The Quarterly Publication of
the British Leprosy Relief Association

LEPROSY REVIEW

VOLUME XXXVIII NO. 2 APRIL 1967

PRINCIPAL CONTENTS

EDITORIAL OFFICE
6 HILLCREST AVENUE, PINNER, MIDDLESEX, ENGLAND

Single Issue 10s. 6d., plus postage

Annual subscription £2 sterling (U.S. $6)

Registered Office of British Leprosy Relief Association
8 PORTMAN STREET, LONDON, W.1

LEPROSY REVIEW

VOLUME XXXVIII NO. 2 APRIL 1967

Contents

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Printed by Rawlinsons (Printers) Ltd., Northwood, Middlesex, England

The All Africa Leprosy and Rehabilitation Training Centre

The following additional medical staff is required for this new Leprosy Teaching Project:—

PHYSICIAN

A physician is required to teach leprosy up to post graduate level in its medical aspects, including histo-pathology.

Qualifications: M.R.C.P. or equivalent, and experience in medicine in the tropics.

The appointment will be in Addis Ababa with visits to a rural area at intervals. Three year contract, renewable. To begin January 1968.

SURGEON

A surgeon is required to teach all aspects of the surgical care of leprosy patients up to post graduate level.

Qualifications: F.R.C.S. or equivalent, and specific training in orthopaedic surgery or plastic surgery with special experience in the surgery of the hand.

The appointment will be in Addis Ababa with visits to a rural area at intervals. Three year contract, renewable. To begin January 1968.

RURAL MEDICAL OFFICER

A medical officer is required to undertake the supervision of a rural leprosy control area under the general direction of the Director of Training.

Qualifications: Basic medical qualification recognised in Ethiopia (such as M.B., B.S., M.D.). Previous experience of leprosy control would be an advantage, but the main requirement is a willingness to work in the field.

The post should attract a young man interested in developing a worthwhile public health programme in the tropics and in teaching public health auxiliary workers.

Adequate auxiliary staff will be provided including an experienced health officer.

Three year contract, renewable. To begin September 1967.

All salaries by arrangement.

For further details apply to P.O. Box 165, Addis Ababa, Ethiopia.

Editorial

1. 'THE REAL MACKAY'. Dr. S. G. Browne has kindly sent us a report of the first General Assembly of ELEP (the Co-ordinating Committee of European Voluntary Agencies engaged in the fight against leprosy) and this report will be found on p. 117. We wish to state that ELEP is 'the real Mackay'. Readers may be puzzled by the weird Scotch expression but will remember that Sir Walter Scott wrote a famous book, 'The Heart of Midlothian', wherein the Duke of Argyll and Jeanie Deans had a conversation in which they agreed that 'the heart aye warms to the tartan', and 'the real Mackay' is only a common expression for real genuine people, and points out that the heart warms to such people. We point out that we are in a state of being warmed by the action of ELEP and in our metaphor we express our gratitude and appreciation for a genuine group of people who have helped leprosy work in supporting the forthcoming International Leprosy Congress in London by making it possible to include two more languages in the very necessary translation and interpretation service in such a congress. French and Portguguese are to be included as well as English and Spanish which alone the congress could afford.

2. HER MAJESTY THE QUEEN AS PATRON OF THE NINTH INTERNATIONAL LEPROSY CONGRESS. The gracious act of Her Majesty the Queen in granting her patronage to the Congress is very cheering. We might also say that the act of Her Majesty justifies our following the same metaphor that she is 'the real Mackay'. All who work in leprosy in the whole world are very appreciative and will give thanks for this gracious act.

3. C.M.G. We are also proud to announce that Dr. J. A. Kinnear Brown has been awarded the C.M.G. by Her Majesty for his services to leprosy and we offer him our hearty congratulations. Dr. Brown went out to Nigeria in 1930 under the Methodist Missionary Society and in 1932 chose the site and started the Uzuakoli Leprosarium which later developed into the famous Uzuakoli Leprosy Research Centre. He then returned to England for health and domestic reasons but after the war he returned to Africa in 1951 as leprologist for Uganda. Among his outstanding pieces of service are the BCG trials carried out at Kumi Leprosy Centre, Uganda, which bore such fruit.

4. OBITUARIES. We regret to announce the loss of 3 stalwart workers.

(1) Dr. W. E. Cooke, F.R.C.S.I., D.P.H., a former medical superintendent of the Hospital for Tropical Diseases, London, died on 3 February, 1967, at the age of 87. Latterly he was a valued member of the Medical Committee of Lepra. He was a Christian and had many other medical interests including the Homes of St. Giles and the Missionary School of Medicine. His life and service will be greatly missed.

(2) Dr. S. G. Spickett, B.SC., PH.D., died of cancer on 22 September, 1966, at the early age of 34. His interests were in Genetics and several valuable papers by him have been published in *Leprosy Review*. We know that his last paper was written for *Leprosy Review* and we are still trying to trace it. His work was such that we would gladly publish this paper posthumously if we could find it. The attention he paid to genetics in leprosy was very valuable and perhaps it is a hint to us to pursue this subject and to encourage present workers to carry on his researches.

Note: As we go to press some notes by Dr. Spickett have reached us and we have printed them on p. 109.

(3) Rev. Joseph Sweeney, M.M., of Korea, died on 27 November, 1966. A full obituary appears in the January-February, 1967, issue of *The Star*, Carville, Louisiana, U.S.A.

5. The Philippine Journal of Leprosy. Vol. 1, No. 1, Jan.-July, 1966. We heartily welcome the first issue of the Philippine Journal of Leprosy which has just reached us and we wish it well. We hope it will have an active life for it will be a great asset to leprosy work in the world. It is printed in English and the first issue contains the following original articles:—

Organizational Set Up of Leprosy Control in the Philippines, by L. V. Uyguanco.

Leprosy Control in the Philippines, by D. Disini.

Mental Health Problems in Leprosy, by F. Jose.

Leprosy in Children. General Considerations: Initial and Early Stages, by C. B. Lara.

Calcium Phenyl Butazone (Pyrazon) in Reactive Episodes of Leprosy, by P. Reyes-Javier.

6. Welcome to Overseas Visitors. Visitors from overseas are gladly welcomed at the Editorial Office of *Leprosy Review*. This office is still in the London area and can be reached easily in 25 minutes by a frequent train service from Baker Street Station. A telephone call to this office (*Tel.*: 01-866 2237) will ensure an appointment.

Ninth International Congress of Leprology

SEPTEMBER 16th-21st, 1968

1. We are most happy to announce that Her Majesty the Queen has graciously consented to grant her Patronage to this Congress.

2. Thanks to the generous gesture of Elep (the Co-ordinating Committee of European Voluntary Agencies engaged in the fight against leprosy), in making available the sum of $5,000 U.S. towards the expenses of the forthcoming Ninth International Congress (to be held in London, 16th-21st September, 1968), the Secretary-Treasurer of the International Leprosy Association is happy to announce that arrangements will be made for simultaneous translations in French and Portuguese in addition to English and Spanish.

S. G. Browne,
Secretary-Treasurer,
International Leprosy Association.

Lep. Rev. (1967) **38**, 2, 77-82

Epidemiological Studies in Leprosy in Gudiyatham Taluk* Part I

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The domiciliary treatment and leprosy control programme for Gudiyatham taluk was inaugurated in the latter half of 1962 by the Schieffelin Leprosy Research Sanatorium, Karigiri, South India, in collaboration with the Swedish Red Cross who undertook full financial responsibility for the entire programme for an initial period of 5 years. This area was chosen because of the known endemicity of leprosy in this region.

MATERIAL AND METHODS

Gudiyatham taluk is in North Arcot district in Madras State. This taluk occupies an area of 481.04 square miles, stretching from 78°35′ to 79°20′ North longitude and 12°40′ to 13°05′ East latitude. It supports a population of 385,228 (in 1961 Census figure (*a*) Gudiyatham Town=50,384, (*b*) Taluk excluding Gudiyatham =334,844) with the sex ratio at 982 females per 1,000 males. Nearly 58% of the total population are non-workers according to the 1961 census. (Estimated population of Gudiyatham taluk during mid 1966 may be around 410,000 (*a*) Gudiyatham=54,000, (*b*) Rest=356,000.)

The leprosy treatment and control area was divided into 3 administrative blocks; in block 1, 17 clinics; in block 2, 7 clinics; and in block 3, 15 clinics have been opened. A population survey was carried out in the first block before starting any clinics in that area. This was time-consuming and the people suspected of the disease had to wait a few months for initiation of treatment. Therefore, in the other 2 blocks, treatment clinics were opened to begin with, followed by survey and education programmes based on the treatment clinics. While in blocks 1 and 2 the patients are treated only at the clinics, in block 3 treatment is given at schools as well.

Till November, 1966, a total of 197,756 persons have been examined out of a total population of 256,103 surveyed. In the rural areas practically 100% of the population surveyed has also been examined. But in urban areas, there is considerable resistance to the idea of examination by paramedical personnel for evidence of leprosy. The more educated and the higher the social strata, the less likely is the person to permit physical examination.

* This work was entirely financed by the Swedish Red Cross, Stockholm.

The block-wise distribution of population surveyed and population examined is given below (Table 1). (These figures include the clinic in Gudiyatham town area also.)

TABLE 1

Population examined in the 3 blocks

Block	*Total Population (covered so far)*	*Population Examined*	*% Examined*
1	110,522	86,710	78.4%
2	71,925	54,909	76.3%
3	73,656	56,137	76.2%
Total	256,103	197,756	77.2%

This report is mainly concerned with the presentation of data regarding patients suffering from leprosy in each block with reference to their sex, age and type of disease, indicating the prevalence of leprosy (per hundred population examined). Details regarding the prevalence of leprosy at individual centres in each block in relation to other factors will be reported in a later communication. Tables 2 and 3 accompanying this report include figures from Gudiyatham centre whereas in the subsequent tables the figures for Gudiyatham centre have been excluded since the correct population figures corresponding to the patients attending the clinic have not yet been fully obtained. The patients presented in this report are those who are resident in the area served by the clinics as of November, 1966, and are registered as patients in the clinics.

Persons aged 15 years and less are grouped as children, while those above 15 years are noted as adults in this report.

RESULTS

(*a*) *General Findings*

In Tables 2 and 3 the characteristics of patients are shown according to their sex, age and classification. In Tables 4 to 10 the prevalence of the disease in relation to certain population characteristics are indicated.

TABLE 2

Distribution of Patients by Sex and Age (including Gudiyatham)

Persons	*Male*		*Female*		*Total*		*Sex Ratio*
	No.	%	*No.*	%	*No.*	%	*M : F*
Adults	2,528	71.0	1,696	68.2	4,224	69.9	1.49 : 1
Children	1,033	29.0	789	31.8	1,822	30.1	1.30 : 1
Total	3,561	100.0	2,485	100.0	6,046	100.0	1.43 : 1

Among patients, there appear to be more males than females. However, among children this sex difference is not significant. The actual prevalence according to sex, however, is different in adults and children as will be shown later.

The proportion of adults seen among all patients is around 70% and this pattern is similar in both males and females.

Table 3 is an expanded form of Table 2 showing the break-up figures according to the type of disease.

Taking all patients together, slightly more than half the patients belong to the tuberculoid type. The picture is, however, different in respect of adults and children as is shown in the table. 47.7% of adult patients have tuberculoid leprosy, whereas the corresponding figure for children is 63.8% The number of patients with indeterminate type of leprosy among children is more than double the corresponding number for adults. An important feature of this table is the sex-difference among adults regarding the type of disease. Only 19.4% among adult females have lepromatous leprosy, whereas the corresponding figure for adult males is 34.5%. The pattern of leprosy according to the different types is similar among male and female children.

TABLE 3

Distribution of Patients by Classification of Disease, Sex and Age (including Gudiyatham)

Class	*Adults*		*Children*		*Total*		*Total*
	Male	*Female*	*Male*	*Female*	*Adults*	*Children*	
Lepromatous	872 34.5%	330 19.4%	45 4.4%	23 3.0%	1,202 28.5%	68 3.1%	1,270 20.0%
Tuberculoid	1,065 42.1%	951 56.1%	662 64.0%	500 63.2%	2,016 47.7%	1,162 63.8%	3,178 52.5%
Borderline	311 12.3%	146 8.6%	36 3.5%	40 5.0%	457 10.8%	76 4.1%	533 8.8%
Indeterminate	280 11.1%	269 15.9%	290 28.1%	226 28.8%	549 13.0%	516 29.0%	1,065 18.7%
Total	2,528 100%	1,696 100%	1,033 100%	789 100%	4,224 100%	1,822 100%	6,046 100%

Table 4 shows the prevalence of leprosy by sex and age in each block. In this and subsequent tables details of Gudiyatham centre are excluded. The lesser prevalence in block 1 as compared with blocks 2 and 3 may be due to the difference in the method of approach which has already been mentioned.

TABLE 4

Prevalence by Sex and Age (excluding Gudiyatham)

Block	*Men*	*Women*	*Male Children*	*Female Children*	*Total*
1	3.50	2.44	1.20	1.20	2.15
2	6.14	3.51	2.04	1.80	3.46
3	4.89	3.75	3.65	2.83	3.82
Total	4.34	3.07	2.13	1.85	2.91
		(1)		(2)	

(1) Probability$<$0.001: statistically significant

(2) Probability$>$.06: statistically not significant

The over-all prevalence of leprosy in the area covered so far works out to 2.9%. The prevalence among adult males is markedly higher than that among adult females. In children this difference in prevalence is not significant.

Table 5 indicates the prevalence of leprosy according to classification of disease.

TABLE 5

Prevalence by Class of Disease (excluding Gudiyatham)

Block	*Leprom.*	*Tubercul.*	*Border.*	*Indet.*	*Total*
1	0.39	1.35	0.18	0.23	2.12
2	0.94	1.73	0.38	0.42	3.46
3	0.75	1.79	0.20	1.07	3.82
Total	0.60	1.55	0.22	0.53	2.91

A little over one-fifth of the total number of patients belong to the lepromatous group with the corresponding prevalence rate of 0.6%.

A frequency distribution of the 37 centres according to over-all prevalence of leprosy is shown in Table 6.

TABLE 6

Distribution of Centres according to Prevalence of Leprosy (excluding Gudiyatham Centre)

Prevalence (%)	*Number*
0-1.99	8
2-2.99	13
3-3.99	6
4-4.99	2
5 and over	9
Total	37

In Table 7 the frequency distribution of centres according to prevalence of leprosy among adult males is given.

TABLE 7

Frequency Distribution of Centres according to Prevalence of Leprosy among Adult Males (excluding Gudiyatham)

Prevalence (%)	*Number*
0-1.99	1
2-2.99	6
3-3.99	6
4-4.99	8
5 and over	16
Total	37

In Table 8 the frequency distribution of centres according to prevalence of leprosy among adult females is presented.

TABLE 8

Frequency Distribution of Centres according to Prevalence of Leprosy among Adults and Females (excluding Gudiyatham)

Prevalence (%)	*Number*
0-1.99	4
2-2.99	13
3-3.99	9
4-4.99	3
5 and over	8
Total	37

In Tables 9 and 10 similar frequency distributions are given for male and female children.

TABLE 9

Frequency Distribution of Centres according to Prevalence of Leprosy among Male children (excluding Gudiyatham)

Prevalence (%)	*Number*
0-1.99	20
2-2.99	4
3-3.99	5
4-4.99	2
5 and over	6
Total	37

TABLE 10

Frequency Distribution of Centres according to Prevalence of Leprosy among Female children (excluding Gudiyatham)

Prevalence (%)	*Number*
0-1.99	21
2-2.99	5
3-3.99	3
4-4.99	2
5 and over	6
Total	37

(*b*) *Intrafamilial Study in Block* 1—*some preliminary results*

While analysing epidemiological data in relation to disease, it is useful to consider the family as one unit. This would also help in the study of genetic factors, if any, pertaining to the transmission and susceptibility to the disease.

There were about 15,210 families examined in block 1 as of November, 1966. Out of these, 1,504 families have at least *one* leprosy patient, giving an over-all prevalence of 10%.

The distribution of families which have leprosy patients is shown according to the number of patients in each family (Table 11).

TABLE 11

Distribution of familes according to number of patients

No. of Patients	*No. of Families*	%
1	1,216	80.90
2	228	15.00
3	43	2.90
4	14	1.00
5	2	0.14
6	1	0.06
Total	1,504	100.00

The average number of members in families which have a leprosy patient is shown in Table 12.

TABLE 12

Average family size

No. of Patients	1	2	3 and over	All
Average Family Size	5	6	7	5

There were a few wherein all the members had leprosy. The number of such families is shown in Table 13.

TABLE 13

Families where all members are patients

Family Size	*Patients*	*No. of such Families*
1	1	35
2	2	12
3	3	2
4	4	2
5	5	1

There were 304 families with at least *one* lepromatous leprosy patient. This indicates that 22.2% of the patient families have at least *one* lepromatous patient, giving a prevalence of 2.1% of all families.

Similarly, there were 998 families with at least *one* tuberculoid patient; thus 68.4% of patient families have at least *one* tuberculoid patient, or a prevalence of 6.6% of all families.

Further analyses will be reported later.

COMMENTS

The different methods of approach in the 3 blocks may make the comparative study of the epidemiology of leprosy in this area somewhat difficult at this stage. Nevertheless, the present programme gives a fair idea of the different characteristics of the patients in relation to similar features in the population of the project area.

The difference in the incidence of leprosy between male and female members of the population is significant only in the adult population. Among children, i.e., those below 15 years of age, however, the incidence of leprosy among males and females is almost the same.

50% of all leprosy patients in this area have tuberculoid type of leprosy; 20% lepromatous type; 20% indeterminate and 10% borderline. However, there is a marked difference in the distribution of leprosy according to classification among adults and children; and among adult males and adult females.

In all the blocks, the prevalence of lepromatous leprosy among adult males is significantly higher than that among females. Sex ratio in the entire population is 982 whereas among patients it is 740. Unknown causes, such as hormonal influences, in determining susceptibility to *M. leprae* may be worth exploring.

The over-all prevalence of leprosy in this area is 2.91% and prevalence of lepromatous type is 0.60%. The over-all prevalence of leprosy among males (adults and children) is higher (3.24%) than that among females (adults and children 2.46%).

10% of the families in the project area have at least *one* leprosy patient among them.

Among the families with at least one leprosy patient in the family, 22.2% have at least *one patient with lepromatous leprosy*, giving a prevalence of 2.1% of all families in the project area.

68.4% of patient families have at least *one tuberculoid leprosy patient*, giving a prevalence rate of 6.6% of all families in the project area.

SUMMARY

1. The over-all prevalence of leprosy in the Gudiyatham taluk is 2.9%.

2. The prevalence rate for lepromatous leprosy is 0.6%, and forms 20% of total number of leprosy patients.

3. There is significant difference in the prevalence of leprosy between men and women, but not so among children.

4. The pattern of leprosy among children is different from

5. Preliminary analysis of intrafamilial incidence of leprosy shows a 10% prevalence among all families. The pattern according to type of leprosy is similar to that observed earlier according to individuals.

ACKNOWLEDGEMENTS

This work could not have been undertaken but for the munificent financial support by the Swedish Red Cross. We would like to express our gratitude to the authorities of the Swedish Red Cross for their continued encouragement and financial support.

We would like to record our deep appreciation of the valuable work done by Dr. and Dr. (Mrs.) Valentine Macaden, whose diligence and hard work laid the foundations of this programme. We acknowledge with gratitude their magnificent contribution to this programme. We are grateful to the many paramedical workers who have worked in the field and without whose steady and loyal service this programme would not have been possible.

We thank Mrs. L. Furness and Mr. P. L. N. Reddy for secretarial assistance; Mr. Chelladurai for statistical assistance, and Mr. Anandaraj for help with the medical records.

Lep. Rev. (1967) **38**, 2, 83-86

The Transient Reappearance of Morphologically Normal M. Leprae in Patients Under Treatment

S. G. BROWNE, O.B.E., M.D., F.R.C.P., F.R.C.S., D.T.M.

Director, Leprosy Study Centre, London

The current interest in drug-resistance in leprosy consequent on the use of the elegant methods of demonstrating such resistance by the mouse foot-pad inoculation technique (Shepard, 1960; Rees, 1964), suggests that the time may be ripe for critical and experimental reassessment, as opportunity offers, of clinically-based claims or suspicions that resistance had developed to one or other of the drugs used in the treatment of leprosy. Many workers who follow the changes in morphology of *M. leprae* as seen in skin-smear preparations taken regularly by standard techniques, are impressed by the reappearance from time to time of 'solid rods' in patients with multibacillary leprosy treated with any of the drugs that have been in widespread use: dapsone (Cochrane, 1951; Wheate, 1960; *British Med. J.*, 1960), thiacetazone (Davey, 1960; Le Khac Quyen *et al.*, 1960), thiambutosine (Davey, 1960), diamino-diphenyl sulphoxide (Browne and Davey, 1961), Vadrine (Jopling and Ridley, 1951, 1958; Allen, 1961), ditophal (Davey, 1959; Davies and Driver, 1960), B 663 (Geigy) (Browne and Hogerzeil, 1962).

In some instances, but not necessarily, this reappearance of solid rods has coincided with the onset of an episode of acute exacerbation (Schujman, 1960). Some patients have shown this phenomenon after months or years of clinical and bacteriological quiescence, while in others the morphologically normal bacilli have reappeared in tissues that have never been entirely free from acid-fast bacilli, intact or abnormal. Some observers have demonstrated that clinical and bacteriological relapses are controllable by the same drug as was previously effective (Garrett, 1956, a and b), whereas others have used another drug on the assumption that the morphologically normal bacilli that had suddenly appeared were resistant to the first. With the object of postponing indefinitely or preventing completely the emergence of drug-resistant strains of *M. leprae*, some workers have, advised the giving of more than one anti-leprosy drug (Dharmendra and Chatterjee, 1956; Floch 1966). Davey (1960) referred to an apparent decline in therapeutic activity during the second or third year of the exhibition of a drug, while other workers have emphasized the distinction to be drawn between the bactericidal or bacteriostatic action of a drug that resulted in a fall to zero of the Morphological Index, and the failure of the same drug to facilitate removal of effete mycobacteria from the tissues (Browne, 1967).

On the analogy of the drug treatment of other diseases, as Spencer Reed (1960) and others have pointed out, it would be most unlikely if resistance to drugs did not develop in leprosy. Until now, apart from the inconclusive method of continuing treatment with the suspected drug and observing no degenerative changes in *M. leprae* as seen in slit-smear preparations or histological sections, no scientifically convincing procedure has been available for demonstrating mycobacterial resistance to drugs used in leprosy. It is possible that instances of the transient reappearance of morphologically normal bacilli have been assumed to be examples of drug resistance.

REAPPEARANCE OF MORPHOLOGICALLY NORMAL FORMS OF *M. leprae* DETERMINATION

It is only when skin smears are regularly and

skilfully examined at frequent intervals that the transient reappearance of morphologically normal forms is noted. At the Uzuakoli (Eastern Nigeria) Leprosy Research Unit, it was the practice to take smears from 6 skin and 2 nasal mucosal sites every month from patients with multi-bacillary leprosy (lepromatous, or highly positive borderline) participating in drug trials.

CRITERIA

Owing to the somewhat fortuitous nature of the smearing technique, it is possible that the point of the scalpel would from time to time take dermal material from atypical areas, and thus sometimes reveal residual nests of normal bacilli in tissue otherwise free from bacilli. However, when routine smears are taken from the same sites by a standard technique, and examined blind by the same skilled technician, normal bacilli are generally found to disappear from all the sites within a few months of each other (Browne, 1959, 1966). When normal forms continue to be absent from all the sites in 3 successful monthly smears, it is unlikely that small pockets of normal bacilli are being missed at these sites.

The criteria adopted in this study were these: complete absence for at least 5 months of solid rods in all the monthly smears from the 8 sites regularly smeared (i.e., the active edge of skin lesions (2), the anterior aspect of the thigh, the posterior aspect of the arm; both ear-lobes; both sides of the nasal septum) followed by the appearance of at least 5% (an arbitrary figure) of solid rods in at least 3 successive monthly smears at one or more of the sites.

FREQUENCY

During a 4 year period, 78 patients out of a total under treatment of 500 with multi-bacillary leprosy, conformed to the above criteria. The population was 'selected' in the sense that all had been admitted as in-patients to the Uzuakoli Leprosy Research Unit. The frequency among the out-patients attending the district leprosy clinics is unknown.

BACTERIOLOGICAL STATE OF THE PATIENTS

There was no difference between the patients in whom solid rods made their reappearance and other patients, as far as the initial heights of the Bacterial and the Morphological Indexes were concerned, nor was there any difference between these groups in the rates of fall of the 2 Indexes.

DURATION OF TREATMENT BEFORE REAPPEARANCE OF SOLID RODS

Over 70% of the patients had had between 10 and 18 months' treatment before solid rods reappeared (average 12½ months), and no solid rods had been seen in the smears for at least 5 months.

In a small proportion of patients (about 10%) solid rods appeared during the second 6 months of treatment; for the most part, these patients had had leprosy for a relatively short time. Special care was taken—because of the rapid disappearance of solid rods in patients with borderline leprosy—to ensure that all patients in this group were indeed suffering from lepromatous leprosy. In the remaining patients, the reappearance of normal forms was delayed for longer than 18 months, sometimes for much longer.

THE DURATION OF SOLID RODS IN THE MONTHLY SMEARS

After their reappearance, solid rods persisted in the monthly smears for an average of from 4 to 5 months, with the great bulk of the patients having solid rods in 3 successive monthly smears.

In half the patients, 2 groups of sites were affected, most often the skin and the ear-lobes; in a quarter, one site only was affected, and where this was the case, the nasal mucosa was by far the most frequent site to be solely affected; in the remaining quarter of the patients, sites in skin and ear-lobes and the nasal mucosa were affected. In some patients, on some occasions, most of the sites would show a few normal bacilli, the numbers varying from site to site; in other patients, many bacilli would be found at one site and none at all elsewhere.

PERCENTAGE OF SOLID RODS

In most patients, the average percentage of solid rods actually present in the smears varied from 5 (the minimum accepted as a basis in this investigation) to 20. In some patients, 100% of a small number of bacilli (for instance, in material from the septal mucosa) might be morphologically normal, and these would disappear like those at other sites within 4 or 5 months on the average.

PERSISTENCE OF BACILLI

No conclusions can be drawn from this series as to the sites (skin, ear-lobes or nasal mucosa) where normal bacilli are most likely to persist.

ACCOMPANYING CONCENTRATION OF *M. leprae*

There was no increase in the Bacterial Index in the great majority of patients, accompanying the reappearance of morphologically normal bacilli. In other words, the addition of normal forms was not of such a degree that the numerical assessment of the Bacterial Index was increased.

PREVIOUS TREATMENT

Solid rods reappear in patients irrespective of the drug used and the dosage used. During the period of this investigation, the commonest drugs given were dapsone, thiambutosine and B 663 (Geigy).

SUBSEQUENT TREATMENT

In most cases, the same drug was continued at the same dose, and the morphologically normal forms disappeared after the lapse of the period indicated above. In the case of ditophal, however, the reappearance of solid rods coincided with the patients' reduced enthusiasm for the evil-smelling compound, and dapsone was substituted for ditophal.

DRUG RESISTANCE

During the period under review, dapsone resistant bacilli were thought to have appeared in one patient. He had been re-admitted because of relapse following irregular and intermittent treatment. While taking dapsone under supervision, the lesions actually became worse and the proportion of normal bacilli in the monthly smears showed a steady increase. Since facilities for inoculation of material from this patient into mouse foot-pads were not then available, scientific proof of resistance is lacking. He improved on B 663 (Geigy), the solid rods disappearing from all sites smeared within a few months.

DISCUSSION

The patients in this group do not include those whose routine smears for many months showed numerous solid rods which eventually disappeared while the same treatment was continued. This slow bacteriological response may or may not be accompanied by a slow clinical response, and is to be distinguished from a relapse which is controllable by the same treatment as was previously effective.

The findings here reported cannot be explained by chance, by poor technique or a change of technicians. It seems that there may be from time to time a relatively sudden burst of activity of *M. leprae* that results in the appearance of solid rods at a rate faster than can be acted upon by the available drug. These bacilli are not resistant to the drug used, but an erroneous impression of resistance may be deduced if recourse is had at once to another anti-leprosy drug.

The reason for the sudden burgeoning of morphologically normal bacilli is not immediately apparent. At one stage, it was thought that climatic factors played a part, since most cases arose in the second quarter of the year when temperature and relative humidity were highest, but this explanation lacked conviction.

The observation that solid rods reappeared at several of the sites and thereafter disappeared—all within a period averaging a little over 4 months—might indicate that some extraneous factor was operative. No obvious factor or single explanation suggests itself. It is possible that the dietary intake or the absorption of para-amino-benzoic acid may vary from season to season, necessitating different amounts of circulating or available dapsone.

The microscopical situations where the normal bacilli have been lurking, unaffected by presumably inhibitory concentrations of drug in the tissues, are not disclosed on histological examination, except insofar as normal bacilli are frequently to be seen between the nerve fibres in the dermis, in the small dermal muscles, and in the endothelial cells of the small interrete blood plexuses. It may be that it is from these situations that normal bacilli suddenly—and in response to some unknown factor—begin to multiply more rapidly in a patient under therapy. As the bacilli become exposed to inhibitory concentrations of the drug employed, their sensitivity to the drug becomes apparent once again, and their subsequent history differs in no essential respect from that of bacilli that have already lived and died *in situ*. Rees (1963) has observed a similar chain of events in the case of *M. leprae* which may 'suddenly decide to multiply'.

SUMMARY

Morphologically normal *M. leprae* may reappear transiently at any of the sites habitually examined by the slit-smear technique. The most common time for this to occur is during the second year of treatment. There are generally no antecedents, clinical or bacteriological, to indicate that solid rods will reappear. There are usually no accompanying signs of acute exacerbation, and the total bacillary load is not as a rule greatly increased. The bacilli are not resistant to the drug given, and will disappear within a few months as treatment is continued with the same drug. The reappearance is to be detected only by the regular and careful examination of skin smears

REFERENCES

ALLEN, J. A. (1961). *Lep. Rev.*, **32**, 191.
BRIT. MED. J. (1960). Editorial, **2**, 655.
BROWNE, S. G. (1959). *Lep. Rev.*, **30**, 174.
BROWNE, S. G. (1966). *Lep. Rev.*, **37**, 23.
BROWNE, S. G. (1967). *Trans. R. Soc. Trop. Med. Hyg.*, In the Press.
BROWNE, S. G. and DAVEY, T. F. (1961). *Lep. Rev.*, **32**, 194.
BROWNE, S. G. and HOGERZEIL, L. M. (1962). *Lep. Rev.*, **33**, 185.
COCHRANE, R. G. (1951). *Lep. Rev.*, **22**, 64.
DAVEY, T. F. (1959). *Lep. Rev.*, **30**, 71.
DAVEY, T. F. (1960). *Trans. R. Soc. Trop. Med. Hyg.*, **54**, 199.
DAVIES, G. E. and DRIVER, G. W. (1960). *Lep. Rev.*, **31**, 53.
DHARMENDRA and CHATTERJEE, K. R. (1956). *Leprosy in India*, **27**, 3.
FLOCH, H. A. (1966). *Bull. Soc. Path. Exot.*, **59**, 188.
GARRETT, A. (1956). *Lep. Rev.*, **27**, 58.
GARRETT, A. (1956). *Lep. Rev.*, **27**, 178.
JOPLING, W. and RIDLEY, D. S. (1958). *Lep. Rev.*, **29**, 143.
JOPLING, W. and RIDLEY, D. S. (1961). *Lep. Rev.*, **32**, 188.
LE KHAC QUYEN, BUU-HOI, N. P. and XUONG, N. D. (1960). *Bull. Acad. Nat. Méd.*, **144**, 535-538.
REED, SPENCER (1960). *Brit. Med. J.*, **2**, 1672.
REES, R. J. W. (1963). The Pathogenesis of Leprosy. Ciba Foundation Study Group No. 15. London. J. & A. Churchill Ltd.
REES, R. J. W. (1964). *Brit. J. Exp. Path.* **45**,, 207.
SHEPARD, C. C. (1960). *Amer. J. Hyg.*, **71**, 147.
SCHUJMAN, S. (1960). *Leprología*, **5**, 32.
WHEATE, H. W. (1951). *Lep. Rev.*, **22**, 80.

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Risk of Infection in Leprosy*

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Part 1

Treatment of Infector and Other Factors

This presentation consists of a statistical study of the risk of infection to contacts of infectious patients registered at the Clinic of the Acworth Leprosy Hospital, Bombay.

Involved in this study is, among other factors, the effect of treatment of the infectors on the risk of infection to their contacts.

Risk of infection has been defined as follows: Considering a group of contacts homogeneous for the factor or factors under consideration, the risk of infection is obtained as the quotient of the number of contacts who develop the disease to the total number of contacts. Thus it is the probability that a given contact from such a group will develop the disease.

MATERIAL AND METHODS

Information on 1,264 family members of patients who apparently commenced contact with their infectors before the age of $5\frac{1}{2}$ years, and their infectors, were obtained from the Contact and Patient Register of the Acworth Leprosy Hospital, Bombay. Only Lepromatous, Infectious Borderline and Reactional Tuberculoid infectors were considered.

Items of information collected were:—

1. Sex of Contact.
2. Age at Start of Contact.
3. Duration of Contact.
4. Adequacy of Treatment of the Infectors.

Generally, the infectors and many of their infected contacts were registered at the hospital some time after the development of the disease. The estimates of the duration of the disease given by the patients themselves are quite unreliable. Hence one of us (N.F.) scrutinized the case sheets of these patients and estimated the probable period between the development of the disease and registration at the hospital. Generally, the conservative estimates of 2 years for L1, 5 years for L2 and 8 years for L3 have been taken.

The estimated number of years of duration of the disease in the infectious state of the infector was subtracted from his or her year of registration to get the year in which he became infectious. Age at start of contact was the age of the contact in the above mentioned year and was obtained from the age of the contact in the year in which he was first examined. This factor is considered at 2 levels: (*a*) at birth and (*b*) after birth.

Age at start of contact was subtracted from the age at last examination (in the case of non-infected contacts) and from the age at the time of becoming infected (in the case of infected contacts) to obtain the duration of contact. This factor is considered at 3 levels: (*a*) short (1-4 years), (*b*) intermediate (5-8 years) and (*c*) long (more than 8 years).

For each infector, Sulphone treatment in months in each year from 1951 through 1962 was available. The period 1951 to 1962 was divided into 4 sub-periods of 3 years each.

* This study was undertaken with a grant given by W.H.O.

Treatment for an average of 4 months per year in a sub-period was taken to be sufficient to assume adequate treatment for that sub-period from the start or from the date of registration if it fell within the sub-period. If a sub-period with adequate treatment on the above basis was followed by one or more sub-periods without adequate treatment, adequate treatment over all the sub-periods was assumed if and only if there was an average of 3 months of treatment per year over all the relevant sub-periods. Irrespective of the above criteria, if a patient became bacteriologically negative, he was assumed to have had adequate treatment for 2 years in case of L1, 4 years in case of L2 and 5 years in case of L3, prior to the date of becoming negative, or from the date of registration whichever was later.

The infector could be untreated or inadequately treated throughout the duration of contact; or, he could be adequately treated for the whole duration; or, he could be inadequately treated for some part of the duration and adequately treated for the remaining part. Treatment status of the infector is correspondingly considered at 3 levels: (*a*) No or inadequate treatment (NT), (*b*) Adequate treatment (FT) and (*c*) Mixed (PT).

Two hundred and eighteen out of 1,264 contacts had to be rejected for various reasons, such as lack of information on infector, presumed contact with non-infectious infectors, late age at start of contact, etc. This left 1,046 contacts who could be considered for analysis.

Most of the comparisons have been made using Chi Square. Interactions were studied using the arcsin transformation of the proportion infected. The effect of duration of contact on risk of infection may more appropriately be studied by the life table method. However, this would require the follow-up of a sufficient number of contacts for a long period (8 years or more) with observations at regular intervals (at least annually). Among the 1,046 contacts in the present study, only 105 had long duration of contact and even for these patients there were no observations at regular intervals. Even if a specific study were to be started with this aim, there would be enormous difficulties in follow-up, since the addresses given vary from 'foot path' and 'hut' to somewhat more permanent locations.

RESULTS

Out of 1,046 contacts, 291 or 27.8% were found to be infected. This high risk might be due to various reasons.

(*a*) Contacts were all young, about 70% having contact at birth.

(*b*) Extreme poverty accentuating crowded living and low nutritional status.

Apart from these, selection of contacts through the Contact Register might have introduced an upward bias in that many of the contacts are

TABLE 1

Distribution of contacts with respect to various factors

Factor	*Levels*	*Total*	*Not Infected*	*Infected*	% *Infected*
Sex of Contact	Male	546	389	157	28.75
	Female	500	366	134	26.80
Age at Start	At Birth	716	536	180	25.14
	After Birth	330	219	111	33.64
Duration of Contact	Short	559	372	187	33.45
	Intermediate	382	295	87	22.77
	Long	105	88	17	16.19
Treatment of Infector	FT	114	97	17	14.91
	PT	289	234	55	19.03
	NT	643	424	219	34.06
	Total	1,046	755	291	27.82

brought to the hospital for examination only when they start showing signs of infection. Two hundred and fifty-six out of the 291 infected contacts were found to be infected at the first examination itself.

Table 1 gives the distribution of contacts according to (*a*) Sex of Contact, (*b*) Age at Start of Contact), (*c*) Duration of Contact, and (*d*) Treatment Status of Infector.

There is no difference in the risk of infection between the 2 sexes, the Chi Square value being 0.50 with 1 degree of freedom and probability great than 0.30.

The risk of infection rises sharply for those contacts who start contact after birth. This rise is highly significant, the Chi Square value being 7.55 with 1 degree of freedom and probability less than 0.01.

The risk of infection decreases with increasing duration of contact. This decrease is very highly significant, the Chi Square value being 20.74 with 2 degrees of freedom and probability less than 0.001.

The risk of infection decreases with rising treatment status of infector. This decrease is very highly significant, the Chi Square value being 33.05 with 2 degrees of freedom and probability less than 0.001.

Treatment status PT is a heterogenous group in that the proportion of the duration of contact lying within the treated period is highly variable. The way to overcome this difficulty is to partition this group into FT and NT according as the infector had been treated for more than half the duration of contact or not. The distribution of contacts according to this modified definition of treatment status is given in Table 2.

TABLE 2

Distribution of contacts with respect to treatment status of infector (PT partitioned)

Treatment Status	*Total*	*Not Infected*	*Infected*	*% Infected*
FT	204	180	24	11.76
NT	842	575	267	31.71
Total	1,046	755	291	27.81

Risk of infection with an untreated infector is almost thrice that with a treated infector. The difference is very highly significant, the Chi Square value being 32.53 with 1 degree of freedom and probability less than 0.001.

In summary, risk of infection rises sharply for those who start contact after birth while it decreases highly significantly with increasing duration of contact and rising treatment status of infector.

It is quite likely that more of the contacts starting contact at birth have also treated infectors. Similarly contacts with longer duration of contact may have a greater chance of having treated infectors. It will be of interest to see whether these interactions are the reasons for the above results.

The distribution of contacts according to age at start and duration of contact is given in Table 3.

TABLE 3

Distribution of contacts according to age at start and duration of contact with % infected and arcsin transformation

Age at Start of Contact		*Duration of Contact*			
		Short	*Intermediate*	*Long*	*Total*
At Birth	Total	423	223	70	716
	% I	26.95	25.11	14.29	25.14
	Arcsin	31.27	30.07	22.21	(30.01)
After Birth	Total	136	159	35	330
	% I	53.68	19.50	20.00	33.64
	Arcsin	47.11	26.21	26.56	(34.86)
Total	Total	559	382	105	1,046
	% I	33.45	22.77	16.19	27.82
	Arcsin	(35.12)	(28.46)	(23.66)	(31.83)

Among those who commenced contact at birth, 60% have short duration, 30% have intermediate duration and 10% have long duration. Among the other contacts, 40% have short duration, 50% have intermediate duration and 10% have long duration. Thus the smaller risk in those commencing contact at birth could not have been caused by a larger proportion of them having longer duration of contact.

Among contacts who had short, intermediate and long periods of contact, 75, 58 and 67% respectively commenced contact with the infector at birth. Thus the smaller risk with increasing duration of contact could not have been caused by a larger proportion of them being contacts starting contact at birth.

Analysis of variance of % infected shows that each factor must be considered separately for different levels of other factors. For contacts starting at birth, short or intermediate duration does not make any difference. But long duration significantly decreases the risk, the Chi Square value being 4.23 with 1 degree of freedom and probability less than 0.05.

For contacts starting contact after birth, intermediate or long duration does not make any difference. But short duration increases the risk very highly significantly. The Chi Square value being 40.11 with 1 degree of freedom and probability less than 0.001.

For contacts having intermediate or long duration, whether the contact started at or after birth does not make any difference. But for contacts having short duration, start of contact after birth increases the risk very significantly, the Chi Square value being 31.83 with 1 degree of freedom and probability less than 0.001.

The distribution of contacts according to age at start of contact and treatment status of infector is given in Table 4.

Among contacts starting contact at birth, about 26% have treated infectors while among the other only 4% have treated infectors. Hence the reduced risk at birth might be due to the higher proportion of treated infectors for this group. Similarly among contacts having treated infectors only 7% start contact after birth while among contacts having untreated infectors this proportion is about 38%.

Analysis of variance of % infected is given in Table 5.

TABLE 4

Distribution of contacts according to age at start of contact and treatment status of infector, with % infected and arcsin transformation

Age at Start		*Treatment Status*		
		FT	*NT*	*Total*
At Birth	Total	190	526	716
	% I	12.63	29.66	25.14
	Arcsin	20.82	33.00	(29.77)
After Birth	Total	14	316	330
	% I	0.00	35.13	33.64
	Arcsin	0.00	36.35	(34.81)
Total	Total	204	842	1,046
	% I	11.76	31.71	27.82
	Arcsin	(19.39)	(34.26)	(31.36)

TABLE 5

Analysis of variance of data in Table 4

Source	*d.f.*	*ss*	*F*
Total	3	44023.3844	
Age at Start	1	5741.7078	6.99
Treatment Status	1	36305.5060	44.22
Interaction	1	1976.1706	2.41

The interaction is not significant.

TABLE 6

Distribution of contacts according to duration of contact and treatment status of infector, with % infected and arcsin transformation

Duration of Contact		*Treatment Status*		
		FT	*NT*	*Total*
Short	Total	96	463	559
	% I	12.50	37.80	33.45
	Arcsin	20.70	37.94	(34.98)
Inter-mediate	Total	79	303	382
	% I	12.66	25.41	22.77
	Arcsin	20.84	30.27	(28.32)
Long	Total	29	76	105
	% I	6.90	19.74	16.19
	Arcsin	15.23	26.38	(23.39)
Total	Total	204	842	1,046
	% I	11.76	31.71	27.82
	Arcsin	(19.88)	(34.14)	(31.38)

The distribution of contacts according to duration of contact and treatment status of infector is given in Table 6.

Contacts with treated infectors increase from 17.2% among those with short duration to 20.7% among those with intermediate duration to 27.6% among those with long duration. Hence, the reduced risk with increasing duration might partly be due to the higher proportion of contacts with treated infectors. Among contacts with treated infectors, 47% are with short duration and 14% with long duration while among contacts with untreated infectors, 55% are with short duration and only 9% are with long duration.

Analysis of variance of % infected is given in Table 7.

TABLE 7

Analysis of variance of data in Table 6

Source	*d.f.*	*ss*	*F*
Total	5	51309.0424	
Duration of Contract	2	17676.6072	10.76
Treatment Status	1	32925.8592	40.10
Interaction	2	706.5760	0.43

Interaction is not significant.

TABLE 8

Distribution of contacts according to age at start of contact, duration of contact and treatment status of infector

Age of Start	*Duration of Contact*		*Treatment Status*		
			FT	*NT*	*Total*
At Birth	Short	T	93	330	423
		% I	12.90	30.91	26.95
	Intermediate	T	75	148	223
		% I	13.33	31.08	25.11
	Long	T	22	48	70
		% I	9.09	16.67	14.29
	Total	T	190	526	716
		% I	12.63	29.66	25.14
After Birth	Short	T	3	133	136
		% I	0.00	54.89	53.68
	Intermediate	T	4	155	159
		% I	0.00	20.00	19.50
	Long	T	7	28	35
		% I	0.00	25.00	20.00
	Total	T	14	316	330
		% I	0.00	35.13	33.64
Total	Short	T	96	463	559
		% I	12.50	37.80	33.45
	Intermediate	T	79	303	382
		% I	12.66	25.41	22.77
	Long	T	29	76	105
		% I	6.90	19.74	16.19
	Total	T	204	842	1,046
		% I	11.76	31.71	27.82

DISCUSSION

The foregoing analysis of the data has clearly shown that treatment of the infector helps to reduce the risk of infection to his contacts highly significantly; and this independently of the age at which the contact started and the period of contact, as shown by the small values for interaction of treatment status with both, age at start of contact, and duration of contact.

Some other interesting results have also evolved from the analysis. Contrary to expectation, it was found that the longer the duration of contact, the less the risk of infection. Again, the risk is less if the contact starts at birth itself rather than later. These unexpected results become meaningful when the interaction between the 2 factors, which is highly significant, is taken into consideration. The only significant difference in the risk between those starting contact at birth and after birth is for short duration. It might be that individuals starting contact at birth might have some amount of immunity at birth itself. This is further borne out by the fact that such contacts maintain the same risk for a longer duration while those who start contact after birth have a precipitate fall in risk from short to intermediate duration.

The distribution of contacts with risk of infection with respect to all the 3 factors is given in Table 8.

It will be seen that, for all groups of contacts, treatment of the infector reduces the risk of infection substantially.

If we consider a cohort of 1,000 contacts starting contact at birth (or *in utero*), 309 will get infected in 4 years, another 215 in the next 4 years, and another 79 subsequently. In all 603 or about 60% will be infected, if the infector is untreated. However, if the infector has adequate treatment, those infected reduce to 129, 116 and 69, or in all to 314 or about 31%.

If contact started after birth, 549 will be infected in the first 4 years, 90 in the next 4 years, and another 90 subsequently, so that in all 729, or about 73%, will be infected if the infector is untreated. However, if the infector has adequate treatment, there is practically no risk.

SUMMARY

Data on 1,046 family members of patients who commenced contact with their infectors before $5\frac{1}{2}$ years of age, was analysed to study the risk of infection. The effect of treatment of the infectors on the risk of infection to the contacts, was also studied.

The risk of infection was found to be reduced substantially when the infector received adequate treatment.

It was also found that when contact commenced after birth higher risk resulted but decreased with increasing duration of contact. These results have been explained as probably due to the built-in immunity of those contacts who started contact at birth.

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Part 2
Chemoprophylaxis

This presentation is a statistical analysis of the results of chemoprophylaxis with DDS, taking into account various factors which influence the risk of infection as shown in Part I of this paper.

MATERIAL AND METHOD

The factors considered in this study are:—

1. Sex of contact: Male, Female.
2. Age at start of contact:
   Child (0-15 years).
   Adult (above 15 years).
3. Duration of contact:
   Short (1-4 years).
   Intermediate (5-8 years).
   Long (more than 8 years).
4. Treatment status of infector:
   Fully Treated: FT.
   Not Treated: NT.
5. Level of Prophylaxis:
   Adequate: AP.
   None: NP.

The methods for obtaining factor (2), (3) and (4) have been detailed in the earlier part. Treatment status has been considered only at 2 levels, with the partly treated group split into fully treated and not treated according to whether the infector has been getting adequate treatment for more than half the duration of contact or not.

Prophylaxis has been considered adequate if there was 3 years or more of prophylaxis with an average of 8 months per year and no long break within the first 3 years.

It may be noted that the infectors may vary in the virulence of their disease and that the contacts may vary in the period spent without prophylaxis. These factors have not been taken into account.

The statistical methods used are the Chi Square and the Analysis of Variance of the Arcsin transformation of % infected.

RESULTS

Out of 575 contacts with full information, 49 were found to be infected, giving a rate of infection of 8.52%. This is only about one-third of the rate of 27.82% found in the earlier report on children. This reduced risk may be due to 2 factors: In the present study, (1) only about 55% of the contacts had a starting age below 5 years and the risk is very much reduced for adults (*vide* Table 2) and (2) all contacts who first came to the hospital in an infected stage are excluded.

Out of 51 contacts with adequate prophylaxis, none was found to be infected, while 49 out of 524 contacts with no prophylaxis were found to be infected, giving a rate of 9.35%. The difference is significant, the Chi Square value being 5.23 with 1 degree of freedom.

Table 1 gives the distribution of the contacts according to levels of prophylaxis and sex of contact.

TABLE 1
Distribution of contacts according to levels of prophylaxis and sex of contact

Prophylaxis	*Sex*	*Total*	*NI*	*I*	*% I*
AP	Male	27	27	—	0.00
	Female	24	24	—	0.00
	Total	51	51	—	0.00
NP	Male	267	237	30	11.24
	Female	257	238	19	7.39
	Total	524	475	49	9.35
Total	Male	294	264	30	10.20
	Female	281	262	19	6.76
	Total	575	526	49	8.52

Males and Females are about equally distributed in both prophylactic groups. The sex difference is not significant either among all patients (Chi Square=2.19, with 1 d.f.), or among those with no prophylaxis (Chi Square=2.28, with 1 d.f.).

Table 2 gives the distribution of contacts according to levels of prophylaxis and age at start of contact.

TABLE 2

Distribution of contacts according to levels of prophylaxis and age at start

Prophylaxis	*Age at Start*	*Total*	*NI*	*I*	% *I*
AP	Child	38	38	—	0.00
	Adult	13	13	—	0.00
	Total	51	51	—	0.00
NP	Child	358	319	39	10.89
	Adult	166	156	10	6.02
	Total	524	475	49	9.35
Total	Child	396	357	39	9.85
	Adult	179	169	10	5.59
	Total	575	526	49	8.52

74.5% of the contacts with adequate prophylaxis are contacts with an earlier starting age, while this percentage is only 68.32 for contacts with no prophylaxis. This difference is not significant (Chi Square=0.83, with 1 d.f.). Even if this was significant, this should tend to give a lower risk for the no prophylaxis group since early starters have a higher risk.

The effect of age at start of contact is to decrease the risk with increasing age at start, even though this effect is not found to be significant either among all cases (Chi Square= 2.87, with 1 d.f.) or among those with no prophylaxis (Chi Square=3.17, with 1 d.f.).

Table 3 gives the distribution of contacts according to levels of prophylaxis and duration of contact.

Most contacts spend a part of the duration of contact in the beginning with no prophylaxis. Also, adequate prophylaxis requires a minimum of 3 years of prophylaxis. These 2 factors together ensure that most of the contacts with adequate prophylaxis will also have long

TABLE 3

Distribution of contacts according to levels of prophylaxis and duration of contact

Prophylaxis	*Duration*	*Total*	*NI*	*I*	% *I*
AP	Short	1	1	—	0.00
	Intermediate	3	3	—	0.00
	Long	47	47	—	0.00
	Total	51	51	—	0.00
NP	Short	103	88	15	14.56
	Intermediate	250	227	23	9.20
	Long	171	160	11	6.43
	Total	524	475	49	9.35
Total	Short	104	89	15	14.42
	Intermediate	253	230	23	9.09
	Long	218	207	11	5.05
	Total	575	526	49	8.52

duration. Since the risk of infection is found to decrease with increasing duration of contact, this could be one of the reasons for the reduced risk with adequate prophylaxis. Comparison of the contacts with long duration shows no significant differences between the adequate and no prophylaxis groups (Chi Square=3.18, with 1 d.f.). However, 53 of the 171 contacts with no prophylaxis and long duration had some prophylaxis and only one of them was found to be infected. Removing these, a rate of 8.47% is found for contacts with no prophylaxis at all and this is found to be significantly different from the rate for these with adequate prophylaxis (Chi Square=4.24, with 1 d.f..

As in the earlier study, the risk is found to decrease with increasing duration of contact. This decrease is significant among all patients (Chi Square=8.14, with 2 d.f.) but not so among those with no prophylaxis (Chi Square=4.91, with 2 d.f.).

Table 4 gives the distribution of contacts according to levels of prophylaxis and treatment status of infector.

TABLE 4

Distribution of contacts according to levels of prophylaxis and treatment status of infector

Prophylaxis	*Treatment Status*	*Total*	*NI*	*I*	% *I*
AP	FT	38	38	—	0.00
	NT	13	13	—	0.00
	Total	51	51	—	0.00
NP	FT	167	160	7	4.19
	NT	357	315	42	16.34
	Total	524	475	49	9.35
Total	FT	205	198	7	3.41
	NT	370	328	42	11.35
	Total	575	526	49	8.52

74.5% of the contacts with adequate prophylaxis have also fully treated infectors while only 31.9% of the contacts with no prophylaxis have such infectors. This difference is found to be highly significant (Chi Square= 36.83, with 1 d.f.). Since contacts with fully treated infectors have a smaller risk, this could be a reason for the apparent reduction in risk with adequate prophylaxis. In fact, prophylaxis is found to have no effect with fully treated infectors (Chi Square=1.65, with 1 d.f.) as well as with untreated infectors (Chi Square=1.73, with 1 d.f.).

Treatment of infector reduces the risk highly significantly among all contacts (Chi Square=10.66, with 1 d.f.) and among contacts with no prophylaxis (Chi Square=7.70, with 1 d.f.).

DISCUSSION

In summary, there is no significant difference in the rate of infection between the 2 sexes or between those who start contact as children or as adults (though the rate for the latter is only about half that for the former). The rate of infection decreases with increasing duration of contact and with treatment of infector. The 2 prophylactic groups do not differ in their distribution with respect to sex or age at start but do so highly significantly with respect to duration of contact and treatment status. Also these significant differences are in the direction which would tend to give a lower rate for those with adequate prophylaxis. In fact, prophylaxis does not appear to have any significant effect

TABLE 5

Distribution of Contacts in a restricted sample (duration more than 8 years)

Prophylaxis	*Age at Start*	*Treatment Status*	*Total*	*NI*	*I*	% *I*
AP	Child	FT	25	25	—	0.00
		NT	10	10	—	0.00
		Total	35	35	—	0.00
	Adult	FT	10	10	—	0.00
		NT	2	2	—	0.00
		Total	12	12	—	0.00
	Total	FT	35	35	—	0.00
		NT	12	12	—	0.00
		Total	47	47	—	0.00
NP	Child	FT	43	42	1	2.33
		NT	65	57	8	12.31
		Total	108	99	9	8.33
	Adult	FT	22	21	1	4.55
		NT	41	40	1	2.44
		Total	63	61	2	3.17
	Total	FT	65	63	2	3.08
		NT	106	97	9	8.49
		Total	171	160	11	6.43
Total	Child	FT	68	67	1	1.47
		NT	75	67	8	10.67
		Total	143	134	9	6.29
	Adult	FT	32	31	1	3.13
		NT	43	42	1	2.33
		Total	75	73	2	2.67
	Total	FT	100	98	2	2.00
		NT	118	109	9	7.63
		Total	218	207	11	5.05

among contacts with long duration or with the same type of infector with reference to treatment status, even though the reductions are very large.

A restricted sample of those with duration of contact more than 8 years give the results shown in Table 5.

The analysis of variance of the arcsin transformation of % I is given in Table 6.

TABLE 6

Analysis of variance of % I (Arcsin transformation)

Source	*d.f.*	*SS* (*MS*)	*F*
Total	7	28569.78	
Main Effects:			
Prophylaxis (P)	1	18495.54	22.53
Age at Start (A)	1	1087.75	1.32
Treatment Status (T)	1	485.35	0.59
Interactions:			
P × A	1	1900.68	2.32
P × T	1	2473.57	3.01
A × T	1	1016.08	1.24
P × A × T	1	3110.80	3.79

The effect of prophylaxis is highly significant with P .001. It must, however, be noted that the sample size for the sub-divisions of the adequate prophylaxis group is very small and that the interactions P × T and P × A × T approach the conventional level of significance of 5%. Also, both the factors, age at start and treatment status have differing distributions in the 2 prophylactic groups.

The 47 cases with adequate prophylaxis had an average duration of 12.3 years (all except one with a duration of 23 years had duration between 9 and 16 years), of which the first 6.4 years on the average was spent without prophylaxis and in the remaining period of 5.9 years (or 71 months) had on the average 57.7 months of prophylaxis, that is, about 10 months per year.

Chemoprophylaxis with DDS does appear to have some real effect on the risk of infection. However, the small samples with adequate prophylaxis render it difficult to disentangle this effect from the effects of duration of contact and treatment status of infector. A fully convincing case could be made only by comparing 2 groups of contacts who have been followed up from birth for a sufficiently long period.

SUMMARY

An analysis of 575 contacts, with at least 2 examinations separated by a year, has shown a significant reduction in the risk of infection where there is adequate prophylaxis. This effect seems to be real but the small samples with adequate prophylaxis render it difficult to disentangle this effect completely from the effects of duration of contact and treatment status of infector.

Lep. Rev. (1967) **38**, 2, 97-101

Advances in Immunology and Biochemistry in Leprosy in the Next Decade

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In an era in which man is concerned with sub-atomic particles and colonisation of the moon and the planet Mars, to speculate on advances that might occur in the realm of scientific knowledge in the next 100 years is not a gainful employment of time, especially since I do not possess the prophetic perception of H. G. Wells. I shall, therefore, confine myself to what seems probable in the next 10 years in the fields of immunology, metabolism and biochemistry in leprosy, in the light of our present experience and knowledge.

IMMUNOLOGY

Immunology of leprosy is an area of scientific work where there is more confusion than clarity of thought. On the one hand we speak of 'high resistance' to infection in the tuberculoid group of leprosy where there is a paucity of anti-bodies against *M. leprae* in the serum and no significant rise in gamma globulin. On the other hand, in lepromatous leprosy one finds a large rise in circulating antibodies against *M. leprae* in the serum and a marked rise in gamma globulin and yet this group of leprosy represents the 'no resistance' end of the spectrum in the host-parasite relationship. This is an enigma which may find a solution in the elucidation of the nature of symbiosis that exists between the intracellular parasite, *M. leprae* and the cells in which they proliferate. The mycobacterial capsular characteristics may be such as to protect it from the effect of the antibodies as well as from the hydrolytic enzymes—'phagolysosomes'. A study of the relationship between lysosomes in the cells parasitised by *Mycobacterium leprae* and the mycobacterium themselves may yield fruitful results. It has been suggested that DDS acts through the lysosomes which release the hydrolytic enzymes in the cells and that the enzymes kill the bacillus and help in the removal of the dead bacillus[1]. The study of lysosomes may not only give some clue regarding the pathogenesis of the reactive phases in leprosy, but also help in devising effective and rapid means of cure of leprosy.

The exacerbated phases in leprosy designated by the familiar term 'reaction' are a mystery. We know very little at the moment about the etiological background and pathogenesis of this distressing complication of leprosy which not uncommonly renders the patient incapable of being treated with the potent antileprosy drugs that are currently available. It is fairly well established that these reactive phases of leprosy are not directly related to mycobacterial activity. Current opinion favours an immunological phenomenon as the basic mechanism of production of these reactive phases.[2 3 4] Whether the reactive phase is a hypersensitivity phenomenon or whether it is fundamentally an autoimmune phenomenon is not yet clear.

No specific antigen-antibody reaction has been demonstrated in reactive phase. The presence of some of the 'markers of auto-immunity' in the sera of leprosy patients such as hypergammaglobulinaemia, anti-thyroid antibodies, anti-nuclear factor, rheumatoid-arthritis factor, lupus erythematous cell, have been well documented.[5 6] What is still open to debate is whether these play a causative role in the pathogenesis of reactive phases or whether they are the result of the tissue damage that occurs during reactive phase.

Paper read at the Scientific Session on the occasion of the Centenary Celebration of the Scudder Memorial Hospital, Ranipet, South India, on 10th December, 1966.

The recent work on lysosomes raises several hitherto unanticipated questions in this regard. Lysosomes are ultra-structural intracellular particles bounded by a membrane and contain hydrolytic and other enzymes, primarily concerned with phagocytosis and destruction of foreign particles.[7] It is not beyond reason to suggest that the hydrolytic and degradative enzymes released from lysosomes, may denature the native constituents of cells or connective tissue. Such denatured protein products would be expected to behave like antigens inducing the formation of circulating antibodies against themselves and the parent cell as part of the normal immune response. Thus the so-called 'auto-antibodies'—at least those encountered in the circulation—may represent a normal reaction to tissue damage and inflammation.[8] The 'auto-antibodies' in these diseases have not been shown to induce tissue damage. On the other hand, the release of lysosomal products into the cell-substance or surrounding tissues has been shown to initiate inflammation and tissue destruction.

In clinical practice, the disruption of lysosomes in living cells by ultra-violet light in patients with systemic lupus causes exacerbation of the disease. On the other hand, cortisone and its derivatives as well as Chloroquin have the property of stabilising the lysosomal membrane and retarding the release of enzymes from lysosomes. This can be demonstrated by pre-treatment with these drugs and exposure to ultra-violet light. Thus these therapeutically potent anti-inflammatory substances may, at least in part, exert their anti-inflammatory action by preventing or retarding release of lysosomes.[8]

The fundamental search, if the above thesis is correct, must shift from search for auto-immune antibodies and auto-immune mechanisms to a study of the characteristics and behaviour of lysosomes. In the next decade, then, I would venture to suggest that lysosomes will merit more attention in the study of immunity in leprosy and in other currently named auto-immune diseases, and may provide the key to unravel the mystery of what we now designate 'auto-immune phenomenon'.

IMMUNOLOGICAL METHODS FOR EARLY DETECTION AND DIAGNOSIS OF LEPROSY

One of the major problems in epidemiology and control of leprosy is of early diagnosis of leprosy, even before clinically detectable skin or nerve lesions are noticed, i.e., in the asymptomatic phase. At the moment there is no means of diagnosing latent or asymptomatic leprosy nor is there a satisfactory means of definitive diagnosis of leprosy when only a hypopigmented macule without sensory loss is found on routine examination. One can arrive at a definite diagnosis in patients with single 'patch' without sensory loss by means of careful and expert histopathological examination of skin biopsy. This can be done in a very few centres in the world.

Lepromin is not a diagnostic test in that it does not signify previous sensitisation with *Mycobacterium leprae*. Lepromin reaction only denotes the cellular response that may be elicited when the individual is challenged by *Mycobacterium leprae*. Thus, lepromin test, as we know it, is a useful prognostic tool but is of no use whatsoever in making a definite diagnosis of leprosy. Much work is in progress on the production of an antigen which is sufficiently specific for *M. leprae* to be capable of being used as a diagnostic tool in the study of asymptomatic, latent leprosy as well as early leprosy. One fondly hopes that such a specific antigen may emerge in the next 10 years and be of immense help to the epidemiologist as well as the field worker who is trying to detect and treat very early cases of leprosy.

Serological test for diagnosis of leprosy may be another important development. As I have already pointed out, in non-lepromatous leprosy there is no significant rise in serum antibody against *M. leprae*. On the other hand, in lepromatous leprosy which can be easily diagnosed by clinical examination and skin smears, there is plenty of antibody against *M. leprae* which can be demonstrated by fluorescence microscopy as well as immuno-

fluorescent techniques. A great deal of work is in progress to find a ready method of serological diagnosis of leprosy like in typhoid, brucella, etc. The standardisation of such a test is a likely advance during the next decade.

PROPHYLAXIS BY MASS VACCINATION

During the last decade striking progress has been made in the attempts to grow *M. leprae* in laboratory animals, in tissue culture and in artificial media. It is now authenticated beyond doubt that one can obtain limited multiplication of *M. leprae* in the footpads of mice by the technique described by Shepard and Rees indepdently.[9,10] Binford also has shown similar findings in the ears of golden hamsters.[11] Chang and Garbutt have demonstrated the possibility of multiplication of *M. leprae* in cell cultures.[12,13] B. R. Chatterjee has tentatively shown that *M. leprae* may be cultured in artificial medium.[14]

It appears very likely that during the next decade one may expect successful transmission of leprosy to laboratory animals and successful culture of *M. leprae* in the laboratory in artificial culture medium and in tissue cultures. If such an advance should result in '*in vitro*' growth of *M. leprae*, then it is not too much to expect the production of a vaccine which would protect against leprosy.

The limited success with BCG both in the footpad work[15] and in the field in protecting against leprosy[16] establishes the hope of the feasibility of the production of a vaccine which could be successfully used in prophylaxis against leprosy. This may well become the most significant advance in the epidemiology and control of leprosy in the next decade.

METABOLIC AND BIOCHEMICAL STUDIES IN LEPROSY

These have so far received step-motherly treatment in leprosy work. But for the early work of Sister Ross,[17] there is precious little done in biochemical and metabolic study in leprosy.

During the last 2 years I have been particularly intrigued by the metabolic and biochemical inter-relationship in leprosy. Shuster in Newcastle has recently demonstrated a whole range of metabolic and other systemic disturbances which are apparently caused by skin diseases themselves.[18] These major syndromes he has described in patients with skin diseases are the association of small intestinal malabsorption of fat, d-xylose, iron, folic acid and calcium; protein losing enteropathy as measured by faecal loss of radio-iodinated (I^{131}) polyvinyl pyrrolidine; villous atrophy in the jejunum in parallel with the chemical evidence of malabsorption; hyperoestrogenism and gynaecomastia.

In my study of the small bowel functions in patients with leprosy, nearly 30% of them are found to have malabsorption syndrome compared to an incidence of 10% in the control group. Nearly half the patients are folic deficient. To my knowledge, no such study has been undertaken among leprosy patients so far and our findings need to be carefully analysed and confirmed. I would suggest that there is much food for thought here.

The role of folic acid in the metabolism of *Mycobacterium leprae* is another aspect that is likely to lead to better understanding of the manifestations of the disease and perhaps to newer methods of treatment of the patient who is refractory to conventional treatment either because of resistance to the drug or because of recurrent attacks of erythema nodosum leprosum. A preliminary trial of one of the less known folic acid antagonists which I have conducted during the last few months has given encouraging results in my patients. This needs to be carefully authenticated before we can come to firm conclusions.

Another aspect of folic acid metabolism has attracted my attention. So far we have taken for granted that all neurological deficit in leprosy is a result of damage to peripheral nerves caused by the activity of *M. leprae*. I am aware that any view expressed to the contrary may raise a hornet's nest around my ears! Yet I cannot help putting it before you—I have often wondered whether the peripheral neuritis of leprosy may not in part be due to, or precipitated by, conditioned deficiency of folic

acid and/or B12. I suggest that much is to be learned by a careful study of these metabolic changes in leprosy patients. We should not glibly accept what appears to be obvious as the whole TRUTH.

Finally, I would like to bring to your attention *Mucopolysaccharide Metabolism in leprosy.* This is a fascinating facet that embraces a wide variety of changes. I shall confine myself to 2 features only:—

First—*C-reactive Protein* in the sera of leprosy patients is seen in some of them during reactive phases of the disease, quite independent of any rise in anti-streptolysin titre and the presence or absence of intercurrent infection.

C-reactive protein is a mucopolysaccharide one usually associates with tissue breakdown. What seems rather fascinating is the tentative conclusion that first, those patients in whom C-reactive protein can be demonstrated during the reactive phase tend to be the patients who are liable to get recurrent episodes of reaction; secondly, those patients who have C-reactive protein in the serum tend to take longer to clear the leprosy bacillus and hence take longer to become negative. These observations are tentative and need to be further studied. If true, this test may be prognostically significant and therapeutically helpful in that such patients may be considered unsuitable for treatment with DDS, at least intially.

The last observation I wish to make is in relation to 17-*Hydroxyproline*, which is a non-essential aminoacid that has been found to occur almost exclusively in collagen where it accounts for 13 to 14% of total aminoacids. A small amount is also found in elastin. With the development of specific methods for analysis, it was found that urinary hydroxyproline is excreted in a free form (3%) and in a polypeptide form (97%). The urinary excretion has been reported to be increased in a variety of clinical conditions ranging from cancer to collagen disease.[19]

We do not yet know of tests that would help the clinician to detect a patient who is likely to develop 'reaction' and pass into the subacute and chronic phases of this complication. During reaction, there is an accelerated breakdown of collagen as judged by the histological appearance of erythema nodosum leprosum. I wondered whether a quantative measurement of a product of collagen breakdown might tell us something about the metabolic make-up of a given patient. We began estimating 17-hydroxyproline, urocanic acid and other fractions of mucopolysaccharides in the urine of healthy controls and of leprosy patients. The preliminary observations suggest that the 'reactors' among our patients have a significantly higher urinary excretion of these metabolites even when they are free of clinically recognisable exacerbation and show further peaks in urinary excretion during phases of clinically obvious 'reaction'.

Metabolic survey of a patient may thus enable us to pick out the potentially difficult patient even before starting on treatment and by a careful choice of appropriate drug help to avoid or reduce the morbidity and mortality of reactions.

I am only bringing these data to your attention in the hope that you will see the wide spectrum of research possibilities and fascination in leprosy work. I am certain you will agree with me when I say that '*what the mind does not know, the eye cannot see*'.

From what has gone before I hope I have convinced you that 'Leprosy is Medicine' and leprosy work calls for the best that the medical profession can give to solve its mysteries which have baffled, frightened and fascinated man from time immemorial. All the newer knowledge and every new research tool in medicine must be harnessed if we are to solve the problem of leprosy. Leprosy is very much with us—should we not try and save the unborn child from a heritage of loneliness, shame, disfigurement and desolation ? Such an objective can only be attained when the modern Medicine Man finds it worth his time and talents to study leprosy and treat leprosy patients.

ACKNOWLEDGEMENT

I am grateful to Mrs. L. Furness for secretarial assistance.

SUMMARY

Advances in the realms of immunology, metabolism and biochemistry in leprosy that are likely to occur during the next decade are discussed in the light of our present experience and knowledge.

It is suggested that a more intensive study of the role of lysosomes in the pathogenesis of 'reaction' (exacerbated phases of leprosy) in leprosy may not only elucidate the mechanism of production of these complications but also help in devising effective and rapid means of treatment.

In the next decade one may look forward to the production of a specific antigen for the diagnosis of leprosy by skin tests. A specific serological test may also emerge.

Advances in prophylaxis against leprosy—chemotherapeutic and immunological (BCG)—can be expected.

A few advances in metabolic and biochemical studies in leprosy and their significance in the diagnosis and treatment of leprosy are discussed.

BIBLIOGRAPHY

1. COCHRANE, R. G. Leprosy Research. *Int. J. Lepr.*, **33**, 406-408, 1965.
2. COCHRANE, R. G. Leprosy Research. *Int. J. Lepr.*, **33**, 408, 1965.
3. JOB, C. K., MACADEN, V. P. and GUDE, S. L. Erythema Nodosum Leprosum. *Int. J. Lepr.*, 1964.
4. SKINSNES, O. K. and TANG, D. T. S. Lepra Reaction: an Immunologic Investigation. *Int. J. Lepr.*, **31**, 539, 1963.
5. BONOMO, L., TINSI, A., TRIMIGLIOZZI, G., DAMMACCO, F. L.E. Cell and Anti-nuclear Factors in Leprosy. *Brit. Med. J.*, **11**, 689, 1965.
6. KARAT, A. B. A., PULIMOOD, B. M., JOB, C. K. and KARAT, S. Unpublished observations.
7. DUVE, C. DE. Subcellular Particles, ed. Hayashi, T., 1959, p. 128. New York: Ronald Press.
8. WEISSMANN, G. Lysosomes, Auto-Immune Phenomena and Diseases of Connective Tissue. *Lancet*, **2**, 1373-1375, 1964.
9. SHEPARD, C. C. The Experimental Disease that Follows the Injection of Human Leprosy Bacillus into Footpads of Mice. *J. Exp. Med.*, **112**, 445, 1960.
10. REES, R. J. W. Limited Multiplication of Acid-fast Bacilli in Footpads of Mice Inoculated with *Mycobacterium leprae*. *Brit. J. Exper. Path*, **45**, 207, 1964.
11. BINFORD, C. H. Histiocytic Granulomatous Mycobacterial Lesions Produced in the Golden Hamster (*Cricetus Auratus*) Inoculated with Human Leprosy. *Lab. Investigation*, **8**, 901, 1959.
12. GARBUTT, E. Studies on *M. lepraemurium* and *M. leprae* in Tissue Culture. *Int. J. Lepr.*, **33**, 578, 1965.
13. CHANG, Y. T. and NEIKIRK, R. L. *Mycobacterium lepraemurium* and *Mycobacterium leprae* in Cultures of Mouse Peritoneal Macrophages. *Int. J. Lepr.*, **33**, 586, 1965.
14. CHATTERJEE, B. R. Growth Habits of *M. leprae*—their Implications. *Int. J. Lepr.*, **33**, 551, 1965.
15. SHEPARD, C. C. *Amer. J. Epid.*, **81**, 150, 1965.
16. KINNEAR BROWN, J. A., STONE, M. M. BCG Vaccination of Children against Leprosy: First Results of a Trial in Uganda. *Brit. Med. J.*, **1**, 7-14, 1966.
17. ROSS, SR. HILARY. Clinical Biochemistry and Immunology in Leprosy—A Review. *Leprosy in India*, **36**, 93-107 and 193-211, 1964.
18. SHUSTER, SAM and MARKS, JANET. Dermatogenic Enteropathy—A New Cause for Steatorrhoea. *Lancet*, **1**, 1367, 1965.
19. BONADONNA, G., MERLINO, M. J., MYERS, W. P. L., SORENBERG, M. Urinary Hydroxyproline and Calcium Metabolism in Patients with Cancer. *New Eng. J. of Med.*, **275**, 298-305, 1966.

Lep. Rev. (1967) **38**, 2, 103-106

Further Advances in Special Footwear and Moulded Soles

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Until recently boots for badly deformed feet of leprosy patients have tended to be very clumsy, broad and heavy looking. In many cases this has been a deterrent to the patient to wear the shoes. The use of tailor-made plastic lasts (Girling *et al.*) has helped to reduce some of this bulk but we were still left with boots that have the typical broad heavy welt that is associated with hand-made footwear. To overcome this a non-welt method of construction has been developed using an applied sole process that is similar to modern methods of shoe construction. With this modern method a high quality of adhesive is used along with special presses both of which are expensive. To reduce the cost we have used an open toe design of upper which allows us to stitch right round the inside of the sole through to the bottom sole with a strong locking stitch. This makes the construction strong enough and eliminates the need for the strong adhesive and special press.

METHOD

The upper of the boot is made in the usual way using an open toe design. In order to hold the foot firmly in place on the moulded sole and to act as a supporting edge to the plastic mould, a heavy bark tan leather heel counter is used. This stiffener extends to just behind the metatarsal heads. It is placed between the lining material and the upper leather and is blocked on to the last while it is wet so that it takes the exact shape of the last. This method of heel counter is only used when a plastic tailor-made last is used, as only then does one have the exact shape of the foot to work with.

The insole is positioned on to the bottom of the last in the usual way and the upper is lasted in place and held with nails. Normally the welt would now be stitched in place; instead the edge of the upper is trimmed to not less than 6 mm. from the edge. The upper is stitched to the insole and the nails removed (Fig. 1). A metal shank piece is placed from the heel to just behind the metatarsal heads (Fig. 2). To prevent the moulded sole from cracking and also to prevent extension of the metatarsal-phalangeal joints at toeing off the fore part of the boot is also made ridged. This is done by incorporating a cork roll in the sole. A piece of cork 15 mm. thick is positioned on the sole and rasped to the required shape. The edges of the cork are then covered with leather (Fig. 3). The rubber sole is stuck into position using a medium grade

† Sponsored by the Swiss Emmaus Association.

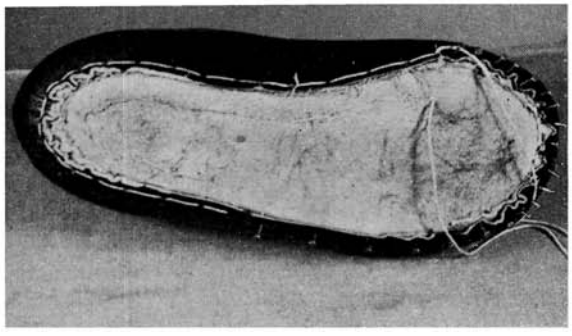

FIG. 1
Showing the stitching of the upper direct to the inner sole.

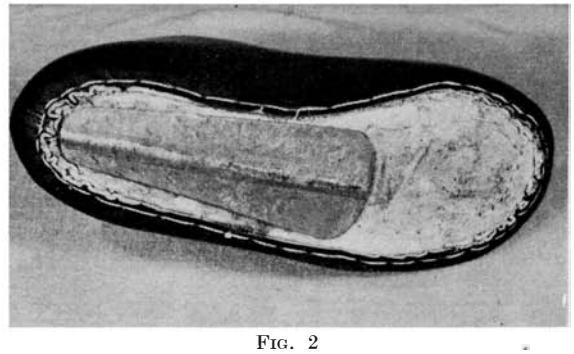

FIG. 2
The metal shank piece in place made from 16 gauge mild steel sheeting, with a ridge down the centre for strength.

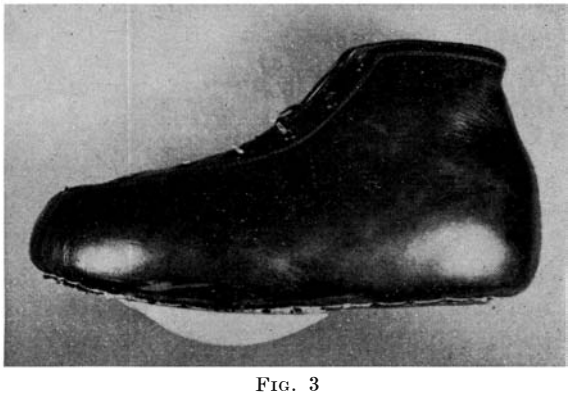

FIG. 3
The cork roll after the cork has been rasped down to shape and the edges covered with sheepskin.

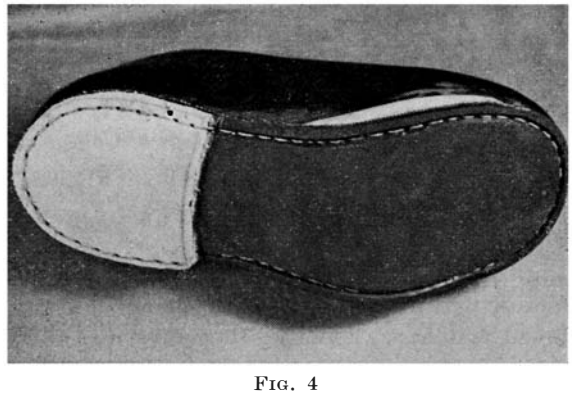

FIG. 4
The sole of the boot showing the locking stitch that passes right through to the inner sole. The heel has yet to have further pieces glued and nailed in place so as to bring it up to the same height as the roll.

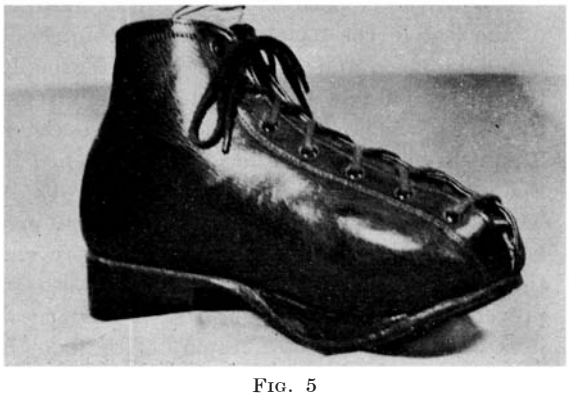

FIG. 5
The finished boot showing the open toe design and the roll. The improved lines and neatness can be compared with Fig. IX of the previous paper, 'Experimental Moulded Soles and Shoe Lasts'.

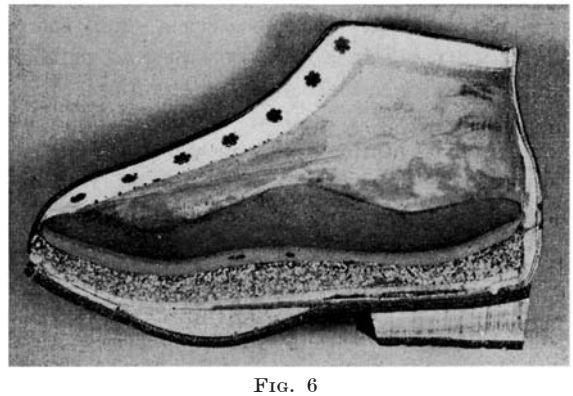

FIG. 6
The same boot cut in half to show the microcellular rubber insole, the cork and polyester planned distribution of pressure mould; good pressure is being taken under the medial arch and reduced pressure under the scarred head of the first metatarsal head. At the toes the locking stitch can be seen, also the shape of the cork roll and the length of the metal shank. At the heel the heavy bark tan heel counter can be seen.

adhesive. Two layers of the heel leather are stuck in place on the sole. The last is removed and the locking stitch using a strong thread is done right round the inside of the boot through to a stitching channel that has been cut in the bottom sole (Fig. 4). The rest of the heel is stuck and nailed in place so that it is the same height as the roll (Fig. 5).

MOULDED SOLES

The success of moulded soles for the prevention of ulcers in deformed feet has now been realized. Various materials for making the moulds have been tried out and it was thought that the answer had been found by using rubber latex and cork granules (Girling *et al.*). Over a period of time it was found that the cork and latex even though protected by a layer of microcellular rubber did not have the lasting qualities needed. The soles disintegrated and the patient was left with a thin sheet of microcellular rubber as the only protection between him and the sole of the boot. Further studies were carried out and it was found that polyester resin and cork granules have the initial moulding qualities as well as the necessary durability.

METHOD

Polyester resin and cork granules are used to make the mould. The polyester resin is mixed in the standard way (Polyester Hand Book). About 50 to 70 grams of resin are needed for each boot. The cork granules are mixed into it to a consistency so that the granules are wetted and stick to each other.

There are two ways of forming the mould. In the first method the aim is to produce a mould that is the same shape as the walking foot. The second method is to make a mould that will distribute greater weight on to parts of the foot that are not scarred and substantially reduce the pressure taken on the scarred areas.

To make the first type of mould the cork and polyester mixture is distributed in the boot nearly evenly with only a little more in the areas of the arch and a little less in the areas where the foot is prominent. The microcellular rubber insole is placed over it and the boot is put on the patient's foot. The patient stands and then walks about gently for a minute, he then sits while the polyester resin sets.

To make the second type of mould that has the planned distribution of pressures, the sole of the foot is studied and its exact position in the boot is observed before the cork and polyester is mixed. The cork and polyester is mixed and distributed in the boot so that there is a substantially greater quantity in the areas where the non-scarred parts of the foot are going to be and very little under the scarred areas (Fig. 6). The microcellular rubber insole is placed over it. The patient stands and takes 3 or 4 steps only. He then sits while the polyester resin sets. The boot is removed and the positioning of the mould is checked by eye; a method of accurately checking the mould is still to be developed. When the planned distribution of pressure mould is used the patient should be kept under observation for at least a week. In the event of the mould giving too high a pressure in any one place, the microcellular rubber insole is removed and that area of the mould is rasped down.

MICROCELLULAR RUBBER INSOLE

This insole which is placed over the cork and polyester should be made from 15 shore microcellular rubber 7 mm. thick. The rubber is cut out so that it is 5 mm. wider than the last all the way around except in the front where it is the same size and in the area of the medial arch where it is 10 mm. wider. The underside of this extra width of rubber is skived so that it will easily curve up around the foot and help encase it snugly in place on the mould.

This special type of footwear is expensive. So special care should be taken when prescribing such footwear that the patient is a suitable type. The best designed and made footwear is not sufficient alone to keep a patient free of ulcers. The patient himself must have a determination and incentive to be ulcer free. These complicated and costly boots will not work when used for the deformed feet of beggars and other patients who lack the necessary incentive. But they will work very successfully on patients who have been

truly rehabilitated and who realize the dangers and horrors of ulcers as well as the financial implications when an ulcer means loss of working hours. For the patient with deformed feet who is to be rehabilitated a well planned and made boot is a necessary part of his rehabilitation.

ACKNOWLEDGEMENTS

This work was supported by grants from the Office of Vocational Rehabilitation, Department of Health, Education and Welfare of the United States Government.

We also thank the firm of Scott Bader & Co. Ltd. for the technical advice and free materials that was given during the initial stages. Mr. Sigamoney is thanked for the photographs.

REFERENCES

1. GIRLING, J., HAMEED, M.A., SELVAPANDIAN, A. J. (1966). Experimental Moulded Soles and Shoe Lasts. *Lep. Rev.*, **37**, 2, 103.

2. Polyester Handbook 1963, Scott Bader & Co. Ltd. Printers: Percy Lund, Humphries and Co. Ltd., London.

Lep. Rev. (1967) **38**, 2, 107-108

Infectivity of Non-Lepromatous Leprosy

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While it is generally accepted that most forms of non-lepromatous leprosy may pass through a phase or phases in which the skin lesions are bacilliferous, very little is known of the frequency of such manifestations and in consequence of their importance from an epidemiological standpoint, though BROWNE (1) and (2) has drawn attention to the frequency with which the so-called 'macular dimorphous' lesions are bacilliferous.

At this leprosarium there has been a deliberate policy of concentration on the earliest possible diagnosis of the infective case at the rural dispensary, with the result that a high proportion of patients have been admitted suffering from an acute phase or reaction in the course of leprosy of a type other than lepromatous.

On the suggestion of Dr. Martinez Domínguez of W.H.O., who recently visited Chazi, the case records of patients admitted in the past 8 years have been analysed. It was found that of a total of 1,034 patients 206, that is 20%, were admitted with non-lepromatous leprosy in an acute phase. As the diagnosis was confirmed histologically in only a few patients, in order to avoid serious inaccuracies, especially those due to personal foibles in nomenclature, these 206 patients have been classified into 3 broad groups:—

(*a*) Tuberculoid in reaction.

(*b*) Indeterminate Leprosy in an acute phase, including the 'macular dimorphous' as described by Browne.

(*c*) Borderline and 'reactional tuberculoid', excluding all patients with lepromatous features clinically. This group is labelled for convenience 'Borderline Tuberculoid' to emphasise that it excludes 'Borderline Lepromatous'.

Bacilliferous patients occurred in all groups, as shown in the following table.

TABLE 1

Type	*Bacteriologically Positive on Admission*	*Bacteriologically Negative on Admission*	*Total*
Tuberculoid in Reaction	38 (66.6%)	19 (33.3%)	57
Indeterminate	52 (78.8%)	14 (11.2%)	66
Borderline Tuberculoid	75 (90.4%)	8 (9.6%)	83
Total	165 (80.0%)	41 (20.0%)	206

It is considered that the period of positivity of skin smears even under treatment is a better indication of potential infectivity than the degree of positivity on admission, this latter being liable to inaccuracy from many sources such as observer error by different microscopists at different times and differences in the positivity of the sites chosen for examination in successive patients. The following table is an analysis of these cases from this aspect.

TABLE 2

Type	*Positive at Initial Exam. only*	*Positive for 3 to 9 months*	*Positive for 9 months or more*	*Total*
Tuberculoid in Reaction	20 (52.7%)	16 (42.1%)	2 (5.2%)	38
Indeterminate	30 (57.7%)	17 (32.7%)	5 (9.6%)	52
Borderline Tuberculoid	26 (34.7%)	28 (37.3%)	21 (28.0%)	75
Total	76 (46.0%)	61 (37.0%)	28 (17.0%)	165

SUMMARY

This series indicates that in this part of Africa 80% of patients with acute ('reactional') phases of non-lepromatous leprosy are potentially infective and that the period of infectivity is likely to persist for several months in over 50% of such patients. It is probable, therefore, that patients of this type are of epidemiological importance.

ACKNOWLEDGEMENT

My thanks are due to the Chief Medical Officer, Ministry of Health, Tanzania, for permission to publish this note.

REFERENCE

BROWNE, S. G. (1) *Int. J. Lepr.*, **27** (1959), 103-109. (2) *Ibid.*, **34** (1966), 175-178.

Lep. Rev. (1967) **38**, 2, 109-11 2

Proposals for Future Studies in Genetics

Posthumous Publication of Notes by
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(With the help of Professor Thoday of Cambridge and Dr. S. G. Browne of the Leprosy Study Centre, 57a Wimpole Street, London, W.1, we have discovered these notes which contain a draft of Dr. Spickett's plans for a study of genetics and leprosy. Dr. Spickett had completed Parts I and II and they were published in *Leprosy Review*, **33**, 1962, and as we may never find the original script of Parts III and IV we have decided to publish this draft, considering that it will be of value to other geneticists who wish to study this important subject in leprosy and as a memorial to his name.)

The suspicion that leprosy is familial has been held since ancient times, and there can be little doubt that the probability of an individual contracting the disease is much higher if there is a member of the family with leprosy than if there is no member of the family so afflicted. It is probable, however, that the familial factor in the epidemiology of leprosy is complex, and that if there is any genetic effect it is but a component of the familial effect.

Whatever the precise mechanism of transmission of the disease may be there is a great weight of evidence to suggest that the probability of becoming infected varies as the intimacy of contact with an open patient. Patients have been known where the contact has been very brief; however they may be regarded as exceptional. It is clear that one component of the familial factor is due to the increased chance of contact when there is an open patient within the family. The mechanism of the transmission of *M. leprae* is a matter of dispute; nevertheless there is wide agreement that the frequency of effective transmission of the bacilli is far higher than the frequency with which new infections are established. This implied that there is variation in susceptibility. This variation in susceptibility may be genetic, environmental or both. There is a tendency for members of any family to be exposed to similar variations in the environment, such as standard of hygiene and diet; such factors may be of importance in their own right or in as much as they affect other factors such as transmission. On these grounds alone it would be expected that there is a familial effect.

It seems undeniable that there is a familial effect, and that this is made up of what may be termed an 'environmental component' and a 'contagion component'. These components will be of epidemiological importance for all population units.

Another possible component of the familial effect is genetic. There has been no reasonable attempt to gather the information from which an opinion can be formed as to the possibility of there being a genetic control of susceptibility. Any consideration of this problem is made difficult by reason of the factors that have already been discussed.

Leprosy is made manifest in many forms; these may be placed in two main categories: lepromatous leprosy and tuberculoid leprosy. Lepromatous leprosy is characterised by the presence of large numbers of acid-fast bacilli in the tissues. It is the form that is believed to be contagious. If untreated, extensive deformation occurs and ultimately death. It would appear that in this form of the disease there is no resistance to the presence and activities of the bacilli. Tuberculoid leprosy would appear to be characterised by a hypersensitivity to the bacilli. Very few bacilli are found in the tissues, the lesions and deformation that result are considered to be attributable to the host reaction rather than to the direct activities of the bacilli. This form of the disease is not lethal. New patients may be lepromatous

or tuberculoid in type or they may enter into a dimorphous or intermediate phase which may develop into one or other of the main forms later.

There are striking differences in the relative incidence of the two main forms in different populations. In negroid peoples about 90% of leprosy patients are tuberculoid and 10% lepromatous. This contrasts with 45% lepromatous and 55% tuberculoid in Caucasians. This could be explained on the basis of environmental variation, but it is found that expatriate peoples show a similar ratio of the two forms to those of their own race living in their native lands, not to those of the indigenous population, and this holds true whether they are living according to the conditions of their own race or according to the conditions of the indigenous population. This must be attributed to genetic differences in race, and it may be presumed that the racial differences are expression of variation in gene frequencies.

It might be considered that the different forms of the disease are expressions of genetic variation in the bacilli rather than in the human hosts. However, this does not account for the evidence of variation within multi-racial communities; furthermore it is difficult to see how the tuberculoid strain could be maintained at a high frequency since new infections are not started from tuberculoid patients. It might be argued that the environment of the host selects one strain over the other in an infection, and that the tuberculoid strain arises by mutation. This cannot be refuted, but it should be noted that it implies host variation.

I intend to collect data of the incidence of the different forms of the disease in a wide variety of communities in order to check the observations quoted. Particular attention will be devoted to the collection of data from areas where the incidence of leprosy has changed as a result of the establishment of leprosy hospitals, and where there are records covering the period of change.

A small amount of data has been gathered concerning the incidence of leprosy of the 2 types in families. These data relate to a comparison between the frequency of similar types of leprosy in identical twins and in sibs of the same sex.

Relationship	*Similar*	*Dissimilar*	*Total*
Identical twin	8	0	8
Sibs of the same sex	15	8	23

These data do not show a significant difference between the identical twins and the sibs, this is probably due to the small size of the sample. This evidence must, however, be regarded as very suggestive of a genetic control over susceptibility to either form of the disease.

It is planned to make a wide-scale survey of the pedigrees of leprosy patients.

It is possible to propose several genetic systems that fit such facts as are known. The ratios predicted from a single locus system are not consistent with the known facts, unless there are multiple alleles. The most probable systems are those with 2 pairs of alleles or gene complexes. Such a system is outlined below:—

A	Wild type	
a	Non-resistance	Locus 1
B	Wild type	
b	Hypersensitive	

A and B partially dominant

Genotypes	*Phenotypes*
AABB	Normal resistance
AABb	Normal resistance
AAbb	Tuberculoid
AaBB	Normal resistance
AaBb	Normal resistance
Aabb	Dimorphous tending to tuberculoid
aaBB	Lepromatous
aaBb	Dimorphous tending to lepromatous
aabb	Dimorphous equal tendency to lepromatous or dimorphous

The frequencies of 'a' and 'b' low as compared with the wild type alleles and varying in populations.

This system is, of course, highly speculative but provides a guide for the collection of data.

Any assumption that variation in the relative incidence of the different forms of leprosy between populations is attributable to variation

in gene frequency implies that different selective forces have operated on the populations. These differences are likely to be highly complex.

In medieval times leprosy was a common disease in Europe. There are now very few parts of Europe where the disease is endemic. This decline in the incidence of leprosy occurred before the introduction of effective drugs. Leprosy has been, and to a lesser extent still is, regarded with abhorrence in Europe. Leprosy patients were strictly segregated and their chances of marriage and parenthood were negligible, consequently genes giving susceptibility to leprosy were in effect sterility genes. If the relevant genes were recessive it can be calculated that the gene frequency would have fallen exponentially. The fall would be linear for a dominant gene with complete penetrance but since the penetrance of a leprosy gene is low and since the penetrance would fall with the decline in gene frequency (since the number of open patients would fall and penetrance depends upon contact with an open patient) a dominant gene would be expected to decline in freuency in a similar way to a recessive gene. It has been shown that when selection against a multifactorial genetic system of recessive genes is relaxed the gene frequency may be expected to rise. It would be expected, therefore, that amongst Europeans there would be a relatively high frequency of genes giving susceptibility to leprosy. This expectation is borne out by observation. There is evidence to suggest that resistance to leprosy confers some degree of susceptibility to tuberculosis and *vice versa*. Therefore, with the decline of leprosy, genes giving susceptibility to lepromatous leprosy would be selected for and those giving susceptibility to tuberculoid leprosy would be selected against on this basis of their effect on tuberculosis. The result of this would be a higher frequency of lepromatous susceptibility genes and hence of lepromatous leprosy in Europeans as compared with the native populations of leprosy endemic areas. This is borne out by observation.

There is not the same intensity of discrimination against leprosy patients in Africa, though there is some discrimination, particularly against people with lepromatous leprosy. In some communities people with lepromatous leprosy may only be able to marry those similarly afflicted. This enforced positive assortative mating would be expected to intensify the effect of selection against the relevant genes, and it is found that the relative incidence of lepromatous leprosy is low in such communities.

It is clear that the problem of gene frequencies in different populations is not simply a genetic problem but a problem of anthropology and social history also. I, therefore, intend to seek the collaboration of workers in the appropriate disciplines.

The work will in the first instance be restricted to the analysis of data obtained by the circulation of questionnaires to leprosy hospitals in a variety of leprosy endemic areas. Further work will depend upon the results of this analysis.

I wish to thank Dr. R. G. Cochrane, Adviser in Leprosy, Ministry of Health, London, for his interest in these proposals and for his offer of help in gathering the necessary information. I also wish to thank Prof. J. M. Thoday for his encouragement and advice as to the form that the investigations should take.

Proposed Investigations into the Genetics of Physiological Systems in the Mouse

The majority of characters that are studed in animal genetics are morphological. Morphology may be considered as the expression of physiological processes. However, the physiological variations that underlie morphological variation are usually obscure, so that the chain of causation between gene and character is very incompletely known. It, therefore, seems desirable to investigate the genetic systems controlling those physiological processes about which there is much detailed knowledge.

The characteristics that make an animal suitable for genetical experiment are often those that make it unsuitable for physiological work. Thus, though *Drosophila melanogaster* is eminently suitable for genetic studies, it is not a good subject for experimental physiology. The

animal that offeres the best compromise between the conflicting demands of the 2 types of experiment is probably the mouse.

There is detailed knowledge of some hormone controlled systems in the mouse. Two systems which appear to be suitable for genetical investigation are the control of water metabolism, and the control of the female sexual cycle.

It is possible to measure an animal's daily intake of water. The ratio of water intake to body weight provides information about the water balance that is being maintained by the animal. It is proposed to select mice for extremes of water balance. Lines of mice with a high water intake per unit body weight and with low water intake per unit body weight will be set up. The selected lines will then be compared in detail, following the methods of genetical analysis developed by Prof. Thoday, and the physiological techniques developed by Prof. Chester Jones.

Techniques have been developed by which it is possible to follow the course of the female sexual cycle of the rat. These techniques are very simple and there is little reason to doubt that they can be adapted for use on the mouse. It is proposed to select lines of mice for variation in the length of the different phases of the cycle. Genetical analysis will then be made on the selected lines. Physiological studies will also be made.

These investigations have not been initiated yet. Even when they are started pilot experiments will be essential and these will take a long time. The project is, therefore, a long-term one and it will be several years before any meaningful results can be expected.

Report

International Seminar on Leprosy, Agra.

January 31 - February 3, 1967

Written by the Chairman of the Scientific Programme Committee of the Seminar.

An International Seminar on Leprosy was held in Agra for 4 days following the inauguration of the India Centre, Japanese Asian Leprosy Mission (JALMA). The Seminar was sponsored by the Government of India in collaboration with the Indian Association of Leprologists and the All-India Workers Conference usually organised biennially by the Hind Kusht Nivaran Sangh. For this purpose the biennial Conferences of the two organisations due to be held at the end of 1966 were dropped and were merged with the International Seminar at Agra.

The Seminar was attended by over 200 delegates from India and about 40 delegates from abroad. The biggest delegation came from Japan, but there were delegates from United Kingdom, United States, Malaysia, etc. The organisations represented at the Seminar included World Health Organisation, UNICEF, Leonard Wood Memorial (American Leprosy Foundation), American Leprosy Mission, Leprosy Mission (the former Mission to Lepers), British Leprosy Relief Association (former British Empire Leprosy Relief Association) and British Medical Research Council.

The Seminar was inaugurated by Dr. Sushila Nayar, Minister for Health and Family Planning, Government of India. There were four Scientific Sessions and a Concluding Session. Each Session generally had two sittings, and the Chairmen of the Sessions were Dr. Dharmendra, Dr. N. Jungalwalla, Dr. P. N. Wahi, Prof. S. Hassagawa, Dr. F. Hemerijckx and Dr. O. W. Hasselblad.

At the inaugural session Dr. N. Jungalwalla, Additional Director General of Health Services, Government of India, welcomed the delegates, and the Seminar was then declared open by Dr. Sushila Nayar, the Union Minister of Health & Family Planning. In her inaugural address, Dr. Nayar highlighted the extent of the leprosy problem in India and the existing and planned anti-leprosy measures. She also referred to the international nature of the problem and expressed her gratefulness to the several international organisations that were lending help in the anti leprosy work in India. After the inaugural address, short speeches were made by Dr. Dharmendra, Chairman of the Scientific Programme Committee; Major General C. K. Lakshmanan, Hon. Secretary of the Hind Kusht Nivaran Sangh, Dr. R. V. Wardekar, President of the Indian Association of Leprologists; and some foreign delegations. Col. R. R. Rao, Deputy Director General of Health services, Government of India, proposed a vote of thanks.

The First Session dealt with the National Leprosy Control Programme in its first sitting, and the prophylaxis of leprosy in the second. In the first sitting, Drs. P. N. Khoshoo, V. Ekambaram and P. Kapoor described the extent of the leprosy problem and the present anti-leprosy measures and the proposals for their future expansion in India as a whole, Madras and Maharashtra States respectively. Dr. V. K. Sharma spoke on the 'Operational Aspects of Methods and Objectives in Leprosy Control Work', and Dr. V. P. Macaden described the results of a pilot study in methods of integrating leprosy work into General Health Services. Dr. A. B. A. Karat presented results of Absentative Survey in a Domiciliary Control Programme. According to Dr. Khoshoo out of 450 million population in India, about 300 million are exposed to leprosy infection, with an estimated 2.5 million cases of leprosy. So far only about one-fifth of the population at risk has been covered, and about 650 thousand cases of leprosy recorded; during the Fourth Plan (till 1971) it is expected to expand the coverage very considerably. Dr. Ekambaram stated that Madras was one of the most highly

endemic state with 35 million people exposed to risk of leprosy infection, and an estimated number of patients of 600 thousand. During the 3 plan periods in the post-independence era, about 5 million population has been covered, and 125 thousand patients brought under treatment. According to Dr. Kapoor there are about 300 thousand cases of leprosy in Maharashtra, of which about half have been recorded, and about 75% of the recorded patients are under treatment. Both these speakers brought out the importance of the extra-familial contact in the transmission of the disease in highly endemic rural areas, a fact which is now generally recognised.

In the sitting on Prophylaxis of Leprosy, Drs. Dharmendra and R. V. Wardekar presented their findings regarding the Chemoprophylaxis with Dapsone (DDS), and Dr. R. J. W. Rees presented the findings of Dr. Kinnear Brown on Immunoprophylaxis with BCG Vaccination. Dr. Dharmendra described the results of a study which has been in progress at the Central Leprosy Institute, Chingleput, for about 5 years; in a highly endemic area covering a population of about 215 thousand, with about 4.5 thousand leprosy patients, and a lepromatous rate of about 15%. The study has been carried out in intra-familial healthy contacts of infective patients, up to the age of 15 years, which were divided into 2 comparable groups—Prophylaxis and Control. The salient features of the results are: (i) There have been 41 leprosy patients in the Control Group (an incidence of 13%) and only 19 patients in the Prophylaxis Group (an incidence of 6%); (ii) There was a lag period of about 9 months after starting DDS prophylaxis during which there was no difference in the incidence of the disease in the 2 groups; and (iii) The protective effect was evident only in contacts up to 10 years of age, the most marked effect being in the contacts up to 2 years of age. In Dr. Wardekar's investigations the entire healthy population up to 25 years of age living in 54 villages has been included in the study. Twenty-seven of the villages have been taken as 'Control' and the other 27 as 'Prophylaxis' villages. During the period under study in the 'Control' villages, there were detected 54 leprosy patients in a population of 11,270 (4.79 per thousand) at the first resurvey after about a year, and 65 patients in a population of 12,124 (5.36 per thousand) at the second survey at the end of another year. The corresponding figures in the 'Prophylaxis' villages were 29 patients in a population of 11,270 (2.53 per thousand) and 14 patients in a population of 11,900 (1.7 per thousand) respectively. Unlike the results in the previous (Dharmendra) study, in Wardekar's study the protective value of DDS was seen in persons beyond the age of 10 years also, in the 10-25 age group. (However, the groups of contacts in the 2 studies were not comparable.) In presenting Dr. Brown's findings in Uganda with a lepromatous rate of 8%, Dr. Rees stated that the early results suggested a protection of 80% by BCG Vaccination, and that the protection was independent of the age at vaccination. In a follow-up study for varying periods up to 3 years, there were in all 107 leprosy patients, 89 among the 8,071 unvaccinated children, and 18 among the 8,091 BCG vaccinated children. Thus the incidence amongst unvaccinated children was 11 per thousand, and in the vaccinated children 2.2 per thousand.

The Second Session was devoted to papers on Recent Advances in Leprosy Research. Dr. C. C. Shepard spoke on 'Recent Advances in Experimental Pathology in Leprosy'; Dr. R. J. W. Rees on 'Recent Advances in Transmission of Experimental Human Leprosy in Mice'; Dr. M. Nishiura on 'Recent Advances in Electron Microscopy of Leprosy in Mice'; Dr. C. K. Job on 'Pathogenesis of Nasal Deformity in Lepromatous Leprosy'; Dr. K. Ramanujam on 'Follow-up Studies in Borderline Leprosy'; Dr. C. G. S. Iyer on 'Pathological Changes in Borderline Leprosy'; and Dr. M. S. Dash on 'Studies on the Mechanism of Cutaneous Sensory Loss in Leprosy, and an attempt for replacement.

Dr. Shepard developed on the practical applications of his now well-known technique of injecting leprosy material into the footpads of

mice. He then described the results of the studies of increasing resistance with BCG vaccination, and of those directed toward more precise understanding of the action of DDS. The results showed that vaccination with BCG afforded mice immunity against *M. leprae*, and that as little as 0.0001% DDS in the diet of mice is enough to prevent multiplication of *M. leprae*. Dr. Rees demonstrated the effect of enhancing infection in mice by depressing the immunological responses of the mice by prior thymectomy plus total body irradiation. The result was multiplication of the bacilli to a greater extent, and the infection, which normally remains localised to the footpad, becoming systemic. Dr. Nishiura presented ultra-structural features of leprosy bacilli in the various kinds of host cells in varieties of leprous lesions. Dr. Job described the pathological changes associated with nasal deformity in lepromatous leprosy. He concluded that in addition to the generally recognised destructive changes in the cartilagenous septum, there was infiltration and destructive changes in the bony part of the septum, and the small bones forming the wall of the nasal cavity. Dr. Ramanujam reported a follow-up study on 170 patients of Borderline Leprosy, with reference to clinical, bacteriological and immunological aspects. The patients had been under study from about 6 months to over 3 years. A significant finding was the very favourable clinical and bacteriological response while under controlled treatment, the response being quicker than observed in classical lepromatous patients under DDS treatment. He however, stressed the need of a follow-up study on a long-term basis, in order to find out whether the initial favourable results are long-lasting. Dr. Iyer reported on the histological findings, initial and repeated, on the above borderline patients. In the initial findings a background of tuberculoid histology predominated. Adopting the Ridley and Jopling histological classification, the initial findings could be put as BT in about 40% patients, 16% as BB, and 14% approaching BL; while the remaining 30% were arbitrarily classified as BT-BB. Thus the histological structure revealed a great variation spread over a large spectrum. During follow-up it was found that patients initially presenting BT or BT-BB histology showed the highest number of histological improvement, the percentage of improvement progressively diminishing with BB and BL categories. Dr. Dash described his observations regarding the restoration of sensation in anaesthetic skin in leprosy, and demonstrated an electronic device which is under study for induction of cutaneous sensation.

The Third Session was devoted to 'Medical Rehabilitation including Reconstructive Surgery and Physical Medicine'. In the morning sitting, dealing with Reconstructive Surgery, papers were presented by Dr. N. H. Antia, Dr. H. Srinivasan, Dr. T. Tamai, Dr. W. M. Lennox, Dr. (Mrs.) S. Karat and Dr. Winch on behalf of Dr. Tovey. Dr. Antia described the methods of plastic surgery for leprous deformities of the nose, loss of eye-brows, lagophthalmos, and facial paralysis. Dr. Srinivasan spoke about the prevention of Neuropathic Plantar Ulcers, specially their recurrence. He emphasised the need for an analytical and dynamic approach, and for each patient with recurrent ulceration to be examined in detail to trace the probable sequence of events since the original ulcer, so that appropriate treatment could be given on an individual basis. He illustrated his point of view by projecting a number of pre- and post-operative pictures from a number of patients. Dr. Tamai pointed out the value and limitations of reconstructive surgery in leprosy. He pointed out that reconstructive surgery was of value, but that it was not always the best method of treatment of deformities. Suitable splints and devices may have a favourable effect comparable to, and sometimes better than, that of reconstructive surgery. Dr. Lennox dealt with the management of advanced deformities in feet and the loss of sensation in hands. Dr. (Mrs.) Karat spoke on the 'Mode of occurence and healing of fractures in anaesthetic limbs in leprosy'. Dr. Winch, who presented a paper on behalf of Dr. Tovey, described the technique of operation for deformed nose devised by Dr. N. J. Cockett using a skin graft bag as in a posterior nasal inlay, and a columnellar bone graft.

In the afternoon sitting of the Third Session, papers on Physical Medicine were presented by Dr. J. Selvapandian, Shri N. Palani and Shri J. Girling. Dr. Selvapandian emphasised the importance of physical methods of treatment in the prevention of deformity; the simple methods of physical treatment include oil massage, wax bath, gentle passive stretching and splinting. Physical methods of treatment are also essential as pre- and post-operative measures. Shri Palani read a paper on 'Pre- and Post-operative Physiotherapy in the Management of Lumbrical Replacement in Leprosy.' These operations are done for the rectification of the clawing of the fingers. He listed the pre-operative and post-operative aims separately, and then described methods to achieve these aims. Shri Girling discussed the merits and demerits of the two standard designs of the Below Knee artificial limbs—the 'Conventional Prosthesis' with thigh corset, and the 'Patella Tendon Bearing' prosthesis. He also described the criteria to be taken into consideration when prescribing one of the two prosthesis in a particular patient.

The Fourth Session was devoted to Social Work and Rehabilitation. Dr. Hemerijckx, Dr. V. P. Dass, Shri Hebendale and Dr. Sharma spoke on the various aspects of the Social Problem in leprosy, and ways to deal with them. Amongst other things, emphasis was placed on the great need for educating the healthy population regarding the disease. In the sitting on Rehabilitation, Dr. O. W. Hasselblad, Dr. Y. Yajim, Miss Wilson, Shri H. D. Pavri and Mrs. K. V. Nimbkar presented their papers.

Speaking on 'Total Rehabilitation of Leprosy Patients', Dr. Hasselblad brought forward the important point that rehabilitation is a 'process needing co-ordination of skills and services tailored to meet the specific requirements of the individual patient'. He listed the skills and services that would be needed in this 'process' of rehabilitation. Further he laid emphasis on the prevention of disability, integration with existing public health services, and leprosy rehabilitation training to students in all medical, paramedical and ancillary professions. Dr. Yajima described the rehabilitation activities in Japan; he stated that systemic medical treatment has made social rehabilitation possible, but that much effort was yet needed to persuade the public to accept the cured patients. Miss Wilson presented the details of an 'Experiment in Agriculture' in progress at the Schieffelin Leprosy Research Laborary, Karigiri. Shri Pavri emphasised the need of vocational evaluation in vocational rehabilitation. This means the screening of the patient regarding his skill, ability, education and aptitude, etc., before training him for a particular job or profession. Mrs. Nimbkar developed on the 'Role of Occupational Therapy in Rehabilitation in Leprosy'. The occupational therapist has an important role to play in the team approach for total rehabilitation of the patient. The greatest challenge to the occupational therapist is from the patients with severely deformed hands, and the occupational therapist must devise special equipment, so that the patient can really look after himself. At the conclusion of the Session, the Chairman requested Shri Amte of Warora to give a brief description of the excellent rehabilitation work that he has been doing. The audience heard the brief account of his pioneer work with rapt attention, and at the end of his address he was given a standing ovation.

In the Concluding Session Dr. Dharmendra summed up the Seminar, Col. R. R. Rao, Deputy Director General of Health Services, Government of India, and Dr. D. N. Sharma, Director of Health and Medical Services, U.P., made speeches proposing votes of thanks. The Concluding Session was also addressed by some foreign delegates, Major General C. K. Lakshmanan, Hon. Secretary, Hind Kusht Nivaran Sangh, Dr. R. V. Wardekar, President, Indian Association of Leprologists, and Dr. P. N. Khoshoo, Director, National Leprosy Control Programme, Government of India. In summing up the Seminar, Dr. Dharmendra highlighted the salient features of the various Sessions, and complimented the participants for the high standard of presentations and discussions. The deliberations at the Seminar indicated that during recent years there has been appreciable

progress in our knowledge with reference to some basic factors regarding the disease, and in controlling the spread of the disease. The recent work on DDS and BCG prophylaxis against leprosy appears to have marked a breakthrough in the field of controlling the disease though much further work in this field remains to be done. He paid tributes to the scientific workers, as also to the field workers, both medical and para-medical, who, he said, were the most important tools in the National Leprosy Control Programme.

ELEP

The first General Assembly of the members of ELEP (the Co-ordinating Committee of European Voluntary Agencies engaged in the fight against leprosy) took place in Wurzburg, Germany, on January 7th and 8th, 1967. Representatives from 11 different member-organizations were present, from Belgium, France, West Germany, Switzerland, Great Britain, Italy and an oberver from Spain. Applications for membership from bodies in Luxembourg and Turkey were approved.

The Medical Commission, consisting of Drs. L. P. Aujoulat, S. G. Browne, M. Gilbert and F. Hemerijckx, had met previously to consider a lengthy agenda of items on which their advice had been sought. It seems that the Commission will be increasingly consulted by the General Assembly in respect not only of schemes already in existence but also of proposals for new projects to be undertaken by one or several of the member-organizations.

The General Assembly of ELEP recommended to its member-organizations that they should between them make a grant of 5,000 $ U.S. towards the expenses of the Ninth International Leprosy Congress to be held in London from 15th to 21st September, 1968. The Assembly also recommended that a total of 12,000 $ U.S. annually should be raised between the member-organizations to enable the Leprosy Study Centre, London, to engage a full-time histopathologist and a laboratory technologist. Continued interest was shown in the dapsone-prophylaxis scheme being supervised by the staff of the Leprosy Research Institute at Chingleput, South India.

Reports were made on certain aspects of leprosy work in Korea, Morocco, India, the Republic of Congo (Kinshasa).

Dr. Gilbert was asked to report on proposals for leprosy work in Morocco; Dr. Hemerijckx will investigate the possibilities of a leprosy control scheme in South India. Correlation of the teaching programme of A.L.E.R.T. (Addis Ababa) and the Institut Marchoux at Bamako (Mali) will be attempted by Drs. Aujoulat and Browne. Very cordial non-official contacts with those in charge of leprosy on the headquarters staff of the World Health Organization had been instituted.

An interesting indication of the changing emphasis apparent in the work of voluntary organizations is shown by the recommendation (which was heartily agreed upon), that an appreciable proportion of the budget of the member-organization should be ear-marked for research. The philanthropic public that contributes large sums of money for the relief of individuals suffering from leprosy, is becoming cognisant of the need to supplement government and academic institutions in research into this disease.

The Brussels bureau will act as a clearing-house for doctors wishing to work in leprosy and organizations having vacancies for such doctors in institutions with which they are connected. Doctors and member-organizations are requested to get into touch with the Secretariat and supply full particulars of their requirements. (Address: ELEP, 106 rue Stévin, Bruxelles 4, Belgium.)

The spirit of mutual helpfulness pervading these meetings, in both their scientific and their humanitarian aspects, augurs well for future working together in the fight against leprosy.

Letters to the Editor

Dear Sir,

I read with a great interest the stimulating article of Dr. R. E. Pfaltzgraff on 'Classification of Leprosy' in the January issue of the Review, and would like to offer the following comments:

Regarding the implication of the inevitability of deformity in leprosy which still remains, may I draw Dr. Pfaltzgraff's attention to paragraph 4 of my Conclusions to the effect that: 'deformity is *not* an inescapable feature of leprosy work. It is preventable by proper measures. All those experienced in leprology are agreed that most of the disabilities in leprosy can be prevented and that those which cannot be can be corrected by reconstructive surgery. *The philosophical acceptance of the inevitable is an attitude which can hardly be tolerated in this day and age*, when the present study shows that there is ample time for therapy to be carried out.'

Dr. Pfaltzgraff states that I have failed to show that the above is not the case, primarily because I do not fully acknowledge the direct relationship of disability to the classification of leprosy. I would point out from the start that disabilities are a *fait accompli* to the tune of several millions throughout the world today, a massive and alarmingly enough evidence in itself which prompted my study whilst adopting, as a working basis and for practical purposes, the Madrid classification recommended by the WHO. Whereas I do subscribe to Dr. Pfaltzgraff's views for the need of relating disability to the classification of the disease, yet I do feel that, at this juncture, it is primarily a question of securing the *consensus omnium* as to a common acceptance of terms in their entirety, hence the remark in the Introduction of my study to the effect that the classification of leprosy is *disputed* still.

Dr. Pfaltzgraff goes on to say that Indeterminate Leprosy, if correctly defined, is a group in whom deformity *never* occurs unless transformed into one of the definitive types of leprosy. I beg to differ here: the Indeterminate group is indeed notably unstable, most of the patients belonging to it changing eventually to either polar type of the disease, but there is still a number of these patients who carry on as such, whether one considers their persistently achromic macules residua or scars indicating healed lesions. There is ample evidence purporting to this fact in Northern Burma. On the other hand, in Pogiri, India—the Danish Centre where I was the WHO Team Leader in 1962-64, now coping with some 35,000 patients—I was able to follow but a dozen Indeterminate patients which changed mostly to the Tuberculoid form within a 6-9 months' period. In effect, out of the 1,568 patients I examined, 186, i.e. 11.2%, were Indeterminate, 25 among whom, i.e., 13.4%, with disabilities; allowing for marginal errors in classification since I worked mostly under field conditions, there still remains a small group of these patients significantly disabled, yet with the least potential.

I do agree with Dr. Pfaltzgraff that it would have been preferable to have divided the Tuberculoid group into its varieties, noting specifically the ones where deformity occurred, but I wish to stress that the majority of the patients I studied were longstanding patients and that it would have been, therefore, hazardous to have done so at their stage of the disease. Furthermore, I cannot concur with Dr. Pfaltzgraff's statement that deformity *never* occurs in Minor Tuberculoid nor that it may occur in one limb alone and seldom in all four in Major Tuberculoid when (i) 432 out of the 700 patients, i.e., 61.7%, showed a combined deformity of hand and foot, (ii) 262, i.e., 60.2%, among them had quadrilateral involvement, and (iii) their comparative frequency between clinical forms, as it would be expected, was identical as in the case of the hand and foot alone, 48.5% and 34.01% concerning the Tuberculoid group alone !

Finally, as regards my not carefully relating the *incidence* of deformity to the spectrum of disease accurately conceived, may I point out that the primary objective of my study was to

establish the *onset* of deformity *per se* and to sort out its pattern within the context of clinical observations, other workers having already shown to what an extent disabilities occur in the various forms of leprosy.

Dr. M. J. Mallac.
P.O. Box 1899,
Kinshasa, Congo.

2nd February, 1967.

Dear Sir,

In *Leprosy Review* of January, 1967, Rodrigo Gutiérrez published a Preliminary Report on the Effects of L-Triiodotyronine, Radioactive Iodine[131] and Methimazole on Experimental Murine Leprosy. The conclusion of this work is as follows: 'Our preliminary data seems to point to some "protective action" of Iodine[131] and of L-Triiodotyronine on experimental infection with the Stefansky bacillus.' On the other hand, Rodrigo Gutiérrez comments that Lurie *et al.* have found that the administration of thyroid hormones can increase the level of native resistance to TB in rabbits and that thyroidectomy and anti-thyroid drugs have the opposite effects. Concerning the conclusions of Lurie and Gutiérrez I must express the following opinions. Gutiérrez notes that all the animals were fed Purina Lab Chow. I do not know what nourishment was used by Dr. Lurie in his experiments with rabbits. It is possible that Dr. Lurie had used a nourishment for the rabbits which was analogous to Purina Lab Chow. Purina Lab Chow contains a quantity of iodine equivalent to 600 microgrammes per kilo. All these nutriments for animals have a content of minerals fixed by the National Research Council, Washington, D.C., U.S.A. I know the facts about nutrient 301 as revised January, 1954, by the Committee on Animal Nutrition.

In previous publications (Rojas) I have suggested the appropriateness of associating a hypo-iodic diet with the treatment of human leprosy per the medium of anti-thyroid substances such as Methimazole. I think that experiments with Methimazole in laboratory animals and other anti-thyroid substances should use a hypo-iodic diet so as to obtain adequate supporting evidence of the action of the drug.

It is my opinion that tactical compatibility between the anti-iodic substances such as Methimazole and the nutriment used (Purina Lab Chow) does not exist and I may mention that military terms are very suitable to the attack against the bacterium of leprosy. I wish to suggest a new experiment for the future, namely to use the nutriment with the lowest content of iodine at least in 50% of any new group of rabbits who should get Methimazole or Triiodotyronine.

The hypo-iodic diet well known at present for experiments on laboratory animals is a Remington diet. It contains 15 microgrammes of iodine per kilo. Though difficult it should be possible to prepare hypo-iodic nutriments for human use analogous to the Remington diet and usable in several pathological conditions. Thus we can initiate a therapeutic procedure wherein iodine will operate not by its presence but by its absence. References about the Remington diet are as follows:—

Levine, H., Remington, R. E. and von Kolnitz, H. *J. Nutr.*, 1933, **6**, 325.
Levine, H., Remington, R. E. and von Kolnitz, H. *J. Nutr.*, 1933, **6**, 347.
Chapman, A. *Endocrinology*, 1941, **29**, 680.
Axelrad, A. A., Leblond, C. P. and Isler, H. *Endocrinology*, 1955, **56**, 387.

Arturo O'Byrne.
Apartado Aéreo 1708
Cali, Colombia, South America.

13th February, 1967.

Lep. Rev. (1967) **38**, 2, 120-127

Abstracts

1. **Experimental Studies in Leprosy. Recent Applications of Experimental Human Leprosy in the Mouse Foot Pad,** by R. J. W. Rees. *Leprosy in India*, 1965, 3A, July Supplement.

We set out several years ago to see whether the viability of leprosy bacilli could be determined indirectly by morphological appearances. In our early studies we used *Myco. lepraemurium* as our model because a final check could be made on the viability (measured as infectivity) by putting the bacilli back into mice or rats and seeing whether they produced disease. The results of those studies showed conclusively that living and dead *Myco. lepraemurium* could be identified by their different morphological appearances and that these appearances were seen in bacilli stained by the classical Ziehl-Neelsen method. All bacilli that showed irregular staining were incapable of producing disease in animals and therefore were considered dead. We then extended our studies to *Myco. leprae* where we were able to show identical morphological differences. Therefore it was reasonable to conclude, since the morphological changes were common to any type of dead bacteria, that these same methods could be used for distinguishing dead and alive *Myco. leprae*. At that time we could not put these observations to direct test with *Myco. leprae* because the organism could neither be cultured nor transmitted to experimental animals. Now that there is available the mouse foot-pad infection it should be possible to carry out the same type of experiments we used for *Myco. lepraemurium*. One approach to this type of study is already in hand in our own laboratories. A series of experiments have been set up inoculating the mouse foot-pad with bacilli from patients who have received 12 or more months' treatment with DDS and where there are very high proportions of 'degenerate', irregularly staining acid-fast bacilli. Preliminary results indicate that in none of these mice followed now for periods up to 15 months has any infection been produced, whereas bacilli from previously untreated patients would have produced active disease and at least 100 fold increase in the number of bacilli within a period of 6-8 months. Therefore, we already have strong evidence to suggest that bacilli coming from these treated patients have very reduced viability and this is consistent with the morphological appearances of these organisms. Shepard and McRae have also analysed their own data in an attempt to correlate infectivity in the mouse foot-pad with the morphological appearance of *Myco. leprae*, and their results show conclusively that there is a complete correlation proving that only solidly stained bacilli are infective (viable).

With these important results it should be possible to test the infectivity of nasal and ulcer secretions containing *Myco. leprae* under various 'natural' conditions in order to determine the importance of such secretions in the spread of leprosy.

(*From the author's summary.*)

2. **75 years of Organized Measures for Leprosy Control in Estonia,** by E. Roigas and R. Uetoa. *J. Dermat. & Venerol.*, Moscow, 1966, Oct.

Some data concerning the history of leprosy in Estonia since 1222 are presented. The foundation of leprosaria by the 'Society for Control of Leprosy in Livland' in 1891 must be considered as the first organized measure for control of leprosy in Estonia. Success achieved by the present time is described.

The following 8 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1966, **63**, 11 :

3. **White Spots in Biblical Times. A Background for the Dermatologist for Participation in Discussions of Current Revisions of the Bible,** by L. Goldman, R. S. Moraites and K. W. Kitzmiller. *Arch. Dermat.*, 1966, June, **93**, 6, 744-54, 7 figs. (12 refs.).

'Discussions of various religions in current revisions of the Bible should be of interest to dermatologists, for these discussions include reviews of the biblical concept of leprosy. Unfortunately, terms now suggested as substitutes for "leprosy", often considered in the Bible as a moral sin, include "affections of the skin" and even "psoriasis". The background of this ancient controversy is presented as regards the significance of white spots, the influences of ancient Greek medicine, current plans of some religions, and recommendations.'

4. **A Comparative Study of the Complementary Activity of Serum in the Polar Forms of Leprosy and in the Leprosy Reaction,** by M. Paca de Azevedo and P. Homen de Melo. *Inter. J. Lepr.*, Wash., 1966, Jan.-Mar., **34**, 1, 34-8, 1 fig.

'The authors studied complementary serum activity in 88 leprosy patients, divided into three groups: GroupT, 33 tuberculoid cases; Group L, 37 lepromatous cases; and Group R, 18 cases in lepra reaction (erythema nodosum and multiform types). The titration technic was that of Maltaner and Maltaner as described by Almeida, and the designations used for component and angular inclination were those of von Krogh. The average of complement unit (K) and of angular inclination (1/n) were compared statistically, with the following results:

'1. The average values of Groups T and L did not present significant differences.
'2. The average values of Group R presented differences that were significant in relation to the other two groups studied.
'3. The complementary activity in Group R was clearly decreased.
'4. It is probable that this decreased complementary activity is related to the autoantigen/autoantibody complement-fixing complexes found in

circulating blood. Their appearance may be explained by an immunologic phenomenon peculiar to lepromatous patients in a reactional stage.'

5. **The Value of Nasal Smears in Lepromatous Leprosy,** by S. G. Browne. *Inter. J. Lepr.*, Wash., 1966, Jan.-Mar., **34**, 1, 23-6.

This paper reports on the analysis of the results of the bacterioscopic examination of material obtained from the nasal mucosa in 100 patients suffering from lepromatous leprosy admitted to the Research Unit, Uzuakoli Leprosarium, Eastern Nigeria. In the routine procedure of obtaining the bacterial material, a Thudicum's speculum was inserted well into the nostril in such a way as to display the nasal septum, and then a swab dipped in spirit passed gently over the mucosa to remove excess mucus. Then, with a blunt spud, the septal mucosa was stroked firmly under direct vision and the material thus obtained was placed on a microscope slide and stained. With data obtained questions were proposed and answered. (1) Can *Mycobacterium leprae* be demonstrated in nasal smears before they appear elsewhere? *Answer:* in no patient in this series was the nasal mucosa the only site to show bacilli, and it is apparently very rare for the nasal mucosa to be the site of initial lesions. (2) Is there any possibility of confusing acid-fast contaminants with *Myco. leprae*? *Answer:* this theoretical objection carries little weight in practice. (3) Do nasal smears reflect the bacterial state in the skin and ear lobes? *Answer:* while examination of nasal smears of patients with lepromatous leprosy in Eastern Nigeria will not help materially in making or confirming the diagnosis of lepromatous leprosy, in about half the patients it provides additional information, for both B.I. and M.I. are higher than those from smears from other sites. (4) Is there additional information from the contralateral septal mucosa? *Answer:* nothing significant. (5) Does the nasal mucosa contain 'solid rods' after their disappearance from the skin and ear lobes? *Answer:* in about half the patients in whom definite differences existed the nasal mucosa harboured 'solid rods' longer than elsewhere. (6) Does the nasal mucosa contain fragmented bacilli after their disappearance from the skin and ear lobes? *Answer:* there is no marked difference. (7) Is there any correlation between the absolute height of the B.I. when the patient is first examined and the proportion of 'solid rods' in the nasal mucosa and at the other sites? *Answer:* no. (8) When morphologically normal *Myco. leprae* reappear after an interval, or when degenerate forms reappear, is the nasal mucosa predominantly involved? *Answer:* there is evidence that the nasal mucosa may be involved precociously when normal or degenerate *Myco. leprae* reappear for a shorter or longer period after they have disappeared for some months from all sites smeared.

Globi are frequently more numerous in the nasal mucosa and persist longer than elsewhere.

The author's bacteriological study is of great interest and this paper merits close study.

J. R. Innes.

6. **Lepra Reaction. Its Relation with Fragmentation of *Mycobacterium leprae* under Sulfone Therapy,** by A. Saul and N. Segura. *Inter. J. Lepr.*, Wash., 1966, Jan.-Mar., **34**, 1, 17-22, 4 figs. (19 refs.).

Some immunological hypotheses relating to lepra reaction are reviewed. The authors set out to investigate the effect of DDS on the fragmentation of leprosy bacilli, and the influence of such fragmentation on the occureence of reactions. For these purposes a retrospective survey was made of the records of 429 patients in Mexico with lepromatous leprosy treated with DDS and a special study was made of 10 new patients who had not received treatment.

Lepra reaction occurred in 237 of the 429 patients. Fragmentation of bacilli was noted in 74% of those who reacted and in 18% of non-reactors. Fragmentation of bacilli was seen before treatment with DDS had begun in 45% of the patients, and 32% had some reaction in the pre-treatment stage. DDS did not seem to be the principal cause of reaction or the sole cause of fragmentation. Of the 10 patients who received special study, 9 had already had lepra reaction before treatment commenced. There was no close correlation between subsequent acute attacks and the appearance of fragmentation, and no cause and effect relationship could be detected between the two.

(Reactions before treatment in 9 out of 10 patients is an exceptionally high incidence. The abstracter's own study of this problem, which is quoted, was concerned with factors affecting the first onset of reaction. Subsequently there is great irregularity in the distribution of solid and fragmented bacilli due to reaction in some lesions and, probably, a recurrence of the infection in others.)

D. S. Ridley.

7. **A Trial of Thalidomide in Progressive Lepra Reactions,** by R. J. Cazort and Ye Kun Song. *Current Therap. Res.*, New York, 1966, June, **8**, 6, 299-311, 3 figs.

The authors describe progressive or recurrent lepra reaction as the most serious of the reactional states in lepromatous leprosy. It is commonly manifested by outbreaks of small subcutaneous nodules, pain in bones and nerves, leucocytosis, fever, insomnia, lethargy, and anorexia, and less frequently by iridocyclitis and orchitis. Various synthetic adrenal corticosteroids have proved to be effective suppressives of lepra reactions, but attempts to stop them result in acute exacerbations in the reactions.

Sheshkin (this *Bulletin*, 1965, v. 62, 1007) reported rapid subjective improvement with the use of thalidomide which was first synthesized by Kuntz *et al.* (*Arzneimittal-Forsch*, 1956, v. 6, 426) as a substitute for the barbiturates, and studies revealed that it possessed hypnotic action. Sheshkin made no mention of toxic effects in his first report, in which the drug was used for periods up to 4 weeks. However, in a subsequent paper he did list numerous toxic effects when thalidomide was used for periods up to 10 months.

The present authors give the results of a therapeutic trial on 24 patients suffering from reactional leprosy in Chiengmai Hospital and McKean Leprosy Hospital, Chiengmai, Thailand. The criteria of entry to the trial were a diagnosis of lepromatous leprosy, a diagnosis of recurrent lepra reaction, previous treatment with prednisolone for periods of at least one week and a period of one week or more since the last treatment with DDS.

Prednisone was discontinued in all but 4 patients, 2 days before thalidomide was commened. However, by this time the corticosteroid had been gradually reduced to half the original dose. In 4 patients no attempt had been made to reduce the dose, or to withdraw it completely. Thalidomide was given orally in tablet form, 3 tablets of 100 mgm. per day.

The authors report efficacy in the relief of severe lepra reactions. The subcutaneous nodules and associated erythema disappeared, pains in muscles, joints and nerves were considerably lessened or completely removed, body temperatures returned to normal, elevated white counts and sediment rates were lowered and general condition of the patients appeared much improved. There is a possibility of an immunosuppressive action by thalidomide in the lepra reactions. Three patients in 2 weeks of the therapy suffered acute exacerbations of the lepra reactions. At the end of the trial when thalidomide was withdrawn all patients had relapses. Thalidomide seemed to offer some protection against reactions induced by DDS. The results over the short period of 2 weeks support the claim of some beneficial effect in progressive lepra reactions. However the occurrence of relapses indicates that thalidomide alone and in the doses used is not continuously effective and the spectrum of untoward effects indicate that after its use for a short time it is not likely to interrupt permanently the cycle of recurrent or progressive lepra reactions.

J. R. Innes.

8. **A talidomida nos surtos agudos da lepra. (Eritema nodoso ou polimorfo.)** (Thalidomide in the Acute Crisis of Leprosy), by D. V. A. Opromolla, L. S. Lima and M. B. Marques. *Hosp.*, Rio de Janeiro, 1966, Apr., **69**, 4, 827-44, 5 figs. and 2 charts.

The authors have confirmed that thalidomide is effective in the control of reactions in leprosy and its continued administration prevents new attacks of reaction (this *Bulletin*, 1966, v. 63, 285).

The authors treated 43 patients who had lepra reaction in lepromatous leprosy, and a group of borderline patients, with thalidomide. The drug was administered in a dose of 100 mgm. daily, and then on alternate days. With the doses used no side effect was observed. When treatment was stopped 5 to 10 days later the nodules of lepra reaction and fever reappeared.

The authors think that thalidomide should be used because it offers a chance of instituting direct attack on the disease itself. This paper calls for careful study throughout.

J. R. Innes.

9. **Vaccination against Human Leprosy Bacillus Infections of Mice: Protection by BCG given during the Incubation Period,** by C. C, Shepard. *J. Immunology*, 1966, Feb., **96**, 2. 279-83, 1 fig. (12 refs.).

The author has already shown that BCG vaccination protects mice against footpad infections with *Mycobacterium leprae* (this *Bulletin*, 1965, v. 62, 880). To see whether vaccination during the incubation period of the experimental infection would provide protection, groups of mice were given 1 or 2 injections of BCG at intervals before or after challenge with *Myco. leprae.* Vaccination 1-2 months before challenge was found to give the expected degree of protection, immediately after challenge it gave no protection, but later on in the incubation period, during the logarithmic phase of growth, vaccination gave increasing protection up to the level attained in the pre-challenge period. By analogy BCG vaccination of human beings early or late during the incubation period would be expected to provide protection against leprosy.

D. S. Ridley.

10. **Further Studies on B.663 in Murine Leprosy. Absence of Resistance of *M. lepraemurium* to B.663 and Delay in Development of Resistance to Isoniazid,** by Y. T. Chang. *Inter. J. Lepr.* Wash., 1966 Jan.-Mar. **34**, 1, 1-6. 1, fig.

Isoniazid has been reported to enhance the action of B.663 (by itself an unusually effective drug) against *Mycobacterium lepraemurium.* A study was made of the influence of the combination on the development of resistance to either alone.

Murine leprosy was induced in mice with bacilli from animals that had been treated with B.663 and isoniazid in combination for 816 days. The newly infected mice were then treated with one or other of the drugs. The preconditioning of the *Myco. lepraemurium* by the combined drugs appeared to prevent the development of resistance to B.663, and to cause a marked delay in the case of isoniazid. The extent of skin pigmentation due to the accumulation of B.663 in tissue was reduced somewhat by concurrent treatment with isoniazid, which suggested that isoniazid had mobilized the stored B.663.

D. S. Ridley.

The following 6 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1966, **63**, 12 :

11. **Application de l'immunofluorescence sur bacille de Stefansky au diagnostic sérologique de la lèpre humaine** (Stefansky's Bacillus (*Mycobacterium lepraemurium*) in the Immunofluorescence Test for the Diagnosis of Leprosy) by F. P. Merklen and F. Cottenot. *Bull. Soc. Path. Exot.* 1965 May-June **58** 3, 332-5.

Mycobacterium lepraemurium was used as antigen for the indirect immuno-fluorescence test with sera of leprosy patients. Fourteen patients with leprosy of the lepromatous type, with bacilli in their nasal mucus, many of them untreated, all gave positive titres of

1/1,024 or higher; sera from patients with tuberculoid leprosy gave titres of 1/512. Twenty-five healthy persons who were tuberculin negative, gaves titres up to 1/16 (but patients with other diseases such as tuberculosis appear not to have been investigated). However, titres of 1/128 or higher are thought to be of diagnostic value in leprosy.

D. S. Ridley.

12. **The Indirect Basophil Test in Erythema Nodosum Leprosum. Preliminary Note,** by S. L. Moschella, W. R. Bell and J. R. Trautman. *Inter. J. Lepr.*, Wash., 1966, Jan.-Mar., **34**, 1, 39-41.

'In this brief and preliminary study, the authors were unable to duplicate the work of Gokhale and Joglekar (*Indian Pract.*, 1964, v. 17, 377) who reported that lepra reactions caused by dapsone could be differentiated from those that occur spontaneously by using the indirect basophil degranulation test. Because of the reasons presented in the discussion, the authors are unable to speculate on the presence or absence of circulating antibodies to dapsone in this study.'

13. **O tratamento das lesões ùlcero-cutnâeas da lepra pelo Vasculat** (The Treatment of Ulcero-Cutaneous Lesions of Leprosy with Vasculat), by J. M. Santos and J. G. De Azevedo. *Rev. Brasileira Med.*, Rio de Janeiro, 1965, July, **22**, 7, 422-7, 27 coloured figs. on 8 pls.

In the many mutilating lesions of leprosy, a broad section are referred to as ulcero-cutaneous, and leprosy can hardly appear as a morbid entity without being associated with other morbid entities which also produce ulcero-cutaneous lesions. Having obtained satisfactory results with Vasculat in non-leprous ulcero-cutaneous lesions, the authors studied results in patients having ulcero-cutaneous lesions in leprosy.

Male and female adults were selected of any state and age, who had suffered from leprosy for some time and had ulcero-cutaneous lesions fairly old and advanced. The patients were in rather a serious condition, so that if a positive result were obtained it could not possibly be attributed to any other medication.

Vasculat was used as tablets: injections were not suitable. The daily dose was 0.075 gm. or 6 tablets (1 tablet of 0.0125 gm. was given every 4 hours). Some patients were receiving treatment with sulphones.

There were 16 patients with bacillary or non-bacillary lesions treated in Brazilian leprosaria for up to 2 months. The paper gives detailed case notes of 8 patients and 27 coloured illustrations. The authors were able to make certain conclusions from their findings:—(1) Vasculat shows itself useful and efficient in the treatment of ulcero-cutaneous lesions of patients with leprosy even when the patients were subject to vascular lesions (varices) or dermatological lesions of other nature (such as eczemas); (2) when auxiliary therapy was not given the therapeutic effects obtained were considered to be entirely due to Vasculat and were of real value; (3) because of these results in the preliminary stage, further investigations on this treatment are called for, together with its possibilities in relation to surgical, antibacterial and other measures.

J. R. Innes.

14. **Primeros resultados del tratamiento de las leprorreacciones con talidomida** (First Results of the Treatment of Lepra Reactions with Thalidomide), by J. Terencio de Las Aguas, and F. Contreras Dueñas. *Rev. Fontilles.*, Alicante, 1966, Jan.-June, **6**, 5, 449-55, 6 figs.

At Fontilles, Spain, the authors treated 6 patients suffering from lepromatous leprosy, 2 men and 4 women, who had also suffered from lepra reactions over several years. Thalidomide was used in an initial maximum dosage of 100 mgm. decreasing slowly to 50 and 25 mgm. and there was improvement in 4 patients. The lepra reaction disappeared in 5 patients, but in 1 patient the treatment had to be suspended after several days because of an allergic incident. The authors say that thalidomide showed its efficacy, and caused a rapid disappearance of the reactional phases in 5 of the patients. The dosage employed was lower than that of Sheskin (this *Bulletin*, 1966, v. 63, 285), but did not surpass 100 mgm. With thalidomide the disappearance of the fever was attained in between 2 and 11 days, with parallel improvement of the cutaneous lesions and above all without the need to continue steroid treatment.

Tolerance was excellent except for 2 patients who had very intense somnolence. The authors believe that thalidomide needs a fuller investigation. (The authors do not explain, or discuss, why this drug is used on females, nor do they discuss its teratogenic properties.)

J. R. Innes.

15. **Effect of Diaminodiphenyl Sulphone and ICRC Bacilli on Acid Phosphatase of Macrophages,** by K. Prabhakaran and C. V. Bapat. *Indian J. Med. Res.*, 1966, May, **54**, 5, 458-61.

Mouse intraperitoneal macrophages showed an increase of 30% in acid-phosphatase activity when incubated *in vitro* or *in vivo* with DDS. The increase was greater in the case of aged cells. It is suggested that DDS may produce lysis of *Mycobacterium leprae* indirectly by causing the release of lysozymes in the host cells.

Incubation of macrophages with ICRC bacilli affected their acid phosphatase activity in much the same way as did DDS.

D. S. Ridley.

16. **Enhanced Susceptibility of Thymectomized and Irradiated Mice to Infection with** *Mycobacterium leprae*, by R. J. W. Rees (Correspondence). *Nature*, 1966, Aug. 6, **211**, 657-8, 1 fig. (15 refs.).

The possibility that thymectomy and X-irradiation of mice would enhance the multiplication of *Mycobacterium leprae* in footpads was tested in 24 animals. Twelve were thymectomized when 2 months old and 16 days later were exposed to 900r and then given a transfusion of marrow; the remaining 12 animals were kept as controls. Four weeks later all animals were

inoculated with 10^4 bacilli. In one experiment the *Myco. leprae* were obtained direct from man and in a second experiment a first passage strain from mice was used. In both experiments the infections were enhanced in the thymectomized irradiated animals, the yield of bacilli being about 10 times greater in the first experiment and a 100 times in the second. But there was no systemic spread of the infection. It is likely that the limitation of infection to the footpad (mainly in muscle fibres) is due partly to an immunological factor but it is not clear whether this is the only factor.

D. S. Ridley.

The following 7 abstracts are reprinted, with permission from *Trop. Dis. Bull.*, 1967, **64**, 1 :

17. **Some Facts about Leprosy—Guide for Social Camps,** by DHARMENDRA. *Leprosy in India*, 1966, Jan., **38**, 1, 18-35, 20 figs.

This article contains clinical photographs, maps, and clinical studies of several aspects of leprosy including eye involvement, and should be intimately studied. Although it is about leprosy in India, it will be of value to all.

(The article is published as a booklet suitable for the use of village workers, teachers, and social workers. It may be obtained from the Director, Central Leprosy Institute, Chingleput, Madras, price 50 paise.)

J. R. Innes.

18. **Sensitivity of *Mycobacterium leprae* to Low Levels of 4,4″-Diaminodiphenyl Sulfone,** by C. C. SHEPARD, D. H. MCRAE and J. A. HABAS. *Proc. Soc. Exper. Biol. & Med.*, 1966, July, **122**, 3, 893-6 (16 refs.).

Multiplication of *Mycobacterium leprae* in mice was completely inhibited by DDS in concentrations as low as 0.00001% of the diet, which is equivalent to 10 μgm./kgm./day. It is only a 100th part of the lowest dose that produced detectable levels of DDS in the blood, and the tissue level achieved by it is about 1,000th of that produced by a therapeutic dose of DDS in man. There was no evidence of concentration of the drug at the site of infection.
(See also this Bulletin 1965, v. 62, 535.)

D. S. Ridley.

19. **A Study of the Transmission of Leprosy in Families,** by E. B. CHRISTIAN, A. SHAMRAO, L. R. CHRISTIAN, J. J. CHRISTIAN and I. V. CHRISTIAN. *Leprosy in India*, 1966, Jan., **38**, 1, 9-17.

The authors studied 793 families in Zaheerabad in India and found that the most favourable condition for the transmission of leprosy in families existed where there was a close, intimate and prolonged contact with a patient suffering from lepromatous leprosy, whether a parent or close relation. Children in close or casual contact with persons with other forms of leprosy are rarely infected, and when such infection occurs it may result from a temporary 'open' stage of the disease, or to contact with a person with an 'open' infection outside the family.

In the present study the infection usually took place in childhood. Leprosy sometimes developed in children in families in which neither the parents nor grandparents were affected. In the children the incidence of the lepromatous type was much higher (14%) than that of the non-lepromatous (9%).

Although the patients with lepromatous leprosy are the most serious source of infection, only about 30% of the children exposed to them in the family get the disease, the remaining 70% escape. This confirms the view that leprosy is only feebly infective, and that infection with *Mycobacterium leprae* is but one of the factors in the transmission of the disease. The factor of immunity calls for study and in this connexion attention is drawn to the infrequency of conjugal infection, and to the rarity of infection among the staff of leprosy hospitals, and their families.

J. R. Innes.

20. **A propos de la valeur immunologique de la réaction de Mitsuda** (On the Immunological Significance of the Lepromin Test), by J. COUDERT, A. BASSET, J. ROUSSET, R. PRADINAUD and LU-HUYNH-THANH. *Bull. Soc. Path. Exot.*, 1965, Mar.-Apr., **58**, 2, 132-40.

The authors cover familiar territory in their findings on the lepromin reaction in patients suffering from lepromatous or tuberculoid leprosy and in contacts, in Africa and Europe, but break comparactively new ground in reporting 2 histologically distinct types of late (or Mitsuda) reaction in patients with lepromatous leprosy. Basing their study on 286 patients in all, they found that intradermal inoculation with various antigens (*Mycobacterium marianum*, BCG and tuberculoid) gave a variably high proportion of positive results, both early and late, in patients with lepromatous leprosy.

About two-thirds of patients who had been treated with a vaccine prepared from killed *Myco. marianum* gave early and late reactions when tested with antigen prepared from *Myco. marianum*, whether they had lepromatous or tuberculoid leprosy. There was incomplete concordance between the early and late reactions. Histological examination of the inoculation sites disclosed 2 distinct types of reaction—typically lepromatous (except for the absence of bacilli) and typically tuberculoid.

The authors conclude that the Mitsuda reaction is a useful investigative tool for ascertaining the degree of tissue resistance shown by patients with tuberculoid leprosy, and for indicating the occurrence of non-susceptibility to leprosy in contacts, but cannot indicate the underlying immunological state of the individual.

It is suggested that the generally recognized anergy of lepromatous leprosy is a concept that should be restricted to patients with leprosy infections of the lepromatous type, and that some signs of hyperergy may appear after injection of an antigen prepared from related mycobacteria.

(This paper incidentally emphasizes the need for some internally accepted standards of preparation and antigenic activity of lepromin as used widely for testing.)

S. G. Browne.

21. **Smallpox Vaccination and Acute Exacerbation of Leprosy,** by K. RAMANUJAM and G. RAMU. *Leprosy in India*, 1966, Jan., **38**, 1, 3-9, 2 figs.

The authors, and others, have found that vaccination against smallpox among persons suffering from leprosy seems to be a definite provocative factor for the precipitation of acute exacerbation of the disease, especially in patients with lepromatous leprosy (this *Bulletin*, 1935, v. 32, 347; 1941, v. 38, 222; 1954, v. 51, 275; 1963, v. 60, 132). Of 567 patients with lepromatous leprosy, 100 (17.6%) developed an acute exacerbation of the disease after vaccination, and in 48 of these 100 patients it was the first exacerbation. It was the authors' experience that such an exacerbation may be the first of several similar episodes. A direct relationship was found between the intensity of local reaction to vaccination and the chances of occurrence and severity of the acute exacerbation of leprosy. The treatment of the acute exacerbation after vaccination is very much the same as for that arising spontaneously, or from other causes; the authors suggest antibiotics could be used with advantage as there is local pustulation and lymphadenopathy. Patients in leprosaria should be revaccinated periodically which would perhaps ensure less severe local reaction to vaccination and thereby reduce the incidence of acute exacerbation of leprosy.

J. R. Innes.

22 **An Interesting Reaction in Leprosy,** by J. C. TILLEY. *Southern Med. J.*, 1966, July, **59**, 7, 766-8, 4 figs.

The author draws attention to an interesting reaction which may occur in leprosy when the skin is frozen. The reaction depends on cryoproteins present in patients suffering from leprosy and the case histories are given of 2 patients in the leprosarium at Carville, Louisiana. The lesions, which are produced by freezing the skin with ethyl chloride, are very unusual. Four figures are given and these show their peculiar nodose type and their association with ulceration. MATTHEWS and TRAUTMAN have demonstrated the presence of a cryoprotein and have shown that 89% of the patients with lepromatous leprosy had cryoproteinemia and so did all of 6 patients with dimorphous leprosy, whereas in tuberculoid leprosy cryoproteins were absent. When leprosy became inactive there were no demonstrable cryoproteins. Further studies are in progress.

(See also this *Bulletin*, 1966, v. 63, 284.)

J. R. Innes.

23. **Lisozima no tratamento de doentes de lepra em manifestação aguda** (Lysozyme in the Treatment of Leprosy Patients with Acute Manifestations), by L. C. PEREIRA. *Publicações Centro, Estudos Leprológicos*, Curitiba, 1965, Nov., **5**, 2, 71-80. English summary.

The author treated 7 patients suffering from the lepromatous form of reaction and 1 with tuberculoid reaction, using lysozyme (Laboratil Lisozyma). He obtained excellent results in acute forms of reaction and found that it worked well with adjuvant cortisone. It allowed a smaller dosage of cortisone and so reduced the side-effects. The daily dose was 150 mgm. intramuscularly and orally for between 13 and 60 days, and the observation period lasted 120 days. Details are given of each of the 8 patients treated.

J. R. Innes.

The following 8 abstracts are reprinted, with permission, from *Trop. Dis. Bull.*, 1967, **64**, 2 :

24. **The Leprosy Problem in the World,** by L. M. BECHELLI and V. M. DOMINGUEZ. *Bull. World Health Organisation.* Geneva. 1966, **34**, 6, 811-26, 1 map on folding pl. (23 refs).

The authors, in an attempt to provide realistic figures, find there is a lack of accurate data on the prevalence of leprosy in the different countries of the world because case-finding has not reached a high level in many countries. In all there are 2,831,775 registered patients and 10,786,000 estimated patients, though this figure may well be an underestimate. The number of patients under treatment is about 2,000,000, about 68% of the registered patients and 18% of the estimated. About 2,097 million people live in areas with prevalence rates of 0.5 per thousand or higher; in these areas nearly one million new leprosy patients can be expected in the next 5 years. The estimated number of disabled patients is 3,872,000.

A useful table, which occupies 9 pages, shows for each country in the world the estimated number of patients and the number registered and treated, together with the date and source of information, though this information is not complete in every instance.

J. R. Innes.

25. **A Culture Medium for the Isolation of Acid-fast Bacteria in Leprous Materials,** by M. C. MABALAY and E. B. MABALAY. *J. Philippine Med. Ass.*, 1966, Apr., **42**, 4, 195-211. (21 refs.)

The authors claim that by using a special medium they have grown mycobacteria from lepromatous lesions of each of 109 patients at the Eversley Child Sanatorium, Cebu, in the Philippines. This medium consisted of a liquid base containing 5 gm. $NaHPO_4$, 1.5 gm. KH_2PO_4, 0.6 gm. $MgSO_4$, 2.5 gm. Na citrate, 5 gm. asparagine, 50 ml. glycerol per litre to which was added, after sterilization, 10-20 gm. of rice flour which had been heated to boiling point until the flour

was cooked and 2 ml. of a 1% alcoholic solution of gentian violet per litre. It was distributed in quantities of 2 ml. and autoclaved at 15 lb. pressure for 30 minutes. At the time of inoculation an equal volume of a mixture of equal parts of the liquid base and bovine serum, which had been sterilized by membrane filtration, was added to the medium. The pathological material consisted of skin biopsy specimens, blood, urine, nasal washings, sputum, skin and ear lobe scrapings, purulent material from ENL lesions and pus from a lung abscess. Some portions of these were treated with 4% sodium hydroxide for 1 hour and immediately neutralized with normal hydrochloric acid before inoculation into the medium (see TERNI and SIGNORINI, this *Bulletin*, 1951, **48**, 266).

Mycobacteria grew from the biopsy material, and from the specimens of pus, which had not received treatment with sodium hydroxide, in a mean incubation period of 111.3 days and 212.2 days, respectively, but from the treated samples the respective times were only 29.3 days and 13.0 days. The first sign of growth in the liquid medium was a change in colour of the gentian violet and later there was pellicle formation. When subcultured on to a solid medium consisting of the fluid isolation medium and whole egg, the organisms produced a bright canary yellow to deep orange pigment. They grew as moist or slimy colonies tending to coalesce or form aggroupments at the sites of inoculation with little or no tendency to spread outside the line of seeding. Microscopically the organisms varied from short, solidly-staining, moderately acid-fast bacilli to long, slender, sometimes beaded, rods. After a few weeks the shorter forms were invariably observed to elongate and become beaded; occasionally globi-like formations were seen.

Intradermal inoculation of the slender rod form into patients suffering from lepromatous leprosy provoked a Mitsuda-type of reaction which sometimes ulcerated, but the shorter strains behaved similarly to regular lepromin in patients with tuberculoid leprosy and in those with the lepromatous form.

The authors also claim to have produced slow but perceptible growth of *Mycobacterium lepraemurium* in this medium. Other mycobacteria, namely *Myco. tuberculosis*, *Myco. phlei* and the Binford bacillus, grew uninhibitedly in the medium.

The authors consider that their success is due in part to the medium, but mainly to the treatment with sodium hydroxide. This process renders the resistant bacilliary membrane permeable so that the bacillus becomes exposed to the nutrients in the media and, in the absence of host tissue cells, the organisms rapidly adapt themselves to their new environment. (In a footnote, the authors state that the strains have been examined by Dr. R. J. W. Rees of the National Institute of Medical Research, London, and that he considers that they belong to the Runyon III group of atypical or unidentified mycobacteria.)

S. R. M. Bushby.

26. **Demonstration of *Mycobacterium leprae* in Tissue. Demonstration by means of Khanolkar's Concentration Test followed by Fluorescent Staining.** by W. A. AKERS and W. C. MORSE. *Arch. Dermat.*, 1966, Sept., **94**, 3, 361-2.

Mycobacterium leprae was demonstrated in human skin by fluorescent staining, after concentration by Khanolkar's technique (this *Bulletin*, 1952, **49**, 1048), when it could not be demonstrated by the usual histological methods. The patient had tuberculoid leprosy and his routine sections were consistently negative. After concentration, bacilli could be found by means of Ziehl-Neelsen's method, but much better results were obtained with auramine O and rhodamine D fluorescent staining. For details of technique the reader should refer to the original paper.

D. S. Ridley.

27. **Miositis lepromatosa** (Lepromatous Myositis). by A. ODERIZ, O. REYES and J. CONVIT. *Dermatología Venezolana*, 1965, Dec.—1966, July, **5**, 1/2, 50-55, 3 figs.

The English summary appended to the paper is as follows:

'The authors described a case of lepromatous leprosy with reactional lesions in an adult male who had not received specific treatment. The patient shows infiltration of the muscular masses of the arms and legs. Biopsies taken from those lesions reveal lepromatous granulomata in the muscular interstices and a degenerative process of the muscular fibres with deteriorated acid-fast bacilli. Special dyes were used for a better study of the case. A review of the literature is made and comments on the frequency, age, sex, etc., of the patients published so far.'

(See also this *Bulletin*, 1960, **57**, 713; 1961, **58**, 1020.)

28. **Dapsone-Resistant Lepromatous Leprosy in England,** by A. R. D. ADAMS and M. F. R. WATERS. (Memoranda.) *Brit. Med. J.*, 1966, Oct., **8**, 872.

This is an account of the first patient in England suffering from leprosy, who has been proved resistant to treatment with dapsone. The authors used techniques described by PETTIT and REES (this *Bulletin*, 1965, **62**, 108) in Malaya. They made a suspension of *Mycobacterium leprae* from biopsy material and inoculated 36 mice with approximately 10,000 bacilli in the pad of each hind foot. The animals were then divided into 6 groups; one group acted as an untreated control group, and the other 5 groups each received one of the following drugs mixed in their diet: 0.1% dapsone, 0.025% dapsone, 0.1% thiambutosine, 0.2% thiacetazone, and 0.1% sulphadimethoxine. The mice were killed after 5 to 9 months. Limited multiplication of *Myco. leprae* was detected in the footpads of both the control animals and also of the animals fed with dapsone. The infection was completely suppressed by thiambutosine and thiacetazone, but only partly suppressed by sulphadimethoxine.

The patient was well on arrival in England from Bengal but 2 years later developed lesions of lepromatous leprosy. He had received treatment with sulphone 15 years previously at a leprosarium in India.

This account should be carefully studied in the original. The resistance to dapsone may be connected with irregular treatment.

J. R. Innes.

29. **Management of Uncomplicated Plantar Ulcers in the Field,** by S. M. MUKHERJEE. *Leprosy in India*, 1966, April, **38**, 2, 107-15, 2 figs.

'The problem of plantar ulcer still remains unsolved. The important role of para-medical personnel in solving this problem has been discussed. He can and should deal with the early and uncomplicated ulcers. The two main things necessary for this are: (i) to protect the ulcer from injury and infection by means of antiseptic dressings, and (ii) to put the foot to rest by means of a plaster-of-paris cast. Details are given of these two procedures.

'Treatment of complicated plantar ulcer has not been described, as patients with complicated ulcers should be treated by the medical personnel.'

30. **An Epidemiologist's View of Leprosy,** by K. W. NEWELL. *Bull. World Health Organization*, Geneva, 1966, **34**, 6, 827-57. (Numerous refs.)

While leprosy has been studied exhaustively by leprologists, it is only recently that persons in other disciplines have given it the attention it deserves. The author reaches the conclusion that the anergic, or factor N, hypothesis (ROTBERG, this *Bulletin*, 1958, **55**, 50; DOULL, *ibid*, 1962, **59**, 981) evolved to relate the lepromin test to the findings in clinical leprosy is most promising, and if this should be proved to be correct, he thinks it unlikely that BCG vaccination can be a very useful tool in the prevention of leprosy. The argument, and the very full review and discussion can be appreciated only in the original

J. R. Innes.

31. **Rehabilitation Project at Purulia Leprosy Home and Hospital,** by J. PITTS. *Leprosy in India*, 1966, Jan., **38**, 1, 43-8. (Reprinted from *J. Rehabilitation in Asia*, 1965, Oct., **6**, 4.)

The author in making a study of rehabilitation at Purulia Leprosy Home and Hospital, India, has decided on 3 ways in which help may be given to patients: (1) by close contact with their homes and families by regular periods away from the hospital at home as well as help from the welfare officer; (2) by learning a skill or trade so that, when discharged, the patient can support himself; (3) by providing industrial work at the leprosarium and later in village centres linked with the leprosarium or perhaps later with government rehabilitation schemes. The paper is practical and worthy of study in the original.

J. R. Innes.

Book Reviews

Leprosy. New Hope and Continuing Challenge, by STANLEY G. BROWNE, O.B.E., M.D., F.R.C.P., F.R.C.S., D.T.M., 68 pages, 19 illustrations, published by The Leprosy Mission, 7 Bloomsbury Square, London, W.C.1, price 2s.

The book is a lucid account of modern leprosy and is much needed because, in spite of out boasted modernity and the fact that leprosy is curable, the attitude of most people to leprosy is barbarous and prejudiced. Dr. Browne's first chapter considers the new hope for leprosy sufferers. His second chapter defines ideas about it, including the Biblical attitude that the sufferer was 'stricken by God', until the Christian attitude considered it curable and that it can be cured. May the reviewer point out his opinion that Christ was in fact the first human being to touch a leprosy patient and to cure him. In the third chapter the author recognises the apparent 'uniqueness' of leprosy because it is a miserable disease and he mentions the Leprosy Mission and other Missions which have grown up to bring special mercy and give the special effort which the disease demands. The fourth chapter is a practical one about the origin and spread of leprosy and shows that leprosy spreads by people. There is a causative agent, a germ *M. leprae* and it is spread by human beings. Leprosy is not highly contagious, but it *is* contagious, and probably the invasion is helped by a genetic susceptibility, and by the victim being young in most cases. Dr. Browne outlines the new hope for the deformed in leprosy. He outlines the new treatment for the disease and a leprosy service in action. There is a great need of young people to volunteer for this wonderful service.

Dr. Browne's book is very good value for 2s. and should be read by every person.

The Changing Pattern, by S. G. BROWNE, O.B.E., M.D., F.R.C.P., F.R.C.S., D.T.M., 7 pages, 1 illustration, published by The Leprosy Mission, 7 Bloomsbury Square, London, W.C.1, price 10d.

This is such a valuable pamphlet of an address by Dr. S. G. Browne that it should be thoughtfully acquired and added to his book, 'Leprosy', perhaps as an inset.

Mahatma Gandhi Answers the Challenge of Leprosy, by T. N. JAGADISAN, 53B Edward Elliot Road, Madras, 27 pages, 5 illustrations, printed at the Diocesan Press, Madras, India, price Rs. 2.

This delightful books deals intimately with that great soul, the only national leader in the world whose heart was big enough to be concerned with his brethren who suffered from leprosy and to seek to help them as Mahatma Gandhi did in so many ways which the author enlightens the reader about. He makes it clear to us that the answer to the challenge of leprosy is love and sacrifice. It is fascinating that he gives us facsimiles of so many holographs of Gandhi. We end with gratitude to T. N. Jagadisan and gratitude to God for the Mahatma.

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