has frequently observed that lepromatous leprosy developed in individuals who had previously shown a specific positive tuberculin reaction or who suffered from tuberculosis long before the first signs of leprosy were seen. Although true epidemics of leprosy in New Guinea were found exclusively in areas with a low prevalence of tuberculosis, fairly high prevalences of leprosy were also found in areas with a high prevalence of tuberculosis. There was, however, a conspicuous difference in type distribution of leprosy between areas of low and of high prevalence of tuberculosis. In the former the prevalence of mild, high resistant tuberculoid leprosy, with only one or a few self-healing lesions, was markedly higher than in the latter

areas. These findings suggest that tuberculosis may have reduced the incidence of high resistant tuberculoid leprosy, but that progressive forms of leprosy were not prevented.

Tuberculin-lepromin surveys have shown that part of the people with a specific positive tuberculin reaction do not show a strongly positive lepromin reaction and that in a small proportion of these individuals the lepromin reactions is even frankly negative. The size frequency distribution of lepromin reactions after BCG vaccination shows a similar pattern.

The lepromin reaction is regarded as a measure of the resistance to *M. leprae* at the moment of testing. The fact that in some individuals the lepromin reaction remains weak or is absent after tuberculosis infection or BCG vaccination, suggests that these individuals are not capable of developing a high resistance to *M. leprae*. When they become infected with *M. leprae* they will acquire an intermediate or a lepromatous form of leprosy. The majority of people are capable of reacting strongly to lepromin after BCG vaccination or tuberculosis infection and they will, after infection with *M. leprae*, not develop leprosy. Such individuals probably have a genetically determined potential resistance that has been transformed into an effective resistance with the aid of *M. tuberculosis*. If they had not been previously sensitised by infection with *M. tuberculosis* or by BCG vaccination they would, because of their potential resistance after leprosy infection, have developed effective resistance with the aid of *M. leprae*, and therefore would have shown a mild, self-healing, high resistant tuberculoid form of leprosy.

This hypothesis is further supported by the finding (Leiker, 1960) that the percentage of specific positive tuberculin reactions in patients who recently developed high resistant tuberculoid leprosy was lower than in healthy people of the same age and living in the same area. The evidence derived from tuberculin-lepromin studies corresponded with the epidemiological findings in New Guinea.

The size of the lepromin reaction in low resistant tuberculoid leprosy and in borderline tuberculoid leprosy, although on the average considerably smaller than in high resistant tuberculoid leprosy, is far from negligible. The size of the reaction is evidence of some resistance. This corresponds with the course of disease, a temporarily progressive course, not infrequently relapses, but ultimately followed by arrest of the disease. It is theoretically possible that in individuals with such a moderate degree of potential resistance a tuberculosis infection or BCG vaccination will produce just sufficient effective resistance that at least in some instances the few bacilli that have entered after incidental infection with *M. leprae* are destroyed rapidly before being able to produce symptoms of disease. Leiker has observed some patients with a specific positive tuberculin reaction who a few years later developed a single tuberculoid lesion. These lesions, however, showed typical signs of low resistant tuberculoid leprosy such as incomplete central healing, broad micro-papular edge and satellite lesions. This shows that early low reistant tuberculoid leprosy is not always prevented by previous tuberculosis infection.

It is regrettable that in the trial in Uganda no attempt was made to classify the patients with leprosy more accurately. It is often difficult to differentiate the early lesions in children on clinical symptoms alone, but a classification can frequently be based on lepromin reaction and histo-pathological examination. At present many of the children are receiving treatment and no conclusions can be drawn any more from the course of the disease. The incidence of lepromatous leprosy in children in Uganda is low. Unless the lepromin test is carried out in all patients so far discovered and lepromin test and histo-pathological examination are carried out in the new patients, the trial may not give an answer to the leading question whether BCG vaccination also protects against more progressive forms of leprosy or not.

SUMMARY

Re-surveys of schoolchildren in a highly endemic area in Kenya, 2 years after a BCG vaccination campaign, showed a marked decrease in the

incidence of mild, non-lepromatous leprosy. No conclusion could be drawn as to the preventive effect of BCG vaccination against progressive forms of leprosy. Such an effect is not expected.

The BCG trial in Uganda too may not give an answer to the leading question of protection against progressive forms of leprosy because the incidence of such forms in children is low; accurate clinical classification is difficult in the early stage and many patients receive treatment in the early stage. It is suggested to carry out lepromin tests and histo-pathological examination in all patients for a more accurate classification in the uncharacteristic early stage.

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Urinary Excretory Pattern of DDS in Leprosy Patients *

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Selection of diamino diphenyl sulphone (DDS) as the drug of choice for leprosy is validated by experience for over a decade, but its intolerance in a significant proportion of patients and its apparent failure to meet the challenge of *M. leprae* in some patients makes further investigations necessary in these 2 directions. Pettit, Rees and Ridley (1966) claim to have demonstrated the phenomenon of drug resistance in 9 patients in one of the largest in-patient leprosaria in the world, in Malaysia.

In the Acworth Leprosy Hospital when promin was the first sulphone tried it was noted that some patients did not improve. Such patients were found to be excreting the drug rapidly. An increase of the dose resulted in satisfactory improvement. Thus was engendered the concept in the Acworth Leprosy Hospital that the rate of excretion of sulphones had some correlation with improvement.

In recent years 2 patients were encountered in which a satisfactory response could be obtained after raising the dose of DDS to 150 and 200 mgm. daily† (i.e., 0.9 and 1.2 gm. per week).

Patient No. 1: B.M.P.
Hindu, male, aged 19 years. Type: Reactional Tuberculoid.
Treated on routine dosages of dapsone for 2 years. At the end of this period during which mild reactions occurred twice, increase in the number of lesions was noted and the patient continued to remain bacteriologically positive for acid fast bacilli. It was found that he was excreting 55.14 mg. DDS during 24 hours following an oral test dose of 100 mgm., the test being performed after stopping DDS treatment till the urine was free from even a trace of DDS. The dose was increased gradually from 100 mgm. to 200 mgm. daily for 6 days per week. After 3 months of treatment with 150 mgm. daily marked improvement was observed and later he became negative for bacilli on the 200 mgm. dose.

Patient No. 2: S.M.
Hindu, male, aged 29 years. Type: Tuberculoid Major.
Treated on routine dosage for 5 years. The only lesion on left knee persisted without showing any appreciable change. The DDS excretion test revealed that he was excreting 55.1 mgm. out of the 100 mgm. test dose. The dose was increased gradually to 150 mgm. Nine months after the dose was raised the lesion had definitely flattened and at the end of one year only faint hypopigmentation could be seen.

Improvement noticed with high dose treatment in a few patients prompted us to study the rate of excretion and blood concentration of DDS in different subjects after a test dose.

MATERIAL AND METHODS

Two hundred patients (182 males and 18 females) of ages ranging from 12 to 65 years attending the Acworth Leprosy Hospital, Wadala, were the subjects for the study. Only patients without evident kidney disease were selected. The types of leprosy from which these patients were suffering were as follows:—

* Paper read at the Seminar conducted under the auspices of the Indian Association of Leprologists at the Central Leprosy Teaching and Research Institute, Chingleput on 10th February, 1968.

† Routine dose schedule followed in the Acworth Leprosy Hospital, Wadala: 25 mgm. daily for 6 days per week for 3 months, increased by 25 mgm. (daily for 6 days per week) every 3 months till the maximum of 100 mgm. daily for 6 days per week is reached.

TABLE 1

Type	*No. of Patients*
Tuberculoid	63
Intermediate	56
Lepromatous	81
Total	200

Before investigation routine anti-leprosy treatment was stopped in all patients for varying periods till the urine did not show even a trace of DDS. The minimum number of days after which no DDS was found was 10 days and the maximum 30 days.

After an oral test dose of 100 mgm. of DDS the quantity of total diazotizable material excreted during the subsequent 24 hours was estimated in all the patients by the method described by Simpson (1949) (calorimetric estimation of the coupled compound of diazotized sulphone with N 1-naphthyl ethylene diamine-dihydrochloride). The estimations were made on a Klett-Summerson Photoelectric calorimeter.

Blood concentration of the drug at 2, 4, 6, 8 and 24 hours after the administration of the drug was studied in 47 patients.

The urinary excretion pattern of 16 patients was studied by repeating the test at intervals of one month, 3 months, and 12 or 14 months.

The weight of the patients was not taken into consideration, though we feel that the dose in relation to the weight should be an important factor to be considered in future investigations.

RESULTS

TABLE 2

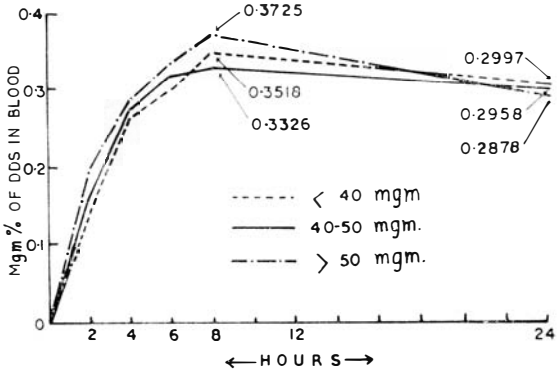
Showing 24-hour urinary excretory pattern following oral test dose of 100 mgm. DDS

Mgm. of DDS excreted in 24 hours	*No. of Patients*
10—20	1
20—30	13
30—35	19
35—40	37
40—45	35
45—50	28
50—55	29
55—60	15
60—70	16
70—80	5
80—90	2
Total	200

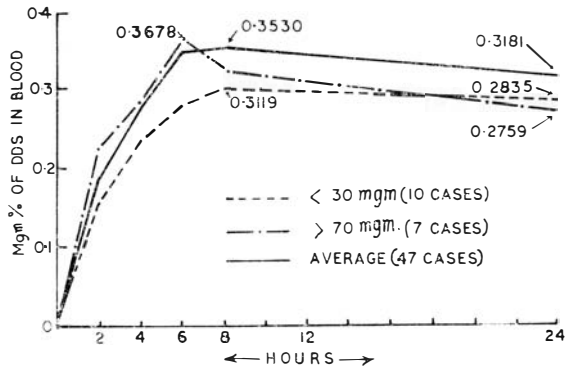
TABLE 3

Showing 24-hour urinary excretion of DDS in mgm. on repeated testing of patients after 1 month, 3 months and 12 or 14 months

Sr. No.	*Patients*	*Excretion Test*				*Range of Difference*
		Initial	*After 1 month*	*After 3 months*	*After 12 or 14 months*	
1	J.S.	34.14	29.68	27.54	41.24	13.70
2	J.D.	45.80	50.29	49.50	53.16	7.36
3	S.N.	33.28	30.63	43.46	25.71	17.75
4	M.R.	51.76	61.53	—	53.16	9.77
5	A.R.M.	44.64	—	49.65	—	5.01
6	A.R.	28.82	20.46	26.73	—	8.36
7	V.B.	66.61	45.80	57.50	46.35	20.81
8	M.V.	36.88	27.38	—	32.60	9.50
9	N.K.	37.99		—	48.63	10.64
10	G.K.	48.61	—	58.04	—	9.43
11	O.K.	23.93	—	—	32.52	8.59
12	T.A.	48.49	—	—	47.53	0.96
13	W.M.	49.93	42.08		—	7.85
14	L.G.	60.43	—	65.32	—	4.89
15	N.G.	39.25	—	—	31.61	7.64
16	K.N.	50.04	—	—	52.96	2.92



GRAPH 1
Showing blood concentration curves following oral test dose of DDS.



GRAPH 2
Showing blood concentration curves of patients excreting less than 30 mgm. and more than 70 mgm. of DDS.

The average of the range of difference is 9.07 mgm. which is within the limits of experimental error.

Here it must be mentioned that wherever possible the collection of urine was done at the hospital. In a few cases the samples of urine were brought by the patients. The completeness of the collection of urine excreted in 24 hours will in future be checked by a determination of its creatinine content.

COMMENTS

From Table 2 it is evident that the 24-hour excretory pattern of DDS following an oral test dose varies within wide limits in different patients. Fairly consistent blood concentration curves of DDS could be obtained (Graph 1) co-relating to the excretory pattern.

In the case of patients excreting more than 70 mgm. in 24 hours (Graph 2) the peak concentration in the blood is reached 6 hours after administration of the drug, while in those excreting less than 30 mgm. it occurs at 8 hours. Though the maximum blood concentration is more in the case of the former there is a tendency for the concentration to drop down earlier during 24 hours than in the latter case. The implications of such a 24-hour study in patients receiving prolonged DDS treatment remains to be investigated. However it may be stated that the possibility of more sustained blood levels of DDS in patients who excrete DDS at a slow rate may account for prolonged tissue concentrations of the drug at high levels in such patients.

The figures in Table 3 point to an apparent consistency of the urinary excretion pattern in the same individual when re-tested at intervals of one month, 3 months, and 12 or 14 months.

The next question that arises is what correlation exists between the excretory pattern and reactions and improvement in leprosy patients under treatment with DDS.

Table 4 shows reactions in all types of patients (lepromatous, borderline, reactional, tuberculoid, tuberculoid major) in relation to their excretion rates.

The majority of patients with reaction are within the 30—55 mgm. excretion group. However, it has to be appreciated that the causes of reactions in leprosy are numerous and some of these reactions may have been due to causes other than DDS treatment.

An attempt was made to study the excretory pattern in patients under treatment when in reaction. It was found that although the usual treatment dose of DDS was stopped excretion of DDS continued in appreciable amounts for as long as the reaction persisted. This aspect is receiving close attention.

With regard to improvement in relation to the excretory pattern the improvement noted

TABLE 4

Showing DDS excretion pattern in patients with reaction

Mgm. excreted in 24 hours	*Lepromatous*	*Borderline*	*Reactional Tuberculoid*	*Tuberculoid*	*Total*
10—20	1	—	—	—	1
20—30	4	—	—	—	4
30—35	7	—	2	1	10
35—40	8	5	3	1	17
40—45	9	1	4	—	14
45—50	6	3	4	1	14
50—55	3	6	1	3	13
55—60	3	1	2	—	6
60—70	3	—	—	2	5
70—80	1	1	1	—	3
80—90	1	—	1	—	2
Total	46	17	18	8	89

in the registers against non-lepromatous patients is subject to human error as there is no yardstick to assess the improvement acurately. In lepromatous patients the number of bacilli is the criterion.

However, it must also be mentioned that a number of patients are given tablets of DDS reguarly but they do not take them regularly. Such patients will not show improvement, but they will be taken for assessment as receiving regular treatment. To give an example, the following may be quoted:—

G.S.R., male, aged 16 years in 1957, noted as taking treatment for 65 months out of 108 months. The DDS estimation done in 1966 showed that he was taking tablets (he may have taken tablets a few days previously) yet there was no improvement. He was admitted as an in-patient and the taking of tablets was supervised. He showed bacteriological improvement.

To avoid all fallacies therefore, lepromatous patients rendered negative without reactions, should be taken for assessment and not patients who show only improvement. In the series of lepromatous patients studied only one such patient exists. This patient was rendered negative by treatment over a period of 10 years. He excreted 41.34 mgm. in 24 hours with the 100 mgm. DDS test dose.

Investigations are proceeding.

SUMMARY

This presentation focuses attention to the wide variations in the urinary excretory pattern of DDS in leprosy patients, the probable immutability of the pattern in individuals, and the apparent correlation of the excretory pattern with improvement and reactions.

In 200 patients studied excretions as low as 18.01 mgm. and as high as 86.07 mgm. were encountered during 24 hours following an oral test dose of 100 mgm. DDS.

The excretory pattern of individuals seemed to be constant on re-testing at intervals of 1, 3 and 12 months.

The majority of reactions were noted in the 30 to 55 mgm. range of excretors. As the causes of reactions are multifarious the findings in reaction patients are not taken as a basis for standardizing slow, moderate or rapid excretors.

Due to paucity of bacteriologically negative lepromatous patients without reactions correlation between excretory rate and improvement could not be determined.

REFERENCES

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Abstracts

Leprosy and Genetics. A Review of Past Research with Remarks concerning Future Investigations, by BERNARDO BEIGUELMAN. *Bull. Wld. Hlth. Org.*, 1967, **37**, 461-476.

The few geneticists who are interested in leprosy have been working in this field only since 1962, and have made little progress in solving the problems presented by susceptibility to this disease.

This paper reviews the research that has been conducted, with particular reference to the search for associations between leprosy and certain genetic markers. In each area, the advantages and limitations of different techniques are described, and attention is drawn to sources of bias that may invalidate many of the results that have been published. Of particular interest is the discussion of a new technique for evaluating resistance to leprosy. The proposed technique is based upon the *in vitro* transformation of blood monocytes into macrophages, and the observation of their behaviour against *M. leprae*.

From author's summary.

The Role of General Practioners in Leprosy Control, by BHOLA NATH. *J. Indian Med. Ass.*, 1967, **49**, 10, 470-472.

The author appeals to all general practitioners to become leprosy conscious and to know enough of the diagnosis and treatment of the disease to recognise signs of leprosy during examination for any other disease so that treatment can be undertaken at once and the chance of complete cure made more certain. He points out that the general practitioner has the most vital role to perform in the control of leprosy today. Society's ignorance of the facts of the disease and the age-old beliefs and prejudices prevent the seeking of medical opinion early enough for complete cure. Leprosy is a disease like any other and should be treated as such in the ordinary clinics and only the the small percentage of patients who have gross deformities should be sent to the leprosy clinics. A united effort on the part of the 40,000 doctors doing general work in the endemic areas, each one treating 10 patients, could immediately bring one-fifth of the estimated number of leprosy sufferers in India under treatment.

It is an encouraging sign that doctors in India should realise that early diagnosis of the disease will mean cure before the patient becomes a menace to himself and others and the author makes many helpful suggestions. This is a valuable paper and it summarises comprehensively the ways in which general practitioners can assist the campaign to stamp out leprosy.

3. **Chemotherapeutic Trials in Leprosy. 5. A Study of Methods Used in Clinical Trials in Lepromatous Leprosy,** by M. F. R. WATERS, R. J. W. REES and IAN SUTHERLAND. *Int. J. Lepr.*, 1967, **35**, 3, 311-335.

Although controlled clinical trials were used from the first introduction of successful chemotherapy of tuberculosis, such methods have been frequently neglected in study of the treatment of leprosy. From experience gained in 2 controlled trials at Sungei Buloh Leprosarium and in the light of the recent advances in experimental leprosy, a re-appraisal of trial methods in lepromatous leprosy is presented. It is considered that untreated L2 and L3 lepromatous leprosy patients remain the most suitable for such trials, and that accurate classification is essential. Methods of clinical, histological and bacteriological assessment are evaluated. The importance of recording morphological changes in *M. leprae* is emphasised and it is considered that only those patients with a pre-treatment morphological index (MI) of 25 or more should be included. The general design of controlled trials is discussed, including the advantages and disadvantages of the method of matched pairs and the difficulties resulting from reactions, especially erythema nodosum leprosum (ENL). The design of pilot trials is also considered and similar careful patient selection is advocated. Furthermore, it is suggested that evidence or otherwise of chemotherapeutic activity may be obtained within 4½ to 6 months by studying the effect of the trial drug on the MI. Finally, the different methods available for evaluating the effect of drugs on the intiation and treatment of ENL are presented.

From the authors' summary.

The following 9 abstracts are reprinted, with permission, from *Trop. Drs. Bull.*, 1967, **64**, 11:—

4. **Epidemiologia de la lepra en el centro Oriente** (The epidemiology of leprosy in the Eastern Central Region of Peru), by E. JUSTO *Revta Sanid. Polic.*, 1965, **25**, 1-3, 40-44.

The author reports on the incidence of leprosy in Peru with special reference to the Eastern Central Region. According to the facts obtained by the Statistics Service the population of Peru increases annually by 2% while leprosy increases by 6.53%, so that leprosy increases 3 times more rapidly than the population in general. In Pucallpa in the Eastern Central Region, leprosy in the last 3 years has shown an increase of 13% annually, while it has decreased by 14% in the country generally. These figures cause the author to conclude that it is necessary to create new anti-leprosy centres. The whole country should become interested in leprosy control and the Army, Navy and Air Force should mobilize personnel to help in the anti-leprosy campaign.

J. R. Innes.

5. **Observations sur l'allergie tuberculinique et léprominique des enfants cliniquement sains vivant au contact de lépreux en Guadeloupe** (Observations on tuberculin and lepromin allergy in Guadeloupe), by A. ESCUDIÉ and E. COURMES. *Bull. Soc. Path. Exot.*, 1966, **59**, 3, 289-96.

In Guadeloupe 465 house contacts of patients with leprosy received simultaneously in different arms an intradermal injection of 10 units of tuberculin and 0.1ml. '*brute classique*' lepromin. The Fernandez, early, lepromin reaction, was considered to be more reliable than the Mitsuda, late, lepromin reaction because the authors consider that the latter may be affected by the injection of tuberculin. Of 14 children aged less than one year 21% were lepromin positive and 0% tuberculin positive. Two tables and a graph illustrate the changes in lepromin and tuberculin positivity rates up to the age of 20 years. In 46 people aged 15-20 years 65% were both lepromin positive and tuberculin positive, a further 22% were tuberculin positive alone, and 4% were lepromin positive alone. In 147 people, aged 15-20 years, who lived in the same district but were not close contacts of leprosy, the tuberculin positive rate was 52.3%. The relative value of the Fernandez and Mitsuda reactions is discussed briefly. A BCG vaccination campaign for the prophylaxis of leprosy was started in Guadeloupe in May, 1965. It is suggested that vaccination of schoolchildren should be supplemented by vaccination of newborn infants because the lepromin positive rate is appreciable in children below school age. (The details of the Fernandez reaction that were considered to indicate a positive lepromin reaction are not delineated, and it would be valuable to record how frequently a negative Mitsuda reaction was observed in Fernandez-positive children.)

C. S. Goodwin.

6. **Leprosy finger,** by L. KLENERMAN. *Pro. R. Soc. Med.*, 1967, **60**, 6, 547 (Sect. Orthopaed. 25).

A male aged 24 years born in Tanzania and resident in India for 4½ years before coming to England, had been in this country for 18 months when he attended a hand clinic complaining of a right middle finger which had been swollen for 6 months. The finger was not painful, but movement was limited. Radiographs of the hand were normal. A biopsy of the finger revealed that 'the swelling was produced by gross thickening of the digital nerves'. (It would seem unusual that while taking a skin biopsy the digital nerves should be exposed, but an interesting fact came to light. The abstracter has experience of dissection and operation revealing swelling of nerves proximal to the heads of the metacarpals, between which a nerve may become entrapped.) A rash on the right leg, which had been present for 6 months, was found by a dermatologist to be anaesthetic to pin-prick and a diagnosis of leprosy was made. Slight thickening of the right lateral popliteal nerve and the left superficial radial nerve was found. It is stated that the patient had the tuberculoid form of leprosy (although the evidence for this classfication is not delineated). This is an interesting case report.

C. S. Goodwin.

7. **Lupoid features in a case of leprosy,** by L. BONOMO, F. DAMMACCO, A. TURSI and G. BARBIERI. *Int. J. Lepr.*, 1967, **35**, 1, 65-71.

The clinical features and laboratory investigations of an Italian woman who died at the age of 42 with a history of leprosy from the age of 14 years are delineated. Initially, the patient experienced joint pains with remittent fever, and 'later' erythematous skin lesions appeared. Bacteriological sampling when she was 27 led to a diagnosis of leprosy, and the course of her disease was unremarkable until 18 months before her death when she developed continual fever with severe joint and muscle pains. Several features of systemic lupus erythematosus (LE) became noticeable including erythema of the nose and cheeks, and later of the whole of the face and neck and the sternal area. The signs and symptoms responded to high doses of prednisone, greater than 25 mgm. per day. Laboratory examinations revealed anaemia, proteinuria and defective liver function; and tests for rheumatoid and anti-nuclear factors were positive with many typical LE cells. Increases in IgG, IgA, and to a lesser extent IgM immunoglobulins, were detected, with decreased albumin and beta 1A/C globulin values. It is suggested that this last feature has not previously been reported in a leprosy patient. Other studies which have revealed auto-immune features in leprosy patients are discussed, and various suggestions made as to the aetiology of certain aspects of this disease. It is suggested that an immunosuppressive drug such as chloroquine may be beneficial (but this drug has been used by some leprologists for many years).

C. S. Goodwin.

8. **Leprotic nerve abscesses in Northern India,** by V. N. SEHGAL, S. M. TULI and B. DUBE. *Int. J. Lepr.*, 1967, **35**, 1, 60-64.

An examination of 4,000 patients with leprosy revealed 10 with nerve abscesses, 9 patients having tuberculoid leprosy and one patient borderline leprosy. Five patients were subjected to 'nerve decapsulation', and smears from the abscess material and biopsy specimens from the abscess walls revealed no *M. leprae*. The clinical histories of 2 of these patients, and of 5 others, are given. Comparison is made with previous surveys for nerve abscesses. It is stated that if operation is performed early, permanent damage to nerve fibres may be prevented (but no evidence for this statement is presented). The beneficial effect of corticosteroids for one patient is mentioned.

C. S. Goodwin.

9. **Etisul in out-patient treatment of leprosy** (Memoranda), by D. S. CHAUDHURY. *Ghana Med. J.*, 1967, **6**, 1, 8-9.

A report on the use of Etisul in mass mobile out-patient treatment in Northern Ghana is described and compared with the findings in a control area. It is observed that the rate of decline of aggregate infectivity in the area where Etisul was used, expressed in percentage reduction of infectivity, was greater than that in the control area. The use of Etisul in suitable cases is recommended together with dapsone in mass out-patient treatment.

J. R. Innes.

10. **Chemotherapeutic trials in leprosy. 3. Pilot trial of a riminophenazine derivative, B663, in the treatment of lepromatous leprosy,** by J. H. S. Pettit, R. J. W. Rees and D. S. Ridley *Int. J. Lepr.*, 1967, **35**, 1, 25-33.

This trial was the authors' first attempt to design a drug trial with a minimal number of patients. The riminophenazine derivative B663 was given in a dose of 100 mgm. 3 times a day for 6 days a week for 5 months to 4 patients with pure lepromatous leprosy (LL) and to 2 with borderline lepromatous leprosy (BL). The investigations performed and the methods of assessing progress were similar to those in previous trials (see *Trop Dis. Bulletin*, 1964, v. 61, 161; 1966, v. 63, 656), and particular attention was given to the morphological index. Smears were taken after 1½ months', 3 months' and 5 months' treatment, from 6 skin sites including both ear lobes, and biopsy specimens of skin were taken at the beginning and end of the trial. An independent assessor estimated the clinical improvement as 'slight' in all patients. The case history of each patient in the trial is given, and a table contains the details of the bacteriological responses to treatment and the falls in the biopsy index. The average bacteriological index was 4.3 at the start of the trial and 3.9 after 5 months. The morphological index fell on average from 26% to 2.5%, and the biopsy index fell on average to 40%. The results indicate that B663 is an active anti-leprosy drug causing leprosy bacilli to become irregularly stained, presumably killing the bacilli. The fall in the biopsy index is 'almost exactly the figure that would have been expected with DDS in a group comprising one BL patient for every two LL patients, which was the proportion in this trial'. The development of a deep and persistent pigmentation of the skin of 4 Chinese patients is detailed, with the histological picture of an appreciable increase in the melanin content of the basal layer of the epidermis. The drug was thus not acceptable to the pale-skinned patients, and a lower dosage scheme may be worth investigating. The trial method was judged a success, but a more satisfactory protocol would exclude all BL patients and those with a morphological index below 25%.

C. S. Goodwin.

11. **Occupational therapy in leprosy with particular reference to activities of daily living,** by P. Regis. *Lepr. India*, 1965, **37**, 4, 468-74, 15 figs. on 4 pls.

'It is concluded that methods of occupational therapy can help patients without deformity as well as those with various stages of deformity. In patients without deformity the purpose is to teach them to use their hands and feet in such a way as to prevent deformities by protecting against injury and burns, etc. In patients with various degrees of deformities the purpose is to rectify or reduce the deformities and to enable the patients to utilise even the deformed limbs. The Occupational Therapist can help them (1) in pre- and post-operative treatment of operated hands, (2) in providing aid to daily activities of life, and (3) in earning a livelihood. General principles of activities directed to these ends are described and some specific recommendations are made. It is stated, however, that each patient needs individual attention and special methods of adaptation may have to be used.'

12. **Effect of DDS on established infections with *M. leprae* in mice,** by C. C. Shepard and Y. T. Chang. *Int. J. Lepr.*, 1967, **35**, 1, 52-7.

The effect of chemotherapeutic drugs against *M. leprae* in experimental footpad infections of mice has previously been tested by administration of the drug from the time the animals were infected. This method produces relatively quick and clear cut results. In the present work a situation analogous to that of therapy in a human infection was created by withholding treatment until the bacilli had completed the most active phase of multiplication.

Treatment with DDS (0.1% of the diet) was found to stop further bacillary increase but it produced little change in the numbers of bacilli. It did not appreciably affect the number of solid-staining organisms during the first 57 days, but after 88 days of therapy solid forms disappeared. This is about the same period of time as would be required to bring about a similar result in human leprosy. The viability of the bacilli was not found to be diminished until 88 days, a period which is 7 times the calculated generation time, and viable bacilli persisted in very small numbers even at 318 days despite the high blood level of DDS. The time that DDS takes to kill leprosy bacilli is probably governed by their metabolic activity.

D. S. Ridley.

The following 9 abstracts are reprinted, with permision, from *Trop. Dis. Bull.*, 1967, **64**, 12:—

13. **De ontwikkeling in de lepra-situatie in Nederland tussen 1945 en 1965** (The leprosy situation in the Netherlands, 1945-1965), by D. L. Leiker. *Ned. Tijdschr. Geneesk.*, 1967, **111**, 32, 1401-6.

The English summary appended to the paper is as follows:—

'The total number of leprosy patients residents in the Netherlands during the last 20 years has been estimated at 600. In *c.* 100 cases the diagnosis was never established. About 300 patients still require treatment. An analysis of the data on 450 leprosy patients in the Netherlands showed that the incidence of new patients among immigrants was highest within 4 years of their immigration. After this the rate fell sharply, until after 6 years new patients were only found sporadically. In nearly all patients the infection had been acquired in the country of origin; a few patients were infected by relatives in the Netherlands, although only one such patient has been established beyond doubt. Endemic leprosy among Dutchmen of Eurasian parentage is declining sharply; among the Amboinese it seems to have disappeared almost completely. Immigrants from the West Indies, however, now are a considerable source of new patients, with a leprosy rate of nearly 1%.

'Chemotherapy has probably been the main factor in the reduction of endemic leprosy among immigrants. It has caused a rapid percentage increase of deformed bacteria, which are incapable of trasmitting the disease. They increase more rapidly than the bacteria eliminated from the body.'

14. **Phenoloxidase of** *M. leprae* (Correspondence), by K. Prabhakaran. *Nature*, London, 1967, July 22, **215**, 436-7.

It has already been reported that *M. leprae*, alone among a number of mycobacteria tested, is able to oxidize 3,4-dihydroxyphenylalanine (DOPA) to pigmented products (see below). It is now found that in the range of substrates oxidized the phenoloxidase of *M. leprae* resembles more closely the enzyme of plants than that of mammalian origin. It oxidizes both D and L forms of DOPA and in addition catechol and catecholamines. Taxonomically *M. leprae* belongs to the same class as fungi, which are rich in phenolase. This enzyme might provide an alternative pathway for the utilization of various substrates, which could be used either for cultivation of the organisms or for selective inhibitors.

D. S. Ridley.

15. **Metabolism of** *M. leprae* **separated from human leprosy nodules,** by K. Prabhakaran. *Int. J. Lepr.*, 1967, **35**, 1, 34-41.
Oxidation of 3,4-dihydroxyphenylalanine (DOPA) by *M. leprae*, by K. Prabhakaran. *Ibid.*, 42-51.

In the first of these papers the author reports that suspensions of *M. leprae* obtained from human lepromatous material by the method described earlier (*Nature*, London, 1962, v. 196, 589; *Trop. Dis. Bulletin*, 1963, v. 60, 229) oxidized *p*-phenylenediamine, as as measured by oxygen-uptake in the Warburg apparatus. By measuring the increase in absorbance at 550 mμ. the author detected succinate-cytochrome C reductase activity, and also lactate dehydrogenase activity by the increased absorbance at 340 mμ. in the presence of nicotinamide adenine dinucleotide. The formation of pyruvate from lactate was detected by the carbonyl test, but as the oxygen-uptake in the presence of lactate was inversely related to the pyruvate accumulation, the pyruvate produced was presumably further oxidized.

In the second paper, the author describes experiments with *M. leprae*, in which DOPA oxidase activity was detected. The activity was determined by measuring in the Warburg apparatus an increase in exogenous respiration when DOPA was added. The possibility of the increase being due to auto-oxidatio was excluded by measuring auto-oxidation at *p*H 6.8 and at *p*H 8.3; a considerable increase occurred at *p*H 8.3 whereas at *p*H 6.8 (the *p*H used in the mycobacterial tests) there was no significant increase. Indole-5, 6-quinone was formed from DOPA by oxidation by the leprosy bacilli but not by *Myco. lepraemurium*, *Myco. tuberculosis* (H37Rv, H37Ra) BCG, *Myco.* 607. *Myco. smegmatis*, *Myco. phlei* or Kedrowsky's bacillus,

The nature of the enzyme that catalyses the oxidation of DOPA is not clear for it failed to oxidize tyrosine to melanin, and the significance of its presence in the leprosy bacillus is discussed. The author concludes that in this organism the oxidase probably provides an alternative mechanism by which different substrates can be oxidized effectively by the organism.

S. R. M. Bushby.

16. **Cryoproteinemia in leprosy,** by L. J. Matthews and J. R. Trautman. *Derm. Int.*, 1965, **4**, 3, 164-8.

Cryoproteinaemia was detected in 40 out of 41 patients with active lepromatous leprosy who were not receiving corticosteroid therapy. Eight of the 41 had acute erythema nodosum leprosum at the time, and in these the cryoprotein level was high: 600-900 mgm.% as against 200-400 mgm.% in those without reaction. However, high blood levels up to 600 mgm.% were also found in 6 out of 6 patients with dimorphous leprosy. No cryoproteinaemia was detected in the following groups (numbers of patients in brackets): active lepromatous leprosy with corticosteroid therapy (4), inactive lepromatous leprosy (5), tuberculoid leprosy (4) and healthy control subjects (19).

D. S. Ridley.

17. **Association between lepromatous leprosy and Australia antigen,** by B. S. Blumberg, L. Melartin, M. Lechat and R. S. Guinto. *Lancet*, 1967, July 22, 173-6.

Australia antigen was found to be more common among patients with lepromatous leprosy than in those with tuberculoid leprosy or in those without leprosy. The frequency was higher in males than in females and in the young than in the old. In the Philippines the incidence among male patients aged less than 20 years was 27% for lepromatous leprosy, 12.5% for borderline and 8% for tuberculoid leprosy; among those without leprosy it was 5.5%. The differences were less striking among females or older patients. These results are analysed statistically. A similar study is being undertaken in India.

Australia antigen was first detected in an aborigine, and has been found to occur mainly in South East Asian populations. Apart from lepromatous leprosy it has been found to be associated also with leukaemia and hepatitis. It is suggested that subjects with Australia antigen have an inadequate immune response and are especially susceptible to these illnesses.

D. S. Ridley.

18. **Morphology of** *M. leprae* **in tissue sections,** by L. Levy, P. Fasal and L. P. Murray. *Arch. Derm.*, 1967, **95**, 5, 451-5.

Estimates of the morphological index (MI) of leprosy bacilli in histological sections were compared with similar estimates made on homogenates of the same pieces of tissue. The results indicated that the differences between the 2 estimates would not be expected to exceed a value of 4 on 19 out of 20 occasions. However,

the highest MI value observed in any of the tissues examined was 14%. The method of estimating the MI on sections was to count only single, isolated bacilli. (It would be interesting to know what the difference between the 2 estimates would have been with more active lesions, in which the solid-staining bacilli sometimes lie preponderately in clumps. The abstracter has noticed also that disproportionate numbers of solid forms are often found in the superficial part of the granuloma.)

D. S. Ridley.

19. **Alopecia mucinosa simulating leprosy,** by J. Fan, Hsin-Shiang Chang and Biao Ma. *Arch. Derm.*, 1967, **95**, 4, 354-6.

In countries where leprosy is endemic and carries a serious social stigma, minor features of the disease may stigmatize a leprosy patient. Two case reports from Taiwan of eyebrow alopecia originally diagnosed as leprosy, but found after histological examination to be alopecia mucinosa are presented. One patient had a slightly elevated hairless plaque in the medial part of the eyebrow (the eyebrow alopecia of leprosy characteristically involves the lateral portion initially). The clinical details of the other patient are not described. No other lesions suggestive of leprosy were found in either patient, although the second patient had been in a leprosarium for 2 years. Histological examination of a skin biopsy specimen in both patients showed 'a marked inflammatory infiltrate in the corium' in association with the hair follicles. In sections stained by the Ziehl-Neelsen method no acid-fast bacilli were found. The sebaceous glands and the hair follicles were degenerate, and PAS and toluidine blue stains revealed the presence of mucin in the degenerate follicles. Treatment with 'topical and oral steroids' resulted in the induration subsiding and regrowth of lanugo hair. In Taiwan there is a 'lay belief that eyebrow alopecia is a sure sign of early leprosy'. The authors point out that this alopecia is usually associated with the advanced form of leprosy disease, and may not be present at all. They rightly emphasize the need, both for medical and social reasons, for an exact diagnosis of leprosy, which in doubtful cases involves histological examination of a skin biopsy specimen.

C. S. Goodwin.

20. **Dislocations du tarse dans la lèpre** (Dislocation of the tarsus in leprosy), by A. Carayon, P. Bourrel, M. Bourges and J. Languillon. *Bull. Soc. Med. Afr. Noire Lang. Fr.*, 1967, **12**, 1, 69-80.

This article, well illustrated with 7 pages of X-ray photographs and diagrams of the disintegrating tarsus in leprosy, summarizes the findings of previous workers and reports briefly on the lesions found and treatment adopted in 19 patients suffering from diverse bony changes in the tarsus associated with leprosy. The causes of the tarsal dislocation (or disintegration) were complex: specific leprotic intramedullary granulomata, neuropathy (*i.e.*, unappreciated traumata to anaesthetic articular surfaces), and infection entering through deep perforating ulcers of the sole. When surgical correction of the drop foot has failed to prevent progressive deterioration of the bones and joints in the tarsal region, the authors advocate early mid-tarsal or subastragaloid arthrodesis. When the metatarsus is destroyed, amputation is the only solution.

S. G. Browne.

21. **Prophylactic value of DDS against leprosy—an interim report,** by P. M. Ali, Dharmendra, S. K. Noordeen and K. Ramanujam. *Lepr. India*, 1965, **37**, 4, 447-67, 3 maps (2 folding) on 3 pls.

In 1960 the Indian Council of Medical Research appointed a Working Group including a statistician to plan a double-blind trial of dapsone used prophylactically against leprosy. The Central Leprosy Teaching and Research Institute, Madras, was selected to carry out the investigation because it is situated in an area where the leprosy prevalence rate is over 2% and because of the facilities of the Institute.

In December, 1961, a house-to-house survey was started of an area including 75,000 people, to diagnose and record leprosy patients. However, because the lepromatous rate was found to be 'a little below 15%, and the average number of child contacts per source was surprisingly low, the survey area was enlarged to include 213,721 people of whom 96% were examined. This survey occupied one year. The survey area of 325 square miles included 381 villages. A detailed map of the area shows the names of villages and where the paramedical workers lived.

All the patients with bacteriologically positive leprosy were listed, with a total of 732 intrafamilial healthy child contacts of 'source cases'. To obtain a statistically sufficient number of child contacts all those below the age of 15 were included. 4,370 persons with leprosy were detected, a prevalence rate of 21 per 1,000, 624 having lepromatous leprosy, a lepromatous rate of 14.3%. 334 of the patients with lepromatous leprosy were bacteriologically negative, 'due to treatment', but they were known to have had 'active' lepromatous leprosy and 52 of the non-lepromatous patients were bacteriologically positive. Of the 676 'source' cases only 362 had healthy intrafamilial child contacts.

Owing to death, emigration and 'refusal' only 585 contacts were studied; and these were divided into 2 comparable groups based only on age and sex, by random allocation.

The dose of dapsone for prophylaxis was 5 mgm. twice a week for children aged 0-2 years; each dose was increased by 5 mgm. at monthly intervals to 20 mgm. twice a week, during the 4th month; from the 10th month onwards the dose was 10 mgm. twice a week. Children aged 3-5 years were started on 10 mgm. twice a week and the dose was increased to 40 mgm.; those aged 6-10 years were given from 25 mgm. to 100 mgm. twice a week, and those aged 11-14 years from 50 mgm. to 150 mgm. twice a week. From the 10th month onwards all received half the maximum dose. 291 children were placed in the dapsone group and 294 in the control group; the latter received a

similar looking tablet of calcium lactate. All tablets were to be swallowed in the presence of a paramedical worker.

A considerable amount of information in this lengthy report defies summary and the original should be consulted. Details are given of the double-blind method, supervision by the paramedical workers, and periodic examination, including examination by a doctor of suspected cases. Ten tables contained details of the source cases and their contacts and many facts concerning the 43 child contacts who developed leprosy during the first 2¼ years of the trial. Fourteen children (4.81%) in the dapsone prophylaxis group and 29 (9.86%) in the control group developed leprosy, this difference being significant at the 2% level, t=2.36. None of the children developed lepromatous leprosy, and all were bacteriologically negative except one child in the control group, whose one lesion regressed spontaneously and 'disappeared'.

During the first 9 months of the trial no difference was observed between the 2 groups in the number of children developing leprosy, but thereafter 17 in the control group and 4 in the dapsone group developed leprosy. By the end of 2¼ years the reduction in leprosy incidence was 'of the order of about 50%'. Dapsone prophylaxis was found to be effective up to the age of 10, but 'there has been practically no protective effect in the contacts above that age'. The conclusion is drawn that dapsone prophylaxis should be started 'as soon as possible after exposure to infection'. Dapsone prophylaxis was found to be more effective in males.

All the 43 contacts developing leprosy were given 'therapeutic' doses of dapsone, and the subsequent clinical response of those in the dapsone prophylaxis group was in some respects more 'favourable' than the control group.

An addendum records the development of leprosy in 7 children during a further 3 months of the trial, giving a rate of 4.90% in the dapsone group and 11.81% in the control group.

Among the child contacts under the age of 10 years, after the first year of the trial only one child in the dapsone prophylaxis group has developed leprosy, while 16 in the control group have developed the disease. (This latter observation is of great importance.)

The trial continues, and details of further studies and their application are discussed. (This trial is a most significant contribution to the study of the prophylaxis of leprosy. If it was possible to know the BCG status of the child contacts this might be a significant area of study.)

C. S. Goodwin.

The following 6 abstracts are reprinted, with permission from *Trop. Dis. Bull.*, 1968, **65**, 1:—

22. **Lucha contra la lepra en la República Dominicana** (The leprosy campaign in the Dominican Republic), by H. Bogaert Díaz. *Revta Dominicana Derm.*, 1967, **1**, 2, 106-10.

The English summary appended to the paper is as follows:—

'Between the 3rd February, 1966 to 1967, 15,903 new patients with skin diseases were seen in the Institute of Dermatology discovering 314 patients of leprosy of which 252 were new patients. 209 came from the Distrito Nacional and San Pedro de Macoris. 88 were lepromatous, 84 indeterminate, 79 tuberculoid and one dimorphous.'

23. **Hepatocyte functional state. Quantitative evaluation with I^{131} rose bengal in lepromatous leprosy patients,** by N. Carvalho, M. P. Azevedo and A. C. R. Marques. *Int. J. Lepr.*, 1967, **35**, 2, Pt. 1, 175-83.

'The authors studied the hepatocyte functional state in 29 lepromatous leprosy patients, through the radioiodine-labeled rose bengal test as described by Loewenstein. The procedure for quantitative analysis of the uptake-excretion curve is determined by 3 constants:

'1. Uptake half time or interval of time in which a half part of the dye circulating in the blood is absorbed by the liver.

'2. Excretion half time or interval of time in which a half part of the dye absorbed by the liver is excreted by the biliary ducts.

'3. Liver blood volume in percentage relation with the total blood volume.

'The 29 patients were subdivided into 2 groups: (1) those showing functional lesions of the liver cells, and (2) those without such lesions. Other subdivisions were made according to the presence or absence of excretory dynamic disturbances, to hepatomegaly, to reduction or increase of the liver blood volume, to the evolutive phase of the disease and to response to treatment.

'Of those patients presenting evidence of lesions or disturbances of the cellular function or excretory dynamics, 58.6% showed functional deficit of the polygonal cells; 45% showed excretory functional deficit of the biliary ducts; 44.8% showed reduction in the liver blood volume; and 51.7% showed increase in the liver blood volume.

'The conditions for reduction or increase of liver blood volume did not parallel the functional conditions of the liver cells. Likewise, the presence of hepatomegaly, the disease's evolutive phase, and the response to treatment, did not correspond to the hepatocyte functional state.

'As hemodynamic factors and the functional state of the liver cells may change independently, it is necessary to perform the test simultaneously with the measurement of minimum liver blood flow in order to achieve an effective result.'

24. **The drug treatment of leprosy,** by S. G. Browne. *Trans. R. Soc. Trop. Med. Hyg.*, 1967, **61**, 2, 265-71.

The author, after emphasizing that clinical findings and bacteriological sampling leading to a definitive diagnosis of leprosy are the essential prerequisites of treatment, gives the warning that 'treatment' (presumably chemotherapy) 'should be temporarily withheld from patients whose lesions are in a state of acute

exacerbation when they present themselves, and from those whose peripheral nerves at the sites of predilection are very tender'. Indications for in-patient treatment as opposed to the usual out-patient methods are mentioned. A simple dosage scheme for oral dapsone is given, starting with 25 mgm. once weekly and increasing to 100 mgm. once weekly. The signs of activity of the disease process are delineated. It is advised that treatment should be continued in tuberculoid and indeterminate leprosy for one year after such signs have ceased; and in lepromatous, borderline and low-resistant tuberculoid leprosy for 2 years after clinical and bacteriological activity has ceased. It is mentioned later in the article that some authorities advise that for patients with lepromatous and borderline leprosy dapsone should be continued at half the therapeutic dose for years, if not for life. Solapsone is mentioned, and thiacetazone, ditophal, B663 (Geigy), and long acting sulphonamides are listed; but pride of second place is given to thiambutosine, with a dosage starting at 0.25 gm. daily and increasing to 2 gm. daily. 'During the second half of the second year, dapsone should be introduced while the dose of thiambutosine is gradully reduced.' 10 ml. of intramuscular thiambutosine may be given weekly or fortnightly in place of oral treatment. Drug combinations are not recommended.

Toxic skin rashes due to dapsone are described, and a scheme outlined for 'desensitizing for dapsone sensitivity'. This scheme starts with 5 ml. of an aqueous solution of solapsone, 0.5 gm. in 200 ml. of water, being given orally twice weekly, increasing by 5 ml. to the equivalent of 250 mgm. of (solid) dapsone. Antihistamines are advised for a recurring rash. Treatment of acute exacerbation may require antimonials or chloroquine, or the continual use of corticosteroids. The dangers of acute iritis and neuritis are emphasized, and the treatment advised for neuritis includes a procaine injection 'under the nerve-sheath'. Clinical examination and bacteriological sampling at regular intervals after discharge is recommended. General hygienic precautions to prevent the spread of leprosy are discussed.

(This paper should be studied in the original to appreciate the extensive clinical advice that defies summary. In such an article there might have been more information on the dosage of dapsone than the simple scheme recommended. The fact that the weekly dose may be better tolerated if given in divided doses might have been mentioned.)

C. S. Goodwin.

25. **Tratamiento de la reacción leprosa con Indometacina. Resultados negativos en 5 pacientes** (Unsuccessful results of the treatment of lepra reaction (erythema nodosum leprosum) with Indomethacin), by O. Cañizares. *Dermatología*, Mexico, 1966, **10**, 3, 265-9.

The English summary appended to the paper is as follows:—

'The administration of Indomethacin, an anti-inflammatory analgesic and anti-pyretic of non-steroid chemical structure, was studied in 5 patients with erythema nodosum leprosum.

'Four patients had already previously received corticosteroids. In one of them this medication could be discontinued and replaced by Indocin. In another the administration of Indocin succeeded in reducing the requirements of prednisone. In the other 2 patients Indocin failed to cause any improvement. In one patient of erythema nodosum leprosum of recent origin, not treated with corticosteroids, Indocin even at high doses (200 mg. daily) failed to control the reaction.

'No toxic reactions to the medication were observed even when administered in high doses. The therapeutic results obtained with the administation of Indomethacin (Indocin) in the reactional stages of lepromatous leprosy, of the erythema nodosum type, were in general very unsatisfactory. This medication can be added to the long list of therapeutic measures which only occasionally may be useful in the management of the patient with lepra reaction of the erythema odosum type.'

26. **Lepra manchado de Lucio—antimalaricos en reacción leprosa** (Lucio's phenomenon in leprosy. Antimalarial drugs in the management of lepra reaction) by H. Corrales Padilla *Derm. Int.*, 1965, **4**, 3, 147-50. English summary.

The geographical distribution of leprosy of Lucio is somewhat restricted and outside Mexico it has only been reported a few times: from Costa Rica by Romero and associates in 1949 (*Trop. Dis. Bulletin*, 1950, v. 47, 371), and Honduras in 1962 when the present author reported the first patient seen with it in that country Lucio's phenomenon (necrotizing angiitis) should be considered to be a particular type of reaction of the form described by Lucio and Alvaredo in 1852, and identified by Latapí in 1938.

The author discusses the results obtained with a triple antimalarial agent consisting of quinacrine hydrochloride, chloroquine phosphate and hydroxychloroquine sulphate, in the management of leprosy reaction.

(See also *Trop. Dis. Bulletin*, 1964, v. 61, 928.)

J. R. Innes.

27. **Reactivation of the dorsiflexors of the foot in leprotic paralysis of the common peroneal nerve. Observations on 26 patients,** by A. Carayon, P. Bourrel and M. Bourges. *Int. J. Lepr.*, 1967, **35**, 2, Pt. 1, 111-18.

'The results of reactivation of the dorsiflexors of the foot by 2 muscles from the posterior compartment of the leg (the tibialis anterior by the tibialis posterior; and the extensor hallucis longus and the extensor digitorum longus by the flexor digitorum longus), tend to demonstrate that this operation is to be preferred to (1) the operation of Lambrinudi, which often meets with delayed healing of bone and soft parts and septic complications, and requires a long period of immobilization, (2) transfer of the tibialis posterior muscle to the tarsus, which often results in non-union due to leprous dystrophy of the bone.

'The reactivation of the dorsiflexors of the foot by the tendons of the tibialis posterior muscle and flexor digitorum longus (26 patients) is performed in the leg, at some distance from the site of trophic disturbances, by a surgical technic that is at once simple and lasting. The period of immobilization is short (16 days), and complications are encountered very rarely.'

The following 8 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1968, **65**, 2:—

28. **Nuevos datos en relación con la composición antigénica de** *M. leprae* (The antigenic composition of *M. leprae*), by S. CALDERON MANES, M. SALAZAR MALLÉN and S. ESTRADA-PARRA *Revta Invest. Salud. Publ.*, 1967, **27**, 2, 117-24.

The English summary appended to the paper is as follows:—

'Two extracts were obtained from leproma rich in *M. leprae*. The crude one consisted in pepsin digested material and the purified contained only polysaccharides.

'Agar precipitation using sera from tuberculous and lepromatous patients as well as from rabbits immunized with *Nocardia brasiliensis* showed that the crude extract gave 5 precipitation bands with the lepromatous serum, one of them being identical with that using *Mycobacterium tuberculosis* var *hominis* as antigen. The purified extracts precipitated with the serum from a tuberculous patient giving a band identical with that produced with PolyINb obtained from *N. brasiliensis* and this precipitation could be inhibited through absorption with PolyINb.

'Two lepromatous sera precipitated with the purified extract and with PolyINb giving a band of identity and also one and 2 extra bands, suggesting the presence in this fraction of other species-specific polysaccharide antigens.

'No precipitation was observed with the sera from other 3 lepromatous patients, from one of the tuberculoid type and from 6 healthy donors.'

29. **Treponemal immobilization tests in leprosy,** by H. G. S. RUGE. *Br. J. Vener. Dis.*, 1967, **43**, 3, 191-6.

Sera from 420 patients with lepromatous leprosy were obtained on 5 occasions, with 24 weeks elapsing between each sampling. (All the patients were not tested on each occasion.) Four lipoidal antigen tests and the pallida reaction with Reiter antigen were performed on all sera and each patient's serum was tested at least once by the TPI test; this was repeated when it or the other tests had been found positive on a previous specimen. TPI tests were performed on 618 out of the total of 1,699 sera tested.

The TPI test gave positive or doubtful results on sera from 50 patients; 7 of these had slinical evidence of burnt-out yaws, 35 had latent yaws and 2 had latent syphilis. In 4 patients the TPI test was thought to be non-specific and in 2 it was inconclusive. Of the other tests, the VDRL showed the closest agreement with the TPI (71.2%), followed by the Reiter test (66.2%). Agreement with the TPI was less with the Wassermann reaction, in which the original or cardiolipin antigens were used, and with the Meinicke test.

The TPI test showed some fluctuations in consecutive examinations of the same patients' sera taken at different times. This occurred more frequently in the more seriously affected patients and may be explained by abnormalities in the serum globulins. The frequency of anticomplementary and false positive results with the other tests was lower after treatment with antileprotic drugs and improvement in the serum protein pattern. It is suggested that it is preferable to defer mass investigations of patients with leprosy for treponemal disease until their leprosy has been treated.

A. E. Wilkinson.

30. **Epidemiological significance of skin reaction to Dharmendra antigen in leprosy survey,** by M. MAEDA. *Lepr. India*, 1967, **39**, 2, 44-61.

This is a detailed and painstaking account of a leprosy survey in Japan in which skin reactions to lepromin, tuberculin and certain other mycobacterial antigens were compared, and the influence of previous BCG vaccination on the skin reactions was noted. The lepromin used was of the Dharmendra type, and the results were read at 48 hours. It was found that BCG was more potent in the positive conversion of the lepromin than the tuberculin reactions. The article should be read in the original by those interested.

D. S. Ridley.

31. **Los casos dimorfos de lepra. Una etapa en la evolución de un caso?** (Dimorphous leprosy. A stage in the evolution of the disease?), by A. SAUL. *Dermatologia*, Mexico, 1966, **10**, 3, 465-84. English summary.

In the present-day classification of leprosy the idea of polarity is still valid in that patients with lepromatous and tuberculoid leprosy show opposing characteristics in accordance with the immunological situation of the host. The author discusses the so-called dimorphous patients and advances the hypothesis, giving examples, that patients with dimorphous leprosy do not represent a group within the classification but a transitory phase in the evolution of a lepromatous or tuberculoid patient more or less stable, or of an interminate patient with a doubtful immunological situation. The patient is dimorphous at the time of examination only. The phase is transitory and should be considered as belonging to the acute stage of the disease. The author illustrates his argument with photographs and photomicrographs.

J. R. Innes.

32. **Les manifestations viscérales dans la lèpre** (Visceral manifestations in leprosy), by J. LANGUILLON. *Méd. Trop.*, 1967, **27**, 3, 283-92.

This article provides a useful and moderately comprehensive summary of knowledge concerning visceral damage in leprosy and adds some original data on the histological changes seen in the liver and on liver

function tests. Although attention is usually directed to the manifestations of leprosy in the skin, the nasal mucosa and the peripheral nerves, the lymphatic nodes, the liver and the testes are consistently involved in lepromatous leprosy. On the other hand, the lungs, the kidney and the digestive tract (apart from the naso-pharynx) are but rarely the seat of leprosy lesions.

Of practical importance are the author's observations on the persistence of *M. leprae* in the Kuppfer cells of the liver after they can no longer be found in the skin and nasal mucosa; the possible occurrence of emboli composed of bacilliferous Virchow (lepra) cells; a subclinical malfunctioning of the suprarenal cortex in lepromatous leprosy.

(Many works and workers are cited in the text, but no references are appended—a regrettable oversight.)

S. G. Browne.

33. **Intérêt de l'éthionamide en thérapeutique antilépreuse** (Value of ethionamide in the treatment of leprosy) by H. Floch, N. Rist and J. C. Jacobi. *Bull. Soc. Path. Exot.*, 1966, **59**, 5, 715-24.

A clinical trial of ethionamide (a thioamide derivative of isonicotinic acid) in 19 patients with leprosy was undertaken to resolve the conflicting reports of the efficacy of the drug. Laviron *et al.* (*Trop. Dis. Bulletin*, 1958, v. 55, 1021) reported favourably; but Languillon *et al.* (*ibid.*, 1962, v. 59, 564) concluded that it had no action and was moreover badly tolerated.

The 19 patients were a heterogenous group composed of 13 patients with lepromatous leprosy (of whom 10 had already received treatment for unspecified periods), one borderline, 4 reactional tuberculoid, and one 'simple' tuberculoid. The daily dose (0.25 gm.) was given for a variable period (4 to 18 months). No toxic side-effects were noted with this dose. The clinical improvement was said to be 'striking' or 'spectacular' in all the groups. The bacteriological results were not less impressive. (No information is given concerning bacterial morphology, and smears were not taken from the nasal mucosa.) In both skin smears and histological sections in patients with lepromatous leprosy, *M. leprae* either disappeared completely or their numbers were very much reduced. This result occurred also in the 10 patients who despite previous treatment had remained bacteriologically positive. The possibility of the development of resistance to the drug after the lapse of several months is suggested, but not followed up.

Since strains of *Myco. tuberculosis* have shown a cross-resistance to ethionamide, a thiosemicarbazone and the diphenyl-thioureas, the authors suggest that ethionamide should be given in combination with other anti-leprosy drugs.

S. G. Browne.

34. **Sur la thérapeutique des réactions lépreuses** (Treatment of lepra reaction (acute exacerbation in lepromatous leprosy)), by H. A. Floch. *Bull. Soc. Path. Exot.*, 1966, **59**, 5, 745-52.

During a clinical trial of ethionamide (Floch *et al.*, above) the author was able to wean 14 patients (10 suffering from lepromatous leprosy and 4 from reactional tuberculoid leprosy) from dependence on corticosteroids (unspecified). Within 10 days of beginning treatment with ethionamide (0.25 gm. daily), and in conjunction with a daily intraveous injection of of 10 ml. of a 20% aqueous solution of sodium hyposulphite, and nicotinic acid and B complex, the author succeeded in suppressing the corticosteroid; signs of acute exacerbation began to disappear. This combined medication was apparently efficacious in the treatment of exacerbation occurring in both lepromatous and tuberculoid leprosy. The bacteriological results were equally gratifying, *M. leprae* disappearing in a few months from the skin smears in a high proportion of the patients treated.

S. G. Browne.

35. **L'insuffisance de la corticosurrénale dans la lèpre lépromateuse—essai de pathogénie de la réaction lépreuse** (Cortico-adrenal insufficiency in lepromatous leprosy. Enquiry into the pathogenesis of lepra reaction), by J. Languillon, H. Plagnol and P. Giraudeau. *Bull. Soc. Path. Exot.*, 1966, **59**, 5, 740-44.

By means of Thorn's test (a fall of 50% in the eosinophil count in the peripheral blood, and a 50% increase in the serum uric acid after an injection of corticotrophin), the authors show that 7 out of 10 patients with lepromatous leprosy, and 7 out of 10 with lepromatous leprosy in a phase of acute exacerbation, had cortico-adrenal insufficiency. These findings are held to be in keeping with the well-known clinical observations that mental or physical stress, the administration of potassium iodide, the puerperium, excessive dosage or over-rapid increments of dapsone (DDS, diaminodiphenyl sulphone) may all apparently provoke an acute exacerbation (lepra reaction).

The authors throw doubt on the vaunted efficacy of the extremely numerous and diverse drugs used in the treatment of lepra reaction, and illustrate this by showing a cure rate of 80% (complete with clinical and biochemical amelioration—*e.g.*, fall in the C-reactive protein) in a series of 15 patients who were given a placebo. They suggest that patients who do not respond to either the placebo, or one or other of the standard drugs generally used, really need corticosteroids, which alone will control the exacerbation.

S. G. Browne.

Book Review

Evaluation of Drugs for Tropical Diseases. Proceedings of a Symposium held at the Royal Society of Medicine, London, 17 February, 1967, ed. by Dr. C. Wilcocks and Dr. E. L. Harris, 95 pages, published by the Association of Medical Advisers in the Pharmaceutical Industry. Copies are available from A.M.A.P.I., c/o CIBA Laboratories, Horsham, Sussex, and from Messrs. H. K. Lewis & Co. Ltd., 136 Gower Street, London, W.C.1., price 22s. 6d.

The symposium was convened by the Association of Medical Advisers in the Pharmaceutical Industry under the Chairmanship of Professor A. W. Woodruff and Professor C. G. Maegraith and the proceedings have been published in separate issues of the Transactions of the Royal Society of Tropical Medicine and Hygene, Vol. 61, Nos. 3 and 4. However, the material is so valuable that A.M.A.P.I. thought it should be made available in a complete and durable form. There are 4 subjects—1. Malaria, 2. Amoebiasis, 3. Schistosomiasis, 4. Leprosy, and each subject is divided into a settion dealing with the laboratory and animal methods available followed by a section on clinical trial methods in man. Participants in the Leprosy section were Dr. R. J. W. Rees, Dr. D. S. Ridley and Dr. S. G. Browne.

This is a valuable reference book, excellently produced, which should be in the hands of all who are interested in the testing of drugs.

Report

ELEP Bulletin, No. 2, December, 1967

ELEP, the Co-ordinating Committee of European Voluntary Agencies engaged in the fight against leprosy, has completed its first year and this bulletin gives a summary of the activities during that year—its contacts with member organisations and with proespective members, its office work and its personnel. A list is included of vacancies for doctors in leprosy work in various parts of the world and of doctors available for appointment. It is recorded that the Deutsches Aussätzigen-Hilfswerk of Wurzburg, a member of ELEP, celebrated its 10th anniversary in October, 1967, and that the newly-formed Nederlandse Stichting voor Leprabestrijding will shortly seek admittance as a member.

Note: The office of ELEP was transferred to **198** rue Stévin, Brussels 4, Belgium, on 1 December, 1967.

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