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EDITORIALS.

LEPROSY RESEARCH AND THE LEPROMIN TEST

Within the last few years there has appeared in *Leprosy in India* a series of articles written by Dharmendra and Lowe and one or two other collaborators on the Lepromin Test. We reprint below the last of this series which summarises the previous articles. The fact that the mycobacterium of leprosy has not yet been cultured outside the human body renders difficult the study of the biological, antigenic and immunological features of this organism. No satisfactory serological test has yet been evolved either to help diagnosis or to estimate resistance. The lepromin skin test of Mitsuda, the chief use of which has been its specific negative results in lepromatous cases, is the only test we have.

The antigen originally used was leproma ground up and suspended in saline, but this could not be satisfactorily standardised. Dharmendra has now described a method by which the mycobacteria can, by grinding up the lepromatic chloroform. be obtained separate from each other and free from tissue debris. After drying, the resulting powder can be used to make up a uniform suspension accurately standardised by weight.

With this antigen it is now possible to read the results within 48 hours instead of having to wait for two or three weeks, a most important improvement when the test is being put to mass use. Another interesting observation is that the reactivity of the antigen is enhanced by prolonging the soaking of the mycobacteria in chloroform. The explanation suggested is that the lipoid material surrounding the organisms is removed and the proteins inside their substance can thus be more rapidly set free and act immediately on the tissues. No suggestion is made as to the nature of this lipoid material; is it part of the mycobacterial body, is it an organised capsule, or is it a substance secreted by the organisms or produced by them from the surrounding tissues by an enzyme, a substance in which they lie embedded, the ' gloea ' of the old leprologists?

Another interesting point brought out is that the reaction-producing porti
fractions being active; also that this protein when injected into the skin produces not only a local reaction in a non-lepromatous case, but also focal reaction in distant lesions. This is taken as evidence of allergic action; in any case it is significant as showing that lesions throughout the body can be activated by a specific substance set free from the bodies of lepra bacilli.

The same author (Dharmendra) in another article reviewed in this issue suggests that the reason why sulphonamide drugs are not useful in leprosy is the high lipoid content of the mycobacteria, and that the outer " waxy " layer prevents access of drugs to the interior. He suggests the preparation of lipophilic sulphonamides so as to overcome this difficulty.

With the above in mind, what about the iodides? These are well known to produce reaction even in small doses. How is this reaction produced if not by lipolytic action which sets free mycobacteria from their surrounding lipoids? A combination of sulphones or other similar derivatives with minute doses of iodide might be worthy of trial under carefully regulated conditions.

Another use of the lepromin test, not mentioned in the series of papers referred to above, is in distinguishing organisms suspected of being M.lepra. Ota and Nitto* claim to have obtained multiplication of Hansen's bacillus in fowls through six series after injecting suspensions of leproma mixed with kieselgur, trypan blue and potassium iodide into the breast muscles. He also claims to have confirmed his results not only by histological examination but also by the lepromin test. Emulsion of liver taken from one of the sixth series of fowls gave skin reactions similar to those of control injections of suspension of leproma prepared by the ordinary Mitsuda technique.

Dharmendra and Lowe's paper should be carefully studied by all those in a position to make investigations, especially into such questions as the incidence of types, immunity and hereditary predisposition.

EXPERIMENTAL TREATMENT.

Reports continue to appear of trials with various drugs. On pp. 22 and 32 are conflicting accounts of results from the use of penicillin. There are also encouraging results from the intraveonous use of a sulphonamide preparation which is highly soluble with a low pH of 6 or 7, and therefore not caustic (p. 27). In searching for an effective remedy for leprosy the following points are worthy of consideration. Recovery of even a moderately advanced lepromatous case would necessarily be slow. A fairly high blood concentration of the drug might be necessary; the drug must therefore be non-toxic, or of very low toxicity so that it can be tolerated in a high enough concentration over a long period. If, as was found by Faget and his colleagues in the case of promin, there is less toxicity when given intravenously than

* *Int. Jl. Lep.* (1941) 9, 299.

orally, then the drug must be freely soluble and non-irritant. To ensure complete and permanent recovery it would be necessary that either every bacillus should be eliminated from the body or else that resistance to infection should be raised as shown by a positive lepromin test. The results given by Faget (see page 25) are so far the most encouraging.

THE VIRULENCE OF LEPRA BACILLI.

E. MUIR.

Does the virulence of M. leprae vary to any appreciable extent in nature? Is it stepped up when leprosy is first introduced into a region where it has not previously existed, and where it spreads rapidly among the inhabitants as is reported to have occurred, for instance, in Hawaii and in the island of Nauru? Our inability to culture M. leprae *in vitro,* or to reproduce signs corresponding to human disease in experimental animals, makes it difficult to give a definite answer.

The whole question has been raised in a paper by J. W. Fielding (1945) on Rat Leprosy. The fact that rat leprosy is, like the human disease, confined as far as is known to one genus, and that M. leprae mur. like M. leprae has not been successfully cultured *in vitro,* has encouraged the study of the former disease with the hope of shedding light on the latter. Fielding in his paper assumes that the virulence of rat leprosy varies considerably. He says, for instance :—

" Experimental evidence, however, indicates that the virulence of the bacilli of fresh fæces is greater than that of the same fæces stored dry at room temperature for twelve to fifteen or more months.'

and again :—

" For the production of superficial lesions two things appear to be necessary. The first is the breaking down of local or general resistance accomplished by repeated inunction, or by subcutaneous inoculations with any of the various types of organisms. The second is the use of organisms of a naturally high order of virulence, Such as those from the fæces or urine, or the use of organisms of long-standing ulcers or granulomate whose virulence has been built up by passage through other animals, as the guinea-pig or rabbit by subcutaneous inoculation . . . The first evidence of infection by superficial lesions in my series was obtained by breaking down resistance by combining inoculations of small doses with inunction with large numbers of organisms. Virulent organisms for the final inunction were produced by passage through a guinea-pig, which showed a pyrimidal-shaped lesion with organisms, reaching a maximum diameter of 17 millimetres in seven days. Subinoculated into a rabbit, bacilli from this lesion resulted in a non-vascular nodule of

maximum measurements of 44 millimetres in about thirty days. Subsequently the lesion broke down after an inflammatory reaction, and the organisms being injected into a rat, produced a nine-millimetre nodule, the washings of which were injected into the same rat on the fourth day and resulted in a lesion measuring twelve millimetres. Both these rat lesions ulcerated three days later. Breed counts of bacilli from washings of these ulcers resulted respectively in one to ten fields and two organisms per field. Inunction on three rats with the second washing diluted to contain 60,000 organisms resulted in a permanent lesion in one rat. In all rats inflammatory reactions occurred with thickening of the skin; these reactions subsided in two, but the other was granulomatous, covered the whole treated area by the sixth day and contained loose bacilli; these were obviously increasing in number. By the eighth day a breed count of skin serum yielded sixty bacilli per field, which was equal to 18,000,000 per cubic centimetre; on the twelfth day many organisms had invaded polymorphonuclear leucocytes, which had now been thoroughly mobilized. Owing to interference six weeks later the lesion broke down, but gradually healed, breaking down permanentlly some eleven weeks later. The animal died nine months after primary inoculation, from an extremely heavy generalized infection which was reflected in the uro-genital and alimentary systems. The two rats in which skin thickening subsided were killed at 17 weeks and at 22 weeks respectively; in neither were internal abnormalities detected. The last mentioned rat showed no evidence of infection in lesions or organisms; in the former, however, bacilli were found in kidney, capsules, spleen, heart, liver and inguinal glands."

The evidence here that the organisms used for inunction were more virulent than ordinary rat leprosy bacilli is rather vague. The writer has frequently found that subcutaneous inoculation of a rat with a bacillary emulsion taken from a cutaneous nodule of an infected rat produced a marked local nodule, often followed by ulceration, and intraperitoneal inoculation produced a large tumour (Muir, Henderson, Landeman, 1927); whereas an emulsion prepared from infected liver or spleen seldom produced a marked local reaction, but in practically cent per cent of inoculations caused progressive disease which showed definite clinical signs in a maximum of 4 to 5 months. This tends to show that emulsion prepared from the skin lesions often contains some contaminant which when injected is chiefly responsible for the local reaction. It is not unlikely that the reactions described in Fielding's inoculated guinea-pig, rabbit and rat were due to a contaminant carried over; also that the inflammatory reaction produced in the rats treated by inunction was due to the same contaminant.

When a suspension of rat leprosy bacilli killed by heat is inoculated intracutaneously in man it produces in a majority of cases a local nodule (Muir, 1933); so that the production of a local nodule, however large, in a similarly injected experimental animal is no proof that the bacilli are alive, and still less that the animal is susceptible to rat leprosy, or that the bacilli are multiplying in its tissues. And if no multiplication is taking place then obviously the virulence could not be stepped up by even a series of such passages.

Much stronger evidence is required before it can be proved that the actual virulence of the individual rat leprosy bacillus varies. Disease-producing power of an emulsion containing a hundred per cent of live bacilli would be much greater than that of an emulsion with only ten per cent of the bacilli alive. Also an irritating contaminant such as that mentioned above, or the Kieselgur used in Ota and Nitto's experiments (1941), may possibly produce more active results. But in neither case would it be true to say that the virulence of the bacilli had been increased.

Proof has been obtained that different strains of tubercle bacilli vary in virulence, by injecting pure fresh cultures in laboratory animals, and noting the time required to produce death. Here the bacilli are presumably all, or almost all, alive and no irritating contaminent (dead or alive) is present in the suspension injected. Also a standardized number of bacilli is injected, and the speed of death is increased by injecting subdurally so that extraneous factors associated with a long period of illness are excluded as much as possible.

In the case of rat leprosy an approximately pure and standardized suspension of bacilli might be obtained by Dharmendra's (1941) chloroform method, but it would be impossible to tell how many, if any, of the bacilli were alive after treatment with chloroform.

If it is difficult to estimate the virulence of the rat leprosy bacillus for which we have at least one experimental animal available, how much more difficult is it to estimate the virulence of the human leprosy bacillus, for which we have no practicable experimental animal.

Clinical evidence of varying virulence of M. leprae is no less difficult to find. As has been remarked above, the more prolonged the course of a disease the more opportunity is there for complicating factors to obscure the evidence of the disease-causing power of the specific organism. If the history of a family widely infected with leprosy is studied, severe lepromatous cases are found alongside of cases with only slight neural leprides. The difference is obviously not due to infection with strains of varying virulence, but to varying resistance and degree of infection. As Dharmendra and Santra (1945) have shown :

"A factor which appears to have a bearing on the observed variations [in lepromatous-rate and child-rate] is the attitude of the people towards leprosy, and the presence of a custom of isolation of leprosy patients in a community. In areas in which there exists ostracism of the leprosy cases, and where some sort of isolation is practised, a high lepromatous rate is associated with a low gross incidence, and a low child-rate. On the other hand, in the areas where no isolation is practised, a low lepromatous rate is associated with a higher gross incidence and a higher child-rate."

Lowe (1938) has shown that in Burma the disease is more severe in Burmans than in Indians living in the same climatic conditions, but here again the difference cannot be conceived as being due to varying strains.

Leprosy has been shown to pursue an epidemic curve, increasing for a time and then diminishing. This is best shown in an isolated community such as that on the island of Nauru in the Southern Pacific. But here from the beginning severe and mild cases were found side by side, and the rapid increase and elimination of the disease was obviously not dependent on changing virulence of the infection, but on initial absence of precautions followed later by well-planned preventive regulations.

Leprosy is in a very real sense a sociological disease. It spreads in areas where the sanitary standard is low; it is controlled and stamped out when society reacts against it either by taking special precautions or by raising the general sanitary level.

If the virulence of M. leprae is fixed and, unlike other pathogenic organisms, does not vary appreciably in different strains, can this be accounted for by other peculiarities of the disease? Virulence of organisms can be modified in the case of anthrax by cultivation at a raised temperature, in tuberculosis by growing in the presence of an antagonistic substance like bile, and in smallpox by passage through other species. But such methods are not so far available with the leprosy bacilli. The virulence of influenza or the common cold may be raised by rapid human passage, but one passage of the leprosy bacillus takes at least a year, generally far longer. It may thus be that the slow growth of M. leprae and the practical impossibility of its culture outside the human body may account for its fixed virulence. Even in advanced lepromatous cases with the whole of the skin surface deeply involved, clinical signs of toxicity may be absent and the general health of the patient good, while death is generally the result not of leprosy but of complications. It would thus appear that the toxicity and lethal effect of M. leprae is of a low order, and perhaps because of this its virulence as regards aggressiveness also
at floor level.

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REPRINTED ARTICLE.

STUDIES OF THE LEPROMIN TEST*

by

DHARMENDRA, M.B., B.S., D.B.

and

JOHN LOWE, M.D.,

Leprosy Research Department, School of Tropical Medicine, Calcutta.

Introduction.

About three years ago in the Leprosy Department of the School of Tropical Medicine, Calcutta, a study of the Mitsuda test was planned. The results of this study have been published in *Leprosy in India* in a series of articles under the general title of 'Studies of the Lepromin Test.' The studies started with an investigation of the classical Mitsuda test; during the course of this study, however, a practically new test has been evolved, and it is realised that further work to be done on the subject is really outside the scope of the general title of the present series. It is therefore felt that the present series which has already run into ten articles may be terminated, and the work done so far may be summarised and reviewed in this concluding article of this series. It is true that some of the lines of work that we had suggested in the opening article of this series have not yet been tackled; these lines, however, can be tackled in a better way with the improved test than with the original Mitsuda test.

The lines of work originally suggested.

In the opening article of this series we (Lowe and Dharmendra, 1940) reviewed the literature on the subject, and discussed the lines of further work necessary to fill in the gaps in our knowledge of the subject. The following lines of work were indicated:

1. Standardisation of methods.
2. A study of the nature of the reaction.
3. A study of the significance of positive and negative reactions.
4. A study of the possibility of using lepromin injections as a method of immunising against leprosy.

A perusal of the work reported in the various articles of the present series will show that considerable advance has been made

*Reprinted from *Leprosy In India*, 1943, **15**, 82. This is the eleventh of a series of articles and summarises the work reported in the previous ones.

along some of the lines indicated, while little has been achieved along the other lines. We shall here review the work done so far.

Standardisation of methods.

Widely divergent results of the lepromin test have been reported by different workers in different countries; it is felt that these differences might have been caused partly by the lack of a standard lepromin and of a uniform method of reading results. For an accurate study of this reaction it was therefore desirable that (*a*) a method of preparing standard lepromin be worked out, and (*b*) a uniform method of reading results be adopted.

(*a*) *Preparation of standard lepromin*: At the time of planning this study, no method was available for accurately standardising lepromin. The only precaution taken to ensure some sort of uniformity consisted in keeping a constant proportion between the weight of the lepromatous material used and the saline used to suspend it. Muir (1933) in addition attempted a rough standardisation by making a comparison of bacillary concentration in freshly made material and old material that had given satisfactory results; no actual bacterial count was possible.

During the past two years in the articles of the present series we have suggested three methods for standardisation of the preparations used for the lepromin test. Till a method was available for isolating leprosy bacilli from the nodules, our standard lepromin consisted of a fine suspension of the leprosy bacillus in saline, obtained from the leprous nodules and standardised by making a bacterial count by the Breed's method (Dharmendra, 1941a). Later a method was developed for the complete separation of the bacilli from the leprous nodules (Dharmendra, 1941*b*), and two standard preparations made from these separated bacilli have been described, first a solution of the protein antigen of the leprosy bacilli standardised by weight of the isolated antigen (Dharmendra, 1941*b*) and second, a suspension of the partly defatted bacilli standardised by weight of the bacilli (Dharmendra, 1942). The preparations made from the separated bacilli are undoubtedly better than the fine suspension of the leprosy bacilli obtained from the leprous nodules.

Of the two preparations made from the separated bacilli, the solution of the protein antigen has certain advantages over the suspension of the defatted bacilli; the isolated protein is a pure and refined antigen, and with it the late nodular reactions are altogether eliminated, since it produces an early reaction only.

The suspension of the partly defatted bacilli has the advantage over the isolated protein in that it is simpler in preparation.

It produces a well-marked early reaction and only a slight late reaction; thus by its use the extra labour and special technique involved in isolating the protein is eliminated while many of the advantages of the isolated protein are retained. The suspension of the partly defatted bacilli, standardised by weight, is therefore recommended for routine use. Its preparation has already been described (Dharmendra, 1942). The method consists essentially in obtaining, by the chloroform method, leprosy bacilli free from other elements of the leprous nodules, partly defatting the bacilli by further treatment with chloroform, drying the defatted bacilli, and suspending the dried bacilli in 0.5% carbol-saline, using one milligram of the bacilli to 10 c.c. of the saline. 0.1 c.c. of this suspension is used in the test.

Fernandez and Castro (1941) have recently described a similar method of preparing standard lepromin from bacterial powder. They separate the bacilli from the other elements of the leprous nodules by centrifuging the suspension of the nodules in distilled water at different densities. The yield of the bacilli by this method is, however, much less than by the chloroform method; and weight for weight the chloroform-treated bacilli are more potent than those obtained by the Fernandez method.

(*b*) *Reading of results*: Above we have described three standard preparations, and have recommended one of them (a suspension of the partly defatted bacilli) for routine use. We shall first describe the criterion of a positive result with this preparation, and then with the other two preparations.

The *suspension of the partly defatted bacilli* is capable of producing both the early and the late reactions. The positive early reaction is characterised by the appearance, 24-48 hours after the injection, of a definite area of erythema accompanied by an appreciable degree of oedema and thickening of the erythematous area. The thickened erythematous area varies from 10 to 30 mm. in diameter, occasionally more, the average being 15 mm. The late reaction is seen about two weeks after the injections, that is, slightly earlier than the reaction produced by the injection of ordinary lepromin. The late reaction is considerably less marked than that produced by ordinary lepromin; usually it consists of a small nodule from 2 to 4 mm. in diameter; occasionally the nodule is bigger. As a rule, nodule formation is not accompanied by ulceration; rarely however, there may be some ulceration.

The *protein antigen isolated from the leprosy bacilli* is capable of producing only an early reaction. This early reaction is similar to the one produced by a suspension of defatted bacilli.

The fine *suspension of leprous nodules* (ordinary lepromin) is

capable of producing both the early and the late reaction; the early reaction is less marked and the late reaction is more marked than the similar reactions produced by a suspension of the defatted bacilli. After a study of the late reactions produced by ordinary lepromin in about 500 cases of leprosy of both the types, we (Dharmendra and Lowe, 1942) defined a positive result as follows :—

'A progressive infiltration leading to definite nodulation from the second or third week onwards, persisting till at least the fifth or sixth week, often much longer, the nodule in most cases measuring 5 mm. or more in diameter at the end of the fourth week, but occasionally being smaller. Thus the characteristic feature of a positive result is the nature of the reaction (nodular, progressive and persistent) and not its size. The size of the nodule may, however, be used to grade the degree of positive reactions.'

A study of the nature of the reaction.

A positive Mitsuda reaction is strongly suggestive of an allergic phenomenon; there are, however, certain features of the test which make the acceptance of this view difficult. Our study of this matter has yielded useful information. Our studies planned to elucidate the nature of the Mitsuda reaction have taken mainly two lines : firstly, the isolation of all the active fractions of the leprosy bacilli, and secondly, the testing of non-contacts. The information obtained by these two methods is summarised below.

The isolation of active fractions of the leprosy bacilli : A method was evolved for the separation of bacilli from the other elements of the leprous nodules. The separated bacilli are thoroughly ground and the various chemical fractions are isolated from these ground bacilli. A study of the antigenic action of these various preparations has brought out the following points :—

(1) In the leprous nodule, only the bacillary matter is antigenic, producing both the early reaction (24-48 hours) and the late reaction of the Mitsuda type.

(2) Of all the chemical fractions (protein, polysaccharides, glycerides, phosphatides and waxes) isolated from the bacilli, only the protein is antigenic.

(3) This active fraction (the protein) produces only an early reaction.

(4) None of the isolated fractions produces a late reaction of the Mitsuda type.

(5) Since the protein fraction is the only antigenic material in the bacilli, and since late reaction is not produced

by any of the fractions, the classical Mitsuda test is believed to be caused by the protein fraction, which when isolated produces only an early reaction. According to our view the delayed reaction to ordinary lepromin (Mitsuda test) is caused by the slow breaking down of the bacilli contained in it, with the consequent slow liberation of the antigen over a prolonged period.

(6) By providing an explanation for the lateness of the reaction, the above observations have brought the Mitsuda reaction more into line with the allergic skin reactions.

The test in non-contacts: Positive results in non-contacts with the ordinary lepromin have been reported by other workers, and confirmed by us (Dharmendra and Jaikaria, 1941). By extracting the isolated leprosy bacilli with different solutions, three active protein fractions were isolated, and it was hoped that one of these fractions might be specific to the leprosy bacillus and give negative results in persons not exposed to leprosy. When tested in non-contacts, however, none of the fractions produced uniformly negative results (Dharmendra and Jaikaria, 1943). Nevertheless, with one of the fractions (nucleo-protein isolated by the phosphate-buffer method) the incidence of positive results in the non-contacts was very low (5%). Moreover, there is some other evidence that the nucleo-protein may be the specific fraction of the leprosy bacillus. The lack of specificity may be caused by changes produced in the protein during its preparation by the present method. It may be possible to demonstrate specificity if the protein is isolated in a more natural form.

Conclusion: It is believed that our studies have thrown considerable light on the mechanism of the lepromin reaction. As a result of these studies, the reaction has been brought more into line with the allergic skin reactions. The three features of the test which stood in the way of its being accepted as a test of allergy were as follows: (1) that, clinically, the classical Mitsuda reaction is unlike any other allergic skin reaction; (2) that positive results are seen in persons not exposed to leprosy; and (3) that the patients suffering from the lepromatous (the more serious) type of the disease show negative results.

Our studies have afforded a satisfactory explanation for one of these features, namely, the lateness and the nodular character of the reaction.

There is some hope that as a result of our work a suitable

preparation of the leprosy bacillus may be made available which will not produce positive results in non-contacts; if so, the second anomalous feature will be explained.

Our work has no direct bearing on, and suggests no explanation of, the third anomaly, namely, the negative results in cases of the lepromatous type; however, work with the improved antigen will facilitate the study of this matter. This anomaly undoubtedly needs to be explained; however, its existence should not be considered irreconcilable with the idea of the lepromin reaction being an allergic phenomenon; negative lepromin reaction in lepromatous cases of leprosy may be similar to the negative tuberculin test in advanced cases of tuberculosis, or else it may be caused by some inherent incapacity of the tissues of the lepromatous cases to react allergically to the presence of leprosy bacillus or its products. We may summarise here the evidence for the allergic nature of the test.

1. In appearance, the local changes in the skin produced by the introdermal injection of the isolated antigen are similar to those seen in other allergic skin reactions, for example, the tuberculin test. It is believed that the same antigen is responsible for the nodular reaction seen in the classical Mitsuda test, the lateness and the nodular character of the reaction in this test being caused by the nature of the material injected.

2. In healthy persons living in areas heavily infected with leprosy the incidence of positive results is much higher, and the degree of the reacton is much greater than in healthy persons living in areas where there is little or no leprosy.

3. The response to the injection of active fractions of *Myco. leprae* is seen not only at the site of the injection, but not infrequently, in leprous lesions away from the site of injection, and also at the site of the previous injections of lepromin. This means that the response is not only local but not infrequently focal also. This is a strong indication of the reaction being allergic.

4. Definitely tuberculoid and definitely lepromatous cases of leprosy are generally believed to be two immunologically distinct groups. The lepromin test gives almost uniformly positive result in one of these groups, that is, in the tuberculoid cases, and almost uniformly negative result in the other group, that is, in the lepromatous cases.

6. The lack of power to react to the antigen of *Myco. leprae* found in the tissues of the patients suffering from the lepromatous type is a specific one, since the tissues of such patients retain the power to react to other acid-fast bacilli, to some of their products,

and to some irritating substances that have nothing in common with the acid-fast bacilli such as proteoses, weak acids and alkalis, etc.

A study of the significance of a positive or a negative reaction.

No study has yet been made of the significance of a positive or a negative result in contacts. The study needs to be carefully planned and will involve repeated observations over a long period.

A start has been made of the study of the prognostic value of the test in cases of leprosy. All cases attending for treatment at the Leprosy Department of the School of Tropical Medicine, Calcutta, are being tested as a routine, and in time we hope to collect valuable data on the prognostic value of the test. A study of this nature necessarily involves observations over a long period.

At this stage we are not in a position to report a detailed study and to accurately assess the prognostic value of the test in cases of leprosy. However, an analysis of the results of the test in a large number of cases of leprosy, and subsequent developments in some of the cases during the limited period of about three years, have brought out certain points bearing on this subject.

Our findings, in general, support the view generally held that, in cases of leprosy of all types, the lepromin test is of some value in prognosis, a positive result indicating a favourable prognosis.

Observations in the neural cases: There is some evidence to show that lepromin-negative neural cases are more likely to become lepromatous than the lepromin-positive cases. Only one of the large number of neural cases tested by us has so far become lepromatous since testing; this was a simple neural case with a negative lepromin reaction. We have also some evidence to show that the neural cases with marked reaction to lepromin are more likely to subside. Even apart from actual subsidence, a positive test indicates a better prognosis; for example, bacteriologically positive cases are more likely to become bacteriologically negative if the result of the lepromin test is positive.

Observations in the lepromatous cases: Some workers have studied the results of the test in the lepromatous cases in relation to the subsidence of the disease and have brought out the following points: (1) of active lepromatous cases, those with a positive lepromin test are more likely to improve. (2) When lepromin-negative cases show subsidence of the disease, the lepromin test sometimes becomes positive with the subsidence. (3) A subsided lepromatous case that is lepromin-positive is less likely to relapse than a similar lepromin negative case.

Our work lends support to the first point; of the active lepromatous cases, those with a positive lepromin test are more likely to improve. Of the 141 lepromatous cases tested by us during the months from June 1940 to March 1941, 12 have since become bacteriologically negative and inactive. Seven of these belong to the large lepromin-negative group of 127 cases, and 5 to the small group of 14 cases with a weak positive lepromin reaction.

Our experience with the test in the subsided lepromatous cases does not support the second point, namely, that with the subsidence of the disease in lepromin-negative cases the lepromin test tends to become positive. In none of the subsided cases has a negative lepromin reaction changed into a positive reaction; in some cases with a weak positive reaction the reaction has even become weaker.

None of our subsided lepromatous cases has so far had a relapse, and thus our present work gives no information on the third point, namely, that a subsided lepromin-positive lepromatous case is less likely to relapse than a similar lepromin-negative case. Our general experience of the test, however, would lead us to expect this.

Observations in cases of doubtful classification: In cases of doubtful classification a strongly positive lepromin reaction practically rules out the possibility of the case being lepromatous.

Conclusion: There is, therefore, a considerable indication that, in cases of leprosy of all types, the lepromin test is of definite value in prognosis.

The possibility of using lepromin injections for immunising against leprosy.

A study has not yet been made of the possibility of turning a lepromin-negative healthy person into a lepromin-positive, by means of injections of lepromin. If this were possible, the question whether such a change was followed by increased immunity could then be investigated.

We have, however, attempted without success to change a weak positive or negative reaction seen in lepromatous cases and also in a few neural cases into a positive reaction by means of repeated testing (Dharmendra, Lowe and Mukherji, 1942*a*). Eighty-nine such cases, 27 neural and 62 lepromatous, were tested repeatedly. Monthly tests for a period up to 18 months failed to enhance the reaction to lepromin in the large majority of the cases tested. In only 10 of the 89 was slight increase observed, in 2 of the 62 lepromatous and 8 of the 27 neural cases. Thus the experience of some other workers in this matter has not been confirmed.

The practical value of the work reported in this series.

Above we have indicated the progress made along the various lines of work suggested by us in the opening article of this series. We may now summarise the practical advantages that have accrued as a result of our work.

(1) The test has been simplified both for patients and workers. In the classical Mitsuda reaction the readings have to be made weekly for four weeks or longer; with the defatted bacilli or the isolated protein antigen, the early (24-48 hours) reaction is quite clear-cut and no late readings are needed. The classical Mitsuda reaction usually results in the production of large nodules which may ulcerate; the defatted bacilli produce only a slight late reaction, the nodules usually measuring 2 to 4 mm., rarely ulcerating; the isolated protein antigen produces no late reaction whatsoever.

(2) A refined antigen which is capable of accurate standardisation has been made available for the test. The antigen used for the Mitsuda reaction was very crude; it consisted essentially of a boiled suspension of leprous nodules from which gross tissue particles had been eliminated. The bacterial powder separated from the leprous nodules by the chloroform method is practically free from any tissue and the suspension prepared from this can be standardised by weight of the bacilli; the protein fraction of the bacilli is a still further refined and a chemically pure product and its solution can be very accurately standardised.

(3) The work has thrown a considerable light on the mechanism of the reaction. By providing a satisfactory explanation for the lateness and the nodular character of the lepromin test (the classical Mitsuda reaction), and by demonstrating that a solution of the antigen responsible for this reaction produces only an early reaction of the tuberculin type, our work has brought the lepromin test more into line with other allergic skin reactions. Moreover, results so far obtained with the different protein fractions of the bacilli are very encouraging, and it is possible that further work on these lines might yield a fraction specific to the leprosy bacilli. In that case a diagnostic allergic skin reaction for leprous infection would be evolved.

(4) It is believed that as a result of our present work, further immunological work in leprosy has been facilitated; a refined and pure antigen which can be accurately standardised has been made available, and the investigations have been rendered easier both for patients and workers.

Some other points regarding the Mitsuda test arising out of the present work.

In addition to the progress made along the various lines of work suggested by us in the opening article of this series, certain other points regarding the Mitsuda test have arisen out of the work.

The results in cases of the different types of leprosy: An analysis of the results of the test with ordinary lepromin in over 600 cases of leprosy of all types (Dharmendra and Lowe, 1942) brought out the following points :—

(1) Of the lepromatous cases, 90% gave negative results, 10% weak positive, and none strong positive. The positive results were commoner in cases which showed clinical and/or histological abnormality but were not confined to them.

(2) Of 'doubtful' cases, 40% gave positive results, four-fifths of these being weak positive. A correlation of the results with the histological findings in these cases showed that the positive results were seen chiefly in cases which were either definitely tuberculoid or else showed a tuberculoid element in histology. No 'doubtful' cases which on histological examination showed only lepromatous changes gave more than a weak lepromin reaction, and even such reactions were very few.

(3) In cases classified as 'neuro-anaesthetic' the incidence and the degree of positive results were high.

(4) In the 'neuro-macular' cases there was a high incidence of positive results, the incidence and degree of positive reaction increasing from 'simple' through 'tuberculoid not major' to 'major tuberculoid.' Of 'simple' cases, 20% gave negative results, 34% weak positive, and 44% moderate or strong positive; whereas of the 'major tuberculoid' cases none gave negative results, 16% weak positive, and 84% moderate or strong positive. In cases classified as 'tuberculoid not major,' the figures were intermediate.

Correlation of the results of the lepromin test with bacteriological findings in the neuromacular cases: We (Dharmendra and Lowe, 1942) found that the incidence and degree of positive results

in all the sub-types ('simple,' 'tuberculoid' and 'major tuberculaid') were higher in the bacteriologically-negative cases than in the bacteriologically-positive ones. These weaker reactions have been shown not to be caused by the presence of the bacilli; both the findings are probably caused by a third factor.

Correlation of the results of the lepromin test with the clinical activity of the neuro-macular lesion : We (Dharmendra, Lowe and Mukherji, 1942*b*) have also found that the incidence and degree of positive results are higher in clinically inactive cases than in clinically active cases of the same sub-type. In individual cases, however, the reaction does not become stronger with the subsidence of activity. These findings have been interpreted as indicating that those cases which show the stronger reaction to lepromin are more likely to subside.

Variations in the degree of reaction to lepromin with variations in the time of the year when this test is done : It appears that the degree of reaction to lepromin of many patients showing the neural type of leprosy is influenced, apart from any other factor, by the season of the year. We (Dharmendra, Lowe and Mukherji, 1942*b*) have reported that ,the same lot of lepromin used in the same patients showing no change in the clinical condition, gives a stronger reaction in summer and weaker reaction in winter.

The early reaction to lepromin : Till recently the phenomenon of early reaction to lepromin had attracted little attention. Most workers had considered the early reaction, sometimes seen in the first three days after injections of lepromin, to be of little significance. Fernandez (1940), however, made a special study of the early reaction and reported that it was always present in cases giving marked late reaction and that an early reaction had the same significance as the late reaction.

We (Lowe and Dharmendra, 1941) have confirmed the report of Fernandez that, after the intradermal injection of lepromin, an early erythematous reaction of tuberculin type is seen in most cases of leprosy that give the classical late reaction. We compared the early and late reaction in a series of 300 cases with the ordinary lepromin and found a high degree of agreement. We also confirmed the report of Fernandez that the early reaction is caused by a soluble antigen.

Having confirmed the significance of early reaction to lepromin, we extended our work to find out the mechanism of this early reaction; and we believe that our studies have thrown considerable

light on the mechanism of not only the early but also of the classical Mitsuda reaction.

By making a comparative study of early and late reaction to lepromin and to filtrate from that preparation, Fernandez concluded 'that early and late reactions are probably brought about by different substances or toxins of the Hansen's bacillus.' Our work disproves the presence of two different antigens, one responsible for the early reaction and the other for the late. We have shown that both the early and the late reaction can be explained on the basis of the protein antigen that we have isolated from the Hansen's bacillus. Moreover, our work provides no indication of the existence of a separate antigen producing a late reaction (Dharmendra, 1941*b*); it is the slow liberation of the antigen from the breaking down of the bacilli contained in the lepromin, that is responsible for the late reaction.

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REVIEWS.

Leprosy. Rogers and Muir (3rd Edition).

The third edition of this well-known and standard work on leprosy was expedited owing to a large part of the second edition having been destroyed by enemy action. This has given the authors an opportunity to incorporate news views concerning the disease which have arisen as the result of research during the last six years. The book follows the general lines of previous editions, and much useful information on epidemiological data will be found. Sir Leonard Roger's experience and contacts with so many authorities are clearly evident in the first three sections, and workers in leprosy will appreciate the painstaking way in which the evidence has been amassed. The sections dealing with the clinical aspects and treatment of the disease show the wide experience of Dr. E. Muir, and anything which he writes bears the stamp of authority. We would have preferred to see a description of the clinical signs of neural leprosy placed before those of leproma, for as is rightly said, neural leprosy is a benign manifestation and, generally speaking, an indication of active tissue resistance. We are glad to note that this aspect of the pathology of the disease has been stressed. In future editions it is hoped that greater emphasis will be laid on the pathology of the disease, and that a complete chapter will be devoted to this, with a discussion on the tissue defence mechanism in leprosy, for it is the reviewer's opinion that the study of the cellular reactions in the corium of the skin is one of the keys which will help to open the way to a better understanding of the pathology of the disease.

The illustrations, probably owing to war time difficulties, are not up to the standard one would expect, and the introduction of a series of good photomicrographs of the various lesions would add greatly to the value of the work.

We consider that this book should be in the library of all workers in leprosy, and should be possessed by those who have an interest in the teaching and practice of tropical medicine.

R. G. COCHRANE.

International Journal of Leprosy (1944) Third War Number.

PRELIMINARY REPORT ON DIASONE IN THE TREATMENT OF LEPROSY, by Muir, E.

This was given intravenously and by the mouth, the dosage

being regulated according to the tolerance of patients from 0.3 to 2 g., particular watch being kept over the hæmoglobin percentage. Forty-three patients were treated for more than three months, and forty-one for less than three months.

"Of those treated for more than three months 24 out 43 showed marked improvement and 17 others showed slight improvement. Only two are classed as stationary. Of those treated less than three months none showed marked improvement, but 36 out of 41 showed slight improvement, five remaining stationary. It is interesting that in neither group did the condition of a single patient become worse. On the basis of these figures it is evident that those treated for the longer period showed the greater improvement."

The greatest improvement was found in those in the third stage of the lepromatous type, that is to say the stage in which nodules and thickened lepromatous patches have begun to ulcerate, and in which the eyes and nose are seriously inflamed.

PENICILLIN USED UNSUCCESSFULLY IN TREATMENT OF LEPROSY, by Faget, G. H. and Pogge, R. C.

"Seven patients with the lepromatous (nodular) type of leprosy were selected for treatment, since this is the type of disease which shows the least tendency toward spontaneous remission. The first and second patients were chosen to note if penicillin had any effect on recently developed nodules. From past experience at the National Leprosarium, new nodules seemed most amenable to treatment. Hence it was rational to expect favourable changes in new lesions if penicillin exhibited any specific action in leprosy. This expectation did not materialise.

The third patient was selected because the disease was of an early minimal type of lepromatous leprosy. It was felt that such a case offered penicillin an excellent opportunity to produce a favourable reaction if it had any merit in the treatment of leprosy. It did not do so.

The other four patients treated had more or less advanced lepromatous leprosy which had not responded to any previous treatment. In these cases it was thought interesting particularly to observe whether penicillin had any influence upon certain complications of the disease which were present. These complications included leprous ulcerations, erythema nodosum, iridocyclitis, leprous keratitis, leprous rhinitis and leprous laryngitis. Some of these complications were being activated by secondary infections. No beneficial effects were demonstrated in any of these patients, except for the healing of secondarily infected ulcers in one case."

[These results are different from those reported by Wharton in LEPROSY REVIEW, Aug. 1945, pp. 7-12.]

TRACHEOTOMY IN LEPROSY, by Sloan, N. R.

This is a report of a group of 144 patients in whom this operation was done for obstruction of the larynx. The average interval between admission to hospital and operation is 3 years longer than the average life of all lepromatous cases. This does not mean that presence of a laryngeal lesion prolongs life; it rather seems to indicate that most lepromatous patients do not live long enough to develop laryngeal stenosis. This is borne out by finding that of 32 lepromatous patients now living, whose first admission was prior to July 1, 1929 (15 years ago), 16, or 50 per cent, are

now wearing tracheal tubes; and of the remainder 7 show evidence of larygeal leprosy which may require operation later.

"Leprotic laryngitis is found only in lepromatous patients, usually in those who first present lesions of the mouth or pharynx. The epiglottis is first involved and may become several times normal size; spread to the vocal cords produces gradual narrowing of the glottis, which may become so small that slight swelling of the mucosa can obliterate it and cause death. The narrowing of the glottis causes increased respiratory effort, and perhaps at times mild bronchiectasis. Bronchial secretions are expelled with difficulty, and their accumulation increases the dyspnea, producing a vicious cycle which can be broken only by providing an adequate airway."

TREATMENT OF NEURITIS IN LEPROSY WITH INTRAVENOUS CALCIUM GLUCONATE, by Pogee, R. C.

"It was found that 90 per cent of the patients whose neuritis was not helped by vitamin B_1 or local heat were either completely relieved of nerve pains, or helped so that simple analgesics gave complete relief within a week or two of starting treatment, utilizing intravenous calcium gluconate. When all cases are considered, the average is higher than 90 per cent."

The dose was 1 gm. or up to 8 gm. in a month.

A. R. Davison describes a case diagnosed as one of lepromatous leprosy in which active signs of leprosy and bacteriological findings became negative as the patient gradually developed lymphadenoma (Hodgkin's disease.)

H. J. Henderson found that "injection of acid-fast bacilli, obtained from spleens of human leprosy patients, into normal rabbits did not lead to the development of an anti-serum reacting with the serum of leprosy patients in such a way as to indicate the presence of specific leprosy becillus antigen in leprous serum."

Mom, A. M. and Bosombrio, G. write on THE DIFFUSION FACTOR IN LEPROUS SKIN. Following the work of Durán-Reynals, they found that

"The diffusion activity (R factor) of human skin is 50 per cent that of bovine testicular extract. The R factor is not modified in diseased and in apparently healthy skin of patients with tuberculoid leprosy. In cases of lepromatous leprosy the diffusion activity disappears completely from the skin. The diffusion activity of leprous skin is inversely proportional to the amount of M. leprae it contains. Extract of lepromatous skin appears to exercise an antagonistic effect on the diffusion action of extract of tuberculoid skin."

THE LEPROMIN TEST IN TUBERCULOSIS PERSONS IN A NON-ENDEMIC AREA, by Convit, J., Azulay, R. D. and Salgado, P.

The experiments were carried out at the Seaview Hospital, New York.

"Of ten patients, with various dermatoses, attending the out-patient clinic at New York Skin and Cancer Hospital, all reacted positively to tuberculin. Of this group 9 showed early and 8 late positive reactions to lepromin. Of four patients with Boeck's sarcoid, three reacted negatively to tuberculin and to lepromin. The fourth was weakly positive to

tuberculin, negative to lepromin on the early reading, but did develop a positive Mitsuda reaction. Of 108 tuberculous patients at Seaview Hospital, 70.4 per cent were positive to lepromin on the early reading and 46.2 on the late reading. This high proportion of Fernandez positives may be due to the fact that all idividuals were tuberculin positives. If so, comparative figures for Mitsuda positives would indicate that the Mitsuda reaction is less affected by cosensitization with **M. tuberculosis** than is the Fernandez reaction.'

LEPROSY IN MILITARY SERVICE, Faget, G. H.

This paper is supplementary to a paper by Dr. Hasseltine (*Int. Jl. Lep.* (1940) **8**, 501-508). Of 14 army veterans and 3 seamen, most came from parts of America where leprosy is endemic, and 7 had manifestations prior to enlistment which had been missed by the examining physician. It is considered probable that the hardships of war contributed to the development of latent leprosy. In the Spanish war almost all the 32 cases came from non-endemic states, and therefore probably acquired the disease during the campaign. In World War I the cases were as in this war, chiefly from endemic states. In both of these the cases occurred too soon to have been the result of infection during the campaign. "With the lapse of the long period of incubation of the disease, it can be expected that at least a small number of World War II veterans will become the victims of leprosy contracted on foreign soil."

THE HISTORY OF LEPROSY IN THE NEW ENGLAND STATES is related by H. E. Hasseltine. Most of these were in the State of Massachusetts and were 60 in number. From the other five states there were only 5. Before the founding of the National Leprosarium at Carville, Pa the patients were lodged on Penikese Island. When this was evacuated the island was turned into a bird sanctuary, as no-one would buy it because of the fear of leprosy.

A NOTE ON FAMILIAL RELATIONSHIP AND RISK OF DEVELOPING LEPROSY, by Bancroft, H. *et al.* This is based on work in the Philippines, where the risk of developing leprosy following exposure to a lepromatous case in a household has been shown to be eight times that for those not known to have a household exposure.

"The incidence rates for males are higher than for females for all familial relationships except where the primary case is a mother. Here the female rate of 8.10 per 1,000 person-years is considerably higher than the male rate of 1.95."

The numbers are however too small to be significant and the report is published in the hope that other workers will make further contributions to familial investigation.

Leprosy in India, Vol. XVII, No. 4, Oct., 1945.

TACTICS AND STRATEGY IN THE ANTI-LEPROSY CAMPAIGN, by W. H. Russell. This is a plea for a long-term plan for the control of leprosy in India. Vital to such a plan is the establishment at a suitable site of a Leprosy Institute of India, such as was recommended by the Report on Leprosy and its Control in India (1941). This would be a research and training centre and gradually come to lead the attack on the disease.

"If the main argument of the preceding paragraphs is sound, then it follows that tactics and strategy will always be closely related to one another, and on the whole tactics will be subordinate to strategy. Of course, that does not mean that individual enterprise will de discouraged, or experimental projects disallowed. On the contrary, the grand strategy of the Leprosy Institute of India would make generous provision for these patrols, which go out in advance of our main forces in order to locate the enemy and gain information about his strength. But the wise general, though he makes use of the intelligence provided by his scouts, does not allow them to waste his main strength by leading him hither and thither in a fruitless chase. He has a plan. He modifies it from time to time according to the information he receives, or perhaps even changes the direction of his main front to meet an important change in the dispositions of the enemy. But the plan is there, and all the tactical operations conducted by the general's troops are subordinate to it, because it aims at results required by an agreed strategy."

Dr. Dharmendra reports on *Leprosy in Bengal.* He estimates between two and three hundred thousand cases in Bengal. Of these 786 are segregated in seven in-patient institutions, and 18,960 are treated at some 138 out-patient clinics. He contrasts the comparatively small effort in Bengal as compared with Brazil, a country with approximately the same population.

The Therapeutic Effect of Promin in Leprosy, by G. H. Faget and R. C. Pogge. U.S.A. Public Health Reports (1945) **60,** 1165-1171.

A former report on this subject was abstracted in the August, 1945, number of *Leprosy Review.*

The authors discuss the causes of the favourable results obtained. Are they due to psychological response of the patient, are they spontaneous remissions, is improvement purely symptomatic and lacking in objective substantiation. are the effects limited to secondary infection or other complicating conditions? They argue that none of these fully explains the results of treatment.

' Since the first four hypotheses do not fully explain the improvement produced by promin in leprosy, it is possible that a chemotherapeutic action is tenable. The action of promin in leprosy has been observed to produce favourable changes on the specific lesions, the granulomatous nodules of the disease This improvement may be due to bacteriostatic or bacteriolytic action on Hansen's bacillus, but there is no way to prove this because the causative germ cannot be cultivated and the disease

cannot be reproduced in laboratory animals by inoculation of human material.

"Among the 62 patients treated for more than one year, there has occurred a reversal of bacterioscopy from positive to negative on several consecutive monthly examinations in over ten per cent of cases. An additional 30 per cent have had occasional negative tests since starting on the promin treatment. These laboratory findings tend to show that in at least 40 per cent of cases there has occurred a diminution in the number of infective organisms in the lesions of the disease. This suggests that promin has some chemotherapeutic action in leprosy."

Also during treatment with promin 21.6 per cent of cases changed from a positive Kahn test to a negative and in 0 was this process reversed. In a control group these percentages were respectively 8 and 16. The dose of promin is 1-5 gm. daily intravenously. In some with toxic reactions the maximum daily dose did not exceed 2 gm. 6 days a week in courses of two weeks, with one week of rest between courses. Since this technique has been adopted toxic reactions have been few and of a minor nature.

In their conclusions the authors say :—

"Evidence of clinical improvement in a study of 137 leprosy patients treated with promin indicates that at present it is the treatment of choice for this disease . . . It is hoped, however, that further research will discover a still more powerful chemotherapeutic drug for the mycobacterial diseases."

Treatment of Eye Lesions in Leprosy, by Chorine, V. *Bul. de la Soc. Path. Exot.* (1945) **38**, 255.

The author first refers to the varying incidence of eye lesions in leprosy given by different writers, from 5 to 10 per cent in India to nearly 100 per cent in Hawaii, Paris, Norway and U.S.A., and over 60 per cent in Russia and 80 per cent in Japan. The author attributes this difference to climate, the eyes being more affected where the climate is severe.

[This however would fail to account for the large percentage in Hawaii. Much depends on the type of the disease. In India the lepromatous type rate is less than 25 per cent of the whole, and many of the neural cases are of a mild and localised form and do not affect the face.]

The treatment he recommends is the weekly injection of para-aminophenyl-sulfamide (septoplix) in a 15 per cent solution of distilled water round the circumference of the orbits. This stops the evolution of ocular complications in leprosy and provokes regression, sometimes marked, of recent lesions. He first anæsthetises the skin by injecting at the chosen site 4 to 5 c.c. of 1 or 2 per cent stovaine, and then injects 6 to 10 c.c. of sulfamide solution, half round each eye, in the areas already anæsthetised, either on a level with or above the eyebrows, or on the nasal or temporal side. The injections are made weekly at a different point

each time, and fresh solution should be used. This treatment was first thought of because the author had noticed that infiltration of the base of skin nodules with this drug not only caused benefit at the point of injection, but also cleared up nodules at a short distance.

Thirteen patients were treated by this method. Of 5 with recent lesions, and of whom 4 were practically blind, 4 have recovered eyesight compatible with normal existence. In the case of those with more long-standing lesions, there is little or no amelioration.

Experimental Treatment of Leprosy with Solutiazamide, by L. de Souza Lima. *Revista Brazitiera de Leprologie* (1945), **13,** 97-100.

The writer mentions the difficulty of obtaining a soluble preparation of sulphathiasol which will not be too alkaline and act as a caustic. The preparation he uses (salutiazamide, a soluble modification of sulphur thiazol) has a pH between 6 and 7 and is given intravenously without irritation. The solution used contains 45.30 per cent of the compound, or 20 per cent of the base, 5.3 c.c. containing 1 gram. He begins with the intravenous injection of 1 c.c. and gradually increases the dose to 5 c.c. in children and 10 c.c. in adults. Injections are given daily except Sundays for three weeks, followed by a rest of one week. The dosage is controlled by counting the red blood cells and the hæmoglobin percentage, examining the urine every 10 days and by estimating the blood concentration of the drug.

He treated two groups of lepromatous cases, one of 50 moderately advanced, and the other of 50 more advanced with cutaneous, ocular and nasal complications which had not yielded to chaulmoogra treatment. The results were as follows: The progress of the disease was arrested in certain cases from the beginning of treatment. There was rapid healing of leprotic ulcers, cicatrization of lepromas and flattening of the skin, clearing up of subcutaneous nodules and healing of perforating ulcers of the feet. In some cases the eye condition flared up for a time, but after a short period this disappeared. Patients with scabs and blocking of the nasal passages obtained marked relief; they no longer needed to wash out the nose and they could breathe without obstruction.

As Flacourticeas Antileprocaticas. **(The Plants of the Flacourtiaceae Family used in the Treatment of Leprosy.)** By Helena Possolo of the Pharmaceutical Laboratory of the Department of Prophylaxis of Leprosy, Sao Paulo, Brazil.

This is a most comprehensive work of 132 pages. It describes the botanical features of the various genera and species of this family, and the physical and chemical qualities of the oils extracted from the seeds and used in the treatment of leprosy. The introduction deals with the geographical distribution of the Flacourtiacæ and the history of their use. Only three of the innumerable genera produce oil used in leprosy: Hydnocarpus and (in S. America) Oncoba and Carpotroche. The first chapter describes the tribe Oncobeæ and its genera, indigenous chiefly in S. America. The second chapter is devoted likewise to describing the Hydnocarpus species, while the third deals with the chemical qualities of Hydnocarpus oil. The fourth chapter describes methods of fractionation of Hydnocarpus oil. From the botanical viewpoint this is a most valuable compilation, and the illustrations give full details of the more important species.

One of the most valuable assets of this work is its comprehensive bibliography of over 300 references.

REPORTS

Mission to Lepers. *Report of Seventy-First year of Work in India,* 1944-45.

This booklet is brightly illustrated with scenes from some of the forty-six institutions in India, in which the Mission is concerned. There are 8,830 patients, and 813 healthy children of patients are also looked after. The following quotation shows the hopeful spirit in which the future is being faced:—

"On all sides thought is now given to post-war reconstruction, and those engaged in the long campaign against leprosy earnestly hope that in public health schemes for India adequate provision will be made for a great crusade against this deeply entrenched enemy of man. The Mission to Lepers is considering its own plans for extension of the work in several areas, and hopes to have the privilege of joining Government departments and public bodies in a forward movement. With this in view, two additions have been made to our staff. After last year's report went to the press news was received that the London Council of the Mission of Lepers had taken the important step of appointing Dr R. G. Cochrane, M.D., F.R.C.P. (London) as our Medical Secretary. His name is well known to all interested in leprosy work, and all our supporters will rejoice at this notable reinforcement to our staff. Mr. L. W. Baker has also been appointed as Mission architect, and now comes to India to advise on the numerous building schemes we have before us, as well as to render other service.'

The Solomon Islands. *Searching for a Site for a Treatment Centre*

This is described in a letter from Dr. Austin, Medical Superintendent Makogai Leper Hospital, Fiji. In 1937-38 Dr. Ross Innes* conducted a leprosy survey in the Solomon Islands. Since then the frequent references in the press to the Solomon Islands, and especially to Guadalcanal, during the war have increased the knowledge and interest of the public in this area of the S. Pacific. Dr. Innes from his partial survey computed 900 lepers in the whole protectorate.

Dr. Austin, in company with Dr. Rutter, Acting Senior Medical Officer, and Mr. Twomey of the New Zealand Leper Trust Board, toured the islands in search of a site for a leprosy treatment centre. The difficulty of communications and of water and supplies decided them against a small separate island. One small island off the North West corner of Malaita might have been suitable, but it is popularly supposed to be the home of spirits from the whole of Malaita, which has a population of about 40,000. Another island could not be chosen as some 500 present inhabitants would have had to be evacuated.

They therefore decided to recommend :—

" That the disused Koli Labour Camp situated just to the west of the Nalimbiu river should, if possible, be utilized as the fore-runner of the projected leprosy institution; and that the exact siting of the latter within the area be left for later decision in the light of experience at Koli. The camp consists of 14 leaf huts in good condition, each capable of accommodating say, eight patients, or of conversion to dressing rooms, etc., as required. The former overseer's house would be quite suitable for the use of the Native Medical Practitioner

" On the assumption that the proposal would be acted upon, Mr. Twomey offered, on behalf of the Lepers Trust Board, to authorize the immediate placing at Dr. Rutter's disposal of the sum of £3,000 for the erection of temporary quarters for two European Sisters, and for the purchase from American or New Zealand surplus stores, understood to be now available, of a " truck " and water pump, electric lighting plant (the huts being already wired for lighting), refrigerator, radio sets, etc.) and any other simple amenities regarded as advisable for patients or staff."

" We therefore visited the American Chief of Staff, and later General Barnett, explaining our proposals and requirements. They received us very sympathetically and informed us that at the moment all their stocks were 'frozen' so that they were unable to sell or give any away, but that for such a purpose they would be quite prepared to loan us the required 'utilities'.

' This proposal is in no sense intended to replace, but rather to lead up to, the scheme prepared by Dr. Rutter. The site proposed is near enough to his headquarters, for the Senior Medical Officer to exercise a general supervision over the infant institution. A Native Medical Practitioner from Fiji has voluntered for leprosy work in the Solomon Islands, and has been working for some months at Makogai, and two Sisters of the same Society as those who have done so much for Makogai, who, after

* *Lep. Review*, **9**, 122-128; *Int. Jl. Lep.* **6**, 501-513.

being evacuated from the Solomon Islands, have been undergoing a course of training at Makogai, are also ready to commence the work. If, as is suggested, these Sisters are sent up at once, they will prove of great assistance to Dr. Rutter in generally organizing the camp and installing the first patients. Realizing this fact, Mr. Twomey, on behalf of the Lepers Trust Board, has further generously offered to defray the cost of Air Transport of these Sisters to the British Solomon Islands Protectorate. It will later, also, be necessary to appoint a Lay Assistant or Work Foreman to help with accounts, generally supervise the maintenance of buildings, water and electric light supply, and possibly to advise on agriculture and other matters.

"On our last day at Guadalcanal, His Honour the Resident Commissioner, at the request of Mr. Twomey, enabled us to meet representatives of the various Mission bodies in his office. His Lordship Bishop Baddeley, Monseigneur Bishop Aubin, Pastor Ferris, Chairman of the Seventh Day Adventist Mission, and, in the unavoidable absence of the Reverend Goldie, Dr. Rutter representing the Methodist Mission, constituted such a united gathering of the Missions as had never previously, we were informed, been known in the Solomon Islands. Mr. Twomey explained to the meeting that the present proposal would in no way lessen the need for a number of years of as much assistance as the Missions could render in the solution of the leprosy problem. He promised them, on behalf of his Board, continued financial assistance and, in reply to a question from Bishop Baddeley, assured them of help towards their maintenance expenses as well as capital expenditure. Appreciation of Mr. Twomey's enthusiasm and energy in the cause of leprosy control and of the generosity of the New Zealand public was expressed on all sides, and assurances of full co-operation were forthcoming from all the Missions."

Rotary and Leprosy Relief.

Through the efforts of the Leprosy committee of the Rotary Club of Jamshedpur, India 31,937 persons were examined and 4,982 were visited during the past Rotary year. A total of 43 fresh cases were detected, of which 11 were infectious. The total number of cases discovered since the beginning of the work is 598 plus 305 beggar lepers. Of the 598 non-beggar cases 484 are non-infectious and 114 infectious The number of examinations made since the beginning of the survey in 1939 is 194,506, of which 138,989 were re-examinations. Since the work started 8 non-infectious cases have been cured, 2 infectious cases have turned non-infectious. 68 non-infectious cases have improved and 9 infectious cases have improved.

A recent development is the sponsorship of twelve beds in the Purulia Leprosy Hospital at a first year cost of 10,000 Rs.— and almost the whole of the amount was collected within a month, mostly from Rotarians and their friends.

Leprosy in Cuba. *Revista de Sifiliegrafia, Leprologia y Dermatologia*, October 1945. This journal mentions a survey in Cuba showing 2467 cases of leprosy, of which 1,886 are not interned

Leprosy in Calabar.

Mr. H. D. G. Coffin, working under the direction of Dr. A. B. Macdonald, of the large Leprosy Colony, with over 3,000 patients at Itu, Calabar Pr., Nigeria, made a four days' preliminary leprosy survey chiefly in the Maku district. The following table gives the numbers of cases found which he considers are not by any means exhaustive.

Town	No. examined	Cases.	Percentage.	Free Passes.
Edim Urua	191	1	0.52	1
Obotme	425	9	2.12	6
Iquema	208	19	9.13	11
Usong Usong	7	—	—	—
Edim Edim	35	—	—	—
Ukpa Okon	29	3	10.34	1
Nturi	115	3	2.61	3
Okpoto	232	20	8.62	10
Mbiabong	191	9	4.71	3
TOTALS ...	1433	64	4.46	35

He thinks that 6.0 per cent would be a truer average than 4.46 per cent. He notes that in the Maku area no attempt is made to isolate people suffering from leprosy at present, and that a number of people discovered to be suffering from leprosy were strangers from other villages. He suspected that several of them had been sent away from their home towns upon the appearance of the disease.

[This report shows the importance of combining preventive public health measures in villages with isolation in institutions.]

The Legal Status of Lepers. The Journal of International Law states that preventive Acts have been passed in many parts of the Empire, notably India, Ceylon and the West Indies, but at the present time few of the more stringent laws are in force. The Indian Leprosy Act of 1898 enacted the forcible confinement of pauper lepers and restricted all lepers from engaging in certain trades, but the adoption of the Act was optional in the different provinces, and remained a dead letter in a large part of the country. In Bombay and Bengal, however, the Act had been put into operation and as recently at 1934 was extended in the latter province by a prohibition of lepers from sitting on Union, Local and District Boards.

India also affords an interesting example of ancient laws affecting the status of lepers. Under the oldest Hindu code, The Laws of Manu, no one suffering from incurable disease could inherit property, and this was ruled to include leprosy, but as far back as 1860 the British courts held that "it is a fact well-known

in medical science that the disease of leprosy assumes in some cases a mild and curable form, while in others it appears in a virulent and aggravated type. The Sadr court finds on consulting the best authorities on the subject, that it is in the latter case only that the disease is regarded by Hindu law as a disqualification entailing forfeiture of inheritance." This view has been subsequently accepted by the Privy Council.

Histamine Therapy in the Neuritis of Leprosy, by Florentino Rey Matiz. The author gave intramuscular injections of a 1 in 4,000 solution of histamin in distilled water, the dose being 0.5 to 0.75 c.c. This relieved pain in 86 per cent of cases, lessened œdema in 58 per cent, and improved rhinitis in 45 per cent. The addition of a 1 in 500 solution of pilocarpin nitrate in doses of 0.5 to the histamin gave benefit respectively in 85, 40 and 70 per cent. Where distilled water was used as a control the percentages of relief were 78, 0 and 35. Treatment was continued from 3 to 15 days. Details are given in 41 cases treated.

Penicillin in Leprosy.

"Some 'remarkable' results from experimentation with penicillin in the treatment of leprosy were reported by Dr. E. Van Der Kuyp, Netherlands government physician who has been conducting experiments at the Curacao Leper Hospital at Zaquito. Since only small quantities of penicillin were available, Dr. Van Der Kuyp said, the experiments repeatedly had to be interrupted, but even so the results were 'surprisingly encouraging.' The incidence of leprosy, always high in Curacao, has lessened greatly, lepromata have been vastly decreased in active cases, and old wounds have been healed, he reported. While the final results cannot yet be determined and the maximum doses are not yet fixed, he said, it is known that considerable quantities have to be distributed over a long period of time."

The Japanese and Nauru Island. The island of Nauru has frequently been mentioned in this and other journals on leprosy as the disease was introduced before the first World War, spread rapidly after 1918, and was later brought under control. The *New York Times* reports the fate of the Nauru lepers under the Japanese:

"The Japanese solved the problem of leprosy on Nauru the quick way. They rowed all fifty native lepers to sea at midnight and cast them into the water. An Australian medical officer, Dr. Bernard Quick, and Dispenser William Shugg, whom the Japanese executed, had remained on Nauru to attend the lepers. When a drought came to Nauru, this island, whose superphosphate had brought fertility to millions of Australian and New Zealand acres, could not feed the stranded garrison and a couple of thousand natives and Koreans, and the death toll from starvation was heavy."