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Edited by DR. JOHN LOWE, Medical Secretary of the British Empire Leprosy Relief Association, 8 Portman Street, London, W.1 to whom all communications should be sent. The Association does not accept responsibility for views expressed by the writers.

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EDITORIAL

THE ACTION OF SULPHONES ON VARIOUS INFECTIONS

Sulphones are now well established as the treatment for leprosy. In our last issue we commented on the action of sulphones on the tubercle bacillus.

There is, however, strong evidence that sulphones are active against a wider range of pathogenic micro-organisms. This is to be expected. the sulphonamides themselves show a wide but varying range of activity, and sulphones are sulphonamides. Evidence on this matter can be obtained not only by planning direct experimentation, but also by studying the infections prevalent in treated patients in leprosy institutions, and comparing the findings made with those made in other persons in the same area.

In our present issue we publish an article by Dr. Ida Mann, who studied trachoma in a leprosy institution in Australia and found the active infection completely absent while prevalent in the people of the area. She does not hesitate to attribute this finding to the action of sulphone on the trachoma virus itself, as well as on secondary infections.

Those of us who have done large scale leprosy treatment work in the pre-sulphone (and pre-antibiotic) era, and also in the post-sulphone era, cannot help being struck by the relative rarity in sulphone treated patients of the severe secondary infections of hands or feet, with ascending cellulitis and gangrene, which used to be so troublesome. Infections with gram-positive organisms are now very rare; staphylococcal infections, however, remain fairly common.

The rarity of pneumococcal infection and also of meningococcal infections in sulphone treated patients in areas where these infections are prevalent, has been noted. It is found, by direct and indirect observations, that sulphone has little influence on gonococcal infections.

One infection in which sulphones have been found active is toxoplasmosis. This is a protozoal infection, discovered in 1909 in animals, and since 1939 found to be the cause of disease in human beings. The toxoplasmic etiology of certain types of congenital encephalomyelitis and ocular damage, of certain types of acute encephalitis in older children, of a spotted fever-like disease and pneumonitis in adults, now rests on the firm foundation of demonstration of the organisms in the tissues, recovery of the organisms by passage in experimental animals, and demonstration

of cross-immunity with toxoplasma of animal origin. It is also found that other diseases of obscure aetiology may be caused by toxoplasma, and tests to reveal antibody may in certain countries give positive results in 50 per cent or more of the population over 20 years of age. In England figures of 5.2 %[1] and 7%[2] have been cited, even in children. Now this protozoal infection responds to treatment with sulphonamides, especially to sulphadiazine, sulphamethazine and sulphamerazine, but also to sulphones, (and, it appears, to daraprim). The action of sulphonamides against other protozoal infections is usually very slight.

There have been reports that sulphones are active against filarial and fungal infections, but these have not been confirmed.

There are however these definite indications, here quoted, that sulphones are active against at least one virus (that of trachoma) against certain cocci, bacilli, and mycobacteria, and against at least one protozoon.

In only one of these infections, leprosy, does sulphone at present appear to be the best available agent; in the other infections mentioned, other drugs appear preferable.

1 Macdonald, A. (1950), "Lancet," ii, 560.
2 Cathie, I. A. B., and Dudgeon, J. A. (1953), "Great Ormond Street Journal," 5, 13.

THE LEPROSY BACILLUS AND THE HOST REACTION TO IT

The present issue contains a paper discussing this subject; this paper was contributed to a recent symposium on the tubercle bacillus (with the leprosy bacillus as an added item) organised by the Ciba Foundation in London. This paper brings together material from widely scattered sources in a manner which may not be without interest; we have not seen any other paper which attempts to cover the same ground. In this paper occur the following passages:—

> "I would here mention and emphasize one most striking feature of leprosy, the complete cellular inactivity to the enormous numbers of leprosy bacilli seen in the typical lepromatous case; this I believe has no real parallel in tuberculosis unless it be in the tuberculin negativity of acute miliary tuberculosis, or of advanced generalised tuberculosis . . . .
>
> "One could surmise that with the marked infiltration of the reticulo-endothelial system which is characteristic of lepromatous leprosy, the normal production of protective antibodies by this system might be upset; such findings have been recorded in other affections of this system, for example in Hodgkins disease and in sarcoidosis, in which tuberculin

sensitivity may be suppressed (Hoyle, Dawson and Mather, 1954). But in lepromatous leprosy, there is little or no suppression of tuberculin sensitivity or of other forms of sensitivity or immunity, although lepromin sensitivity is completely absent. No, the anergy, insensitivity, lack of effective response, or whatever name one likes to give to this strange phenomenon, is specific for the leprous bacillus and its antigens. It might be that in lepromatous leprosy, the protective antibodies to the bacillus are produced, but that they are blocked or inactivated in some way, probably by some mechanism associated with the infection. An attempt to study this idea seems worthwhile.''

Also in the present number is reviewed an article by Ridley, part of which bears on this same problem. He quotes an old (1908) report that the serum of a patient desensitised by repeated injections of tuberculin, when mixed and incubated with tuberculin, was capable of inactivating this tuberculin, as shown by the negative results produced by the mixture in the Mantoux test in tuberculin positive persons. Ridley rightly thought the idea worth study in leprosy. He got two lepromin-positive patients and gave each one tests with four intradermal injections (a) ordinary lepromin; (b) lepromin—normal-serum mixture incubated for 24 hours; (c) and (d) lepromin—lepromatous-serum mixture incubated for 24 hours. Injections (a) and (b) gave positive results in both patients. In one patient, injections (c) and (d) gave positive results but weaker than with (a) and (b); in the other patient injections (c) and (d) gave negative results. Ridley interprets these findings as suggesting the suppression of lepromin sensitivity by circulating antibody present in lepromatous serum.

It is a pity that only two patients were available for testing and, further, that only the early 24-48 hrs. reaction was recorded, for the late reaction is usually considered more constant and more significant. In fact, the view that the early 24-48 hrs. reaction and the late 2-5 weeks reaction to lepromin are of the same significance may be untenable, particularly if the finding of Fernandez is confirmed, that by desensitising with leprosy bacillus protein, one can abolish the early reaction, yet maintain the late reaction.

Dr. Ridley in a personal communication says that a third person has been tested, with apparently similar results, and, moreover, that the inactivation by lepromatous serum is dependent on the presence in the serum of complement, and can be inhibited by previous maintenance of the serum to half an hour at 57°C to destroy complement.

This whole subject is one that is full of interest and calls for

investigation. Moreover, investigation of this matter calls for no highly specialised technique or equipment. Work along these lines is already being undertaken by certain workers, and more light on this subject should soon be available. If it is confirmed that lepromatous serum does contain a substance which can inactivate lepromin, and that normal serum does not, this finding will throw new light on the nature of lepromatous leprosy.

The Editor however feels that his own studies, as well as the work of others, as summarised in the article in the present issue, tends to indicate that the presence of reaction to lepromin, and particularly the late reaction to lepromin, is quite independent of the presence of circulating antibodies, and that immunity to leprosy is almost entirely cellular and not humoral. Ridley himself, although he suggests a humoral defence mechanism in leprosy, writes " There are two theoretical reasons why the lepromin reaction in leprosy might be negative (i) that there is no hypersensitivity because there is no fixed antibody, and (2) that the presence of fixed antibody is masked by circulating antibody which neutralizes antigen before it reacts in the tissues." Most students of leprosy have considered that the absence of fixed antibody was the probable explanation. Ridley's findings justify a further consideration of the second hypothesis.

One point in Ridley's paper calls for comment. In cases of leprosy he found no antibody to tuberculin, as revealed by complement fixation tests. He makes no reference to the large mass of previous work on this subject which shows that with antigen prepared from the tubercle bacillus, and also other acid-fast bacilli, complement fixation tests in lepromatous leprosy are nearly always positive. This matter was reviewed by Cooke (1919) and Lowe and Greval (1939). More references to this subject appear in Lowe's article in the present issue. In this matter Ridley's findings appear to be at variance with those of all other workers. If Ridley had prepared his antigen from the tubercle bacillus itself and not from tuberculin, his results would almost certainly have been different.

THE PROGRESS OF ANTI-LEPROSY WORK IN AFRICA

In recent numbers of this journal there has been some discussion on this subject, and some differences, not of opinion, but of emphasis, have become apparent in our Correspondence section. Some editorial comment may clear up misunderstandings and make further correspondence unnecessary.

Twenty years ago anti-leprosy work in most parts of Africa was very limited in quantity and often poor in quality; this was true of Africa as a whole, including British administered areas. The last twenty years have seen the establishment and development in certain parts of Africa of anti-leprosy work on a surprisingly large scale, and this has resulted in a complete change in the outlook. To this change numerous organisations, government, local administration, missions, BELRA, Toc H etc. and many individuals have made important contributions.

Anti-leprosy work in the British Commonwealth and elsewhere owes much to the persistent effort and advocacy of Sir Leonard Rogers over many years; at the age of 86 he contributed to our January, 1954 number an article on " Leprosy Incidence and Control in East Africa, 1924-1952 ". This article provoked certain criticisms from Dr. J. A. K. Brown.

Now Dr. J. A. K. Brown is a worker to whom anti-leprosy work in Africa owes much. It was his pioneer work with the Methodist Mission in East Nigeria in the early 1930's which was the turning point in anti-leprosy work in that country, and which contributed greatly to the subsequent developments there and elsewhere. Unfortunately his work there ended in 1936, when he returned to England. In recent years he has returned once more to leprosy work in Africa, where he is in charge as a Government officer of anti-leprosy work in Uganda, where important progress is recorded. Dr. Brown's letter pointing out certain inaccuracies in Sir Leonard Rogers' article was published in the July, 1954 number, and also Sir Leonard Rogers' comments on these criticisms. As both Dr. Brown in his letter, and Sir Leonard in his reply, point out, it is the " composite co-operative effort " of organisations and individuals that has made the work possible. The organisations included government, missions, and local administrations, and BELRA with Sir Leonard Rogers as Medical Adviser, and Dr. E. Muir as Medical Secretary from 1935. Prominent among the individuals in the 1930's were Dr. J. A. K. Brown and his successor Dr. T. F. Davey.

In the 1930's, BELRA's contribution to leprosy work in Africa in personnel and funds was, to begin with, relatively small, but grew steadily. Sir Leonard Rogers has recently written to the Editor stating that the Annual Medical Report of Uganda for 1931 shows a figure of £9,000 (not £15,350 as he previously stated) as paid by BELRA. In recent years Africa has been BELRA's main field of work, and contributions in workers and money have been on a large scale—over £200,000 in the last five years. But still BELRA and its workers are only members of a group of organisa-

tions and individuals contributing staff, funds, ideas, and willing service to this " composite co-operative effort ", without which no anti-leprosy work can progress.

LEPROSY TREATMENT IN EAST NIGERIA

A recent letter from Dr. T. F. Davey, now (among other duties) continuing research work at the Leprosy Settlement, Uzuakoli, Nigeria, contains the following passages which may be of general interest.

" THIOSEMICARBAZONE.

I have been through the T.B.1 patients for my own sake and think the effort was worth while. The July *Leprosy in India* has arrived with your letter in it.* The main points of my study appear to be as follows:—

(a) Degeneration in lepromatous patients is to be expected in a considerable proportion by the third year (30% of your cases), but with one exception all those concerned have done extremely well subsequently on D.D.S. There is thus no evidence of cross resistance.

(b) In view of this your suggestion of alternating treatment needs going into carefully. One thing that impresses me from the T.B.1 records is the apparent speedy reduction in numbers of bacilli in smears during the first few months. This later tails off of course, but is nevertheless noticeable, and it may therefore be good to start with T.B.1 for a year and then change to D.D.S. Here your considerable number of patients who have had one year on T.B.1 will provide information fairly soon, as already many of them have now had nearly a year's treatment on D.D.S. as well.

(c) So far there have been four relapses among tuberculoid patients discharged after T.B.1 treatment. That is 10% of such discharges. One relapse among lepromatous patients discharged. In all cases the period of treatment would, I am sure, be considered quite adequate."

(A later letter states: " I have to report another relapse, this time in a patient who had a full three years course of T.B.1 before discharge. He relapsed 11 months later, with strongly positive bacteriological findings in multiple smears, bacilli having a normal appearance.')

* The findings recorded in that letter have since been given in detail in " Leprosy Review,' Oct. 1954, p.186, and in the " Lancet," Nov. 20, 1954, p.1065.

" DAPSONE.

I can find no evidence here or at other Nigerian Settlements of resistance developing to D.D.S. We are carefully recording the appearance of the bacilli in all smears done. Some of the old chronic patients still continue to have positive smears, but almost without exception they do not seem to demonstrate the continuance of active looking bacilli, but rather the slow elimination of acid fast debris.'

" OTHER TREATMENTS.

You may be interested in some lesser matters. We are putting as many ulcer patients as possible into walking plasters, with very encouraging results. There are now 20 empty beds in the hospital for one thing, and a much better opportunity to deal with general surgical conditions in clinic patients. A number of exceedingly chronic ulcers have healed completely.

Also we are operating on nerves as soon as any acute signs of neuritis appear, keeping careful records so that ultimately the late results of operative treatment can be assessed. It is here that Dr. Fisher's experience in plastic surgery comes in useful, as she uses special little needles and other means of reducing trauma to a minimum."

OPHTHALMIC IMPRESSIONS OF A LEPROSARIUM

By IDA MANN,

C.B.E., M.A. OXON., D.SC. LOND., M.B.B.S., F.R.C.S. ENG.

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To the average ophthalmologist who has only worked in large cities, ocular leprosy is a rarity and a curiosity. To the leprologist, eye disease in general is often somewhat baffling, and though he may be familiar with ocular leprosy, his attitude is the logical one of attacking primarily the general disease. It is therefore of interest to consider whether ophthalmology has anything to offer in the matter of detailed local treatment in a leprosarium, and whether any observations of interest to oculists can be made there. The following notes were compiled after a stay at the Derby Leprosarium in Western Australia, where 273 patients were examined and some treated for ocular complications.

The ocular complications of leprosy are well known but may be briefly summarised as:

1. Neural complications. The common one is facial paralysis from leprous involvement of the 7th nerve. This prevents proper closure of the eye during sleep and is a source of danger to the cornea. The effect on the eye is an indirect one. The 5th nerve may be involved more rarely but the effect is similar because the anaesthesia of the cornea abolishes the normal blink reflex and dust tends to collect in the eye and produce serious keratitis in the same way as does exposure.
2. Lepromatous leprosy involving the eye itself. This is usually seen as an iritis, a keratitis or both. Sometimes the lacrimal passages are involved in nasal leprosy.

In addition to ocular leprosy, other diseases of the anterior segment of the eye were found in the Derby Leprosarium. Trachoma is endemic in the northern part of Western Australia occurring in approximately 42% of all the inhabitants. It is the disease of greatest sociological and economic importance in that part of the State. Therefore in an ophthalmic survey of the Derby Leprosarium one would expect to find a large number of cases of trachoma. When leprosy occurs in a trachomatous area and when no detailed ophthalmic survey has been done, there is a tendency to confuse the

two diseases, so that blind persons in a leper hospital are often looked on as blind from leprosy when in fact they are blind from the secondary complications of trachoma.

The following table shows the incidence of diseases of the anterior segment of the eye found in the 273 patients examined at Derby:—

Trachoma	172
Ocular complications of leprosy	47
Corneal scars not due to leprosy or trachoma	22
Pterygium	15
Cataract	13
Conjunctival concretions not associated with trachoma	3
Unequal pupils of unknown etiology (?syphilitic)	3
Glaucoma	2
Papilloma of the lid	2
Meibomian cyst	1
Conjunctival Melanoma	1
Fly bite of lids	1
Strabismus	1
Conjunctivitis (mild)	1

Of the cases of ocular leprosy, 22 had leprotic keratitis, 21 iritis and 4 facial palsy.

The cases of trachoma far outnumbered the cases of ocular leprosy, and a fact of great interest and importance was brought to light by the survey. No cases of active trachoma were found. All the cases except four showed no signs of active infectious trachoma with follicles. These four had each a few remaining follicles, practically healed. Of the rest, 136 were completely healed with fine lid scars and preservation of good sight. Eight were healed with some impairment of sight from corneal scarring. Twenty-four were blind from trachoma (gross scarring of cornea, ingrowing lashes and secondary corneal ulceration) and had been blind when admitted to the leprosarium.

These results, in view of the results of the trachoma survey elsewhere, were surprising, and it was immediately obvious that the chemotherapy (Sulphetrone and D.A.D.P.S.) used in the treatment of leprosy had entirely killed the trachoma virus and had also cured any secondary septic infection. No local treatment whatever had been given to any of the eyes. This finding was subsequently confirmed by a clinical experiment with D.A.D.P.S. on a group of

children with active trachoma but no leprosy. Administration of sulphones by mouth cures trachoma but not as rapidly as does sulphadiazine or sulphadimidine by mouth combined with local eye treatment with terramycin or aureomycin ointment. Oral sulphone treatment is not therefore recommended as a routine treatment for trachoma but, conversely, no treatment for trachoma need be given in a leprosarium where sulphones are in use, since the trachoma will heal automatically.

Of the ocular leprosy cases, four were facial palsy in adult males. One was recovering under general treatment with sulphones, two were mild with sufficient covering of the cornea. One was bilateral and severe, the patient being unable to cover his corneae in sleep. I performed a bilateral lateral tarsorrhaphy under local anaesthesia with great relief to his symptoms and improvement in his appearance. I saw him again many months later and the condition was still satisfactory. This operation is simple and should be done in every case where the cornea is exposed at its lower border with the eyes as closed as possible. Novocaine or other local anaesthetic is injected along both lids from the outer canthus. The lid margin is pared with a sharp knife and stitched together for from a third to half of its length from the outer end. No trouble will be encountered from the lashes, which grow through the line of union. The Meibomian glands apparently cease to function after the union. If the condition improves, the tarsorrhaphy can easily be reopened by one snip with sharp scissors. Untold discomfort can be relieved and all risk of loss of the eye from exposure keratitis will be removed by this simple plastic operation, which is not sufficiently practised.

Twenty-two cases had leprotic keratitis. The typical minute bright white dots in the grey infiltrated margin of the cornea make the diagnosis certain. These have been described by King from observations in the leper colony in England. They can be seen with good focal illumination. A corneal loupe is helpful. Three of the 22 cases were active, with circumcorneal redness and discomfort. The margin of the cornea was swollen, especially below. There was a diffuse greyish peripheral corneal haze with minute discrete very white dots scattered through it. These dots persist after the acute stage has subsided. They were seen in the other 19 quiescent cases. These often showed a definite raised grey area along the lower margin of the cornea. This may become vascularised and looks like a pannus with a sharp upper edge.

The three active cases were treated with cortone eye drops but I was only able to observe them for a week. If I had stayed longer I would have tried subconjunctival injection of cortisone. This drug,

which blocks the manifestations of disease but has no therapeutic action, is a very great benefit in the treatment of many acute inflammatory diseases of the eye. It is suitable for use in leprosy since in the sulphones we have a weapon against the infecting organism and what is required in the eye is something to decrease the oedema and exudative processes which are much more harmful to sight than is the disease itself.

The twenty-one cases of leprous iritis are of interest. One was acute, with cloudy aqueous, contracted sluggish pupil, and great pain. Atropine 1% and cortone eye drops were given half hourly. Within four hours the pupil dilated fully and the pain subsided. Treatment was continued two hourly next day and the patient made an excellent recovery with no synechiae. This case also demonstrates the great use of cortone in ocular leprosy. It must, of course, be combined with atropine and if used at once all cases of iritis have an excellent chance of complete recovery. Even if cortone cannot be obtained, atropine must be used liberally since the bad results of leprous iritis are practically all due to blocking of an undilated pupil with exudate.

The other 20 cases of iritis were quiescent, with synechiae of varying extent, and the above mentioned typical white dots on the iris. Three of the healed cases required iridectomy (see footnote), as their pupils were almost completely occluded. In one eye of these, the occlusion was the most complete I had ever seen, the iris stroma running right across, and no pupil being visible at all. Yet there was no iris bombé and no rise of tension. No attempt had been made to treat these cases with atropine in the acute stage. If it had been used, the results would have been very much better. It appears that the use of atropine and cortone is highly to be recommended in all cases of leprous iritis in the acute or reactive stage. It will prevent the formation of synechiae and lead to restoration of vision. There seems little danger in the use of atropine, as glaucoma is admittedly rare among lepers.

On the whole, therefore, the ocular picture in this leprosarium is a cheerful one. No one is blind from leprosy alone and ocular leprosy is not common in any case. The new drug treatments appear to prevent any serious ocular complications.

Of the other eye diseases found at Derby, little need be said.

Pterygia are common throughout Australia. Their exact cause is unknown. Very few among the leprosy patients required operation, though one very large one covering the pupil was seen. They

should, of course, be removed when they approach the pupil margin.

Corneal scars among Australian aboriginals are common. They are usually due to injury.

Cataract (nuclear sclerosis of the lens) is found among old people but is rare in Australia compared with the Asiatic countries.

Conjunctival concretions are of no great importance. They were merely noted for interest.

The cases of unequal pupils were probably syphilitic but just possibly neural leprosy could have been responsible. They were not investigated.

The cases of chronic glaucoma and papilloma of the lid presented nothing unusual.

THE LEPROSY BACILLUS AND THE HOST REACTION TO IT*

JOHN LOWE, C.B.E., M.D. (B'ham.), F.R.C.P.
Medical Secretary, British Empire Leprosy Relief Association

[We have had three days of discussion on the tubercle bacillus and there are indications that it could have gone on for three weeks or three months; the scope of work has been great and workers numerous; and much work has been done and knowledge gained though much remains to be done.

I appear as a student of the leprosy bacillus, and I feel rather like a poor relation at a large family gathering.

Our scope is limited, and our workers have been few; definite knowledge based on direct study is limited. I don't think we could spend even three days on our subject.

When I was asked to present a paper on the leprosy bacillus and the host reaction to it, I wondered whether I had enough ideas to make a paper; but, as is quite common with subjects about which we know very little, there is a great deal that may be said. And as it does appear possible that findings of studies of the tubercle bacillus may be applicable to the leprosy bacillus, and also vice versa, the subject is not perhaps without its interest, to students of tuberculosis—as well as of leprosy.

I will try to summarize what is known of my subject; but I shall not touch on questions of life, growth and metabolism of the leprosy bacillus, for these matters are, I believe, to be dealt with by others. I should, moreover, make it clear that I am not a chemist—nor a bacteriologist, but a clinician and a research worker from the clinical angle, to whom, as I expect you will detect, chemistry and much of bacteriology is a closed book. I hope that you will make a full allowance for this.]

INTRODUCTORY REMARKS.

Since we have no culture and no experimental animal, the only source of bacilli is the tissues of man with lepromatous leprosy, in which bacilli are numerous. For many years it was impossible to separate the bacilli from the tissue, but now two methods are available, those of Dharmendra (1942 and 1942a) and of Fernandez and Castro (1941).

Although Hanks (1945) recorded bacillary counts of over one thousand million per cubic centimetre of tissue, Dharmendra (1942a) found that, in such tissue, the bacilli formed about 0.4% by weight of the tissue, so that from 1 gramme of tissue not many milligrammes of bacilli can be obtained, and that by excision of lepromatous skin, of which supplies are limited. Thus, bacillary material has been scarce, and now with chemotherapy of leprosy being widely practised, it is becoming much scarcer. Some useful work has been done, however, and I will try to summarise it.

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* A paper read at the symposium on the "Tubercle Bacillus and the Reaction of the Host Tissues", with an addendum on comparative aspects of leprosy, held in London, October 5th—8th, 1954, and organised by the Ciba Foundation for the Promotion of International Co-operation in Medical and Chemical Research, 41 Portland Place, London, W.1. The full proceedings are to be published as a separate volume.

THE SEPARATION OF THE BACILLI.

Dharmendra's method is briefly as follows:

Excised lepromatous tissue is autoclaved, cut in small pieces, and ground in a glass mortar in chloroform, the chloroform being pipetted off; this process is repeated until few bacilli remain. The chloroform is allowed to evaporate, and the fatty residue is suspended in ether, which dissolves the tissue fats, and the suspension is then centrifugalised at high speed to deposit the bacilli, and the ether is pipetted off. More ether is added and the centrifugalising is repeated, and the ether again pipetted off. The residue, consisting of bacilli only, is dried and weighed. Lepromin for routine testing is made up at 1 milligramme in 10 c.c. and 0.1 c.c. is injected intradermally as in the tuberculin test.

The method of Fernandez and Castro consists of centrifugalising ground suspensions of leprous nodules in salines of different specific gravities to separate the bacilli from the tissue. The yield of bacilli is lower than with Dharmendra's method, which is now more widely used.

It is possible that Dharmendra's method may denature the bacilli to some extent, but this has not been proved; on the whole it is much the most simple and economical method of getting leprosy bacilli free from tissue.

CHEMISTRY OF THE LEPROSY BACILLUS.

By getting large amounts of nodular material and extracting the bacilli from it, Dharmendra (1942a) got enough bacilli to work with. He ground them in a ball mill for many hours, and from the ground bacilli by simple methods he prepared the following fractions: three protein fractions, a polysaccharide fraction, glyceride and phosphatide fractions, waxes, and final residue.

This work was done about thirteen years ago by methods then available to Dharmendra, and no doubt modern methods would be better. Further, he made these fractions for use in skin testing in a study of the lepromin reaction, and not for a study of chemistry. But as far as I know, no later work of this nature has been done, and what little we know about the chemistry of the leprosy bacillus is what he found out. These fractions are obtainable from the leprosy bacillus in about the same proportion as from the tubercle bacillus, and they show a close resemblance to the fractions of the tubercle bacillus.

BIOLOGICAL REACTIONS TO THE LEPROSY BACILLUS AND ITS FRACTIONS.

From 1916, the Mitsuda test, (Mitsuda 1916), named after its Japanese originator, has been increasingly used and studied, frequently under the name " lepromin test ". Lepromin is the name given to a suspension of lepromatous tissue rich in bacilli. The classical test is positive when, at the site of the intradermic injection of 0.1 c.c. of this suspension, there develops a small nodule, usually

appearing in 1-2 weeks, reaching its maximum size at 3-4 weeks, and then slowly subsiding over a period sometimes lasting many weeks.

The result is negative in most healthy young children, and in lepromatous (anergic) cases of leprosy; it is positive in many healthy adults and in tuberculoid (allergic) cases of leprosy; in other healthy persons, and in other types of leprosy, the results are variable.

This strange phenomenon is different from any other biological skin test that I have heard of.

Fernandez (1950) reported that a positive Mitsuda test at 2-4 weeks is almost invariably preceded by a 24-48 hour reaction of the " tuberculin " type. Lowe and Dharmendra (1941) soon confirmed this, and others also, and the Fernandez phenomenon as it is called is widely recognised.

Thus we have these two phenomena produced by the intradermic injection of lepromin in sensitive persons, the Fernandez reaction at 24-48 hours, and the Mitsuda reaction at 2-4 weeks. We (Lowe and Dharmendra, 1941) found that by grinding the bacilli to break down the bacilli, the Fernandez reaction was increased and the Mitsuda reaction was diminished, and that with complete grinding of the bacilli the Fernandez reaction was increased still more, and the Mitsuda reaction was abolished. Dharmendra (1942a) studied the mechanism of these reactions by the use of the fractions which he had isolated, and he found that the Fernandez reaction was due entirely to the protein fractions. None of the fractions given alone produced the Mitsuda reaction; only the intact bacilli did this. We concluded that the early (Fernandez) reaction was caused by sensitivity to free protein, and that the late (Mitsuda) reaction was caused by the slow liberation, over several or more weeks, of minute amounts of protein from the slowly disintegrating bacilli at the site of the injection. It should be remembered that intact bacilli can be detected at the site of the injection for several weeks.

How do these findings compare with findings made with the tubercle bacillus? The finding that the 24-48 hours reaction is caused entirely by the allergic reaction to the bacillary protein is exactly paralleled in the tuberculin test, I believe. The late Mitsuda reaction has no parallel in skin testing in tuberculosis; the only parallel is in histopathology. The nodule produced in the Mitsuda test is histologically a tubercle, with quite typical epithelioid cells focally arranged, with multinucleated giant cells, and sometimes caseation.

In tuberculosis, the attempt to attribute tubercle formation to a particular chemical fraction of the tubercle bacillus has not been very successful; according to Lederer (1951), the phosphatide

fraction of Anderson, with its phthioic acid content, branched chain fatty acids, lipopolysaccharides, and other fractions have been cited by different workers. I have been much struck by Lederer's comments on this matter, quoted from Rich; he states that a single tubercle bacillus can stimulate giant cell formation; that several bacilli can cause the formation of a typical tubercle; that the intact bacilus is a minute foreign particle possessing a far greater power of evoking giant cell and tubercle formation than has been shown to be possessed by any or all of the lipids exactracted from it.

In leprosy the situation seems to be similar; the tubercle formation seen in the Mitsuda phenomenon seems to depend on the presence of intact bacterial cells, and not on the action of any one constituent. Further, it is possible that the explanation of the Mitsuda reaction advanced by myself and Dharmendra, and quoted above, is wrong. Fernandez (1953) reports that in a lepromin positive person, one can, by repeated injections of the leprosy bacillus protein, desensitize to the protein and abolish the early reaction to lepromin yet leave the late reaction (the Mitsuda phenomenon with nodule formation) unchanged.

Fernandez has abandoned his earlier view that the early and late reactions to lepromin are of the same significance. He regards the early reaction as indicating sensitivity to protein, and the late reaction as indicating resistance to the leprosy bacillus, these ideas of course having parallels in tuberculosis. These views have much to commend them.

There is little more that I can say about direct observations of the leprosy bacillus and its components, and of cellular activity induced by them. I would here mention and emphasize one most striking feature of leprosy, the complete cellular inactivity to the enormous numbers of leprosy bacilli seen in the typical lepromatous case; this I believe has no real parallel in tuberculosis unless it be in the tuberculin negativity of acute miliary tuberculosis, or of advanced generalised tuberculosis.

THE USE OF ANTIGENS PREPARED FROM THE TUBERCLE BACILLUS FOR DETECTING ANTIBODIES IN LEPROSY.

For over forty years, workers have tried various preparations of the tubercle bacillus as antigens for the detection of antibodies in cases of leprosy.

(a) Complement fixation tests.

Numerous such preparations have been used in complement-fixation tests. The matter was reviewed by Lowe and Greval (1939). They used the preparation of Witebsky, Klingenstein, and Kuhn (1931), (WKK antigent), which was prepared by taking

up in benzine the residue left after extracting tubercle bacilli with alcohol, pyridin, and acetone. It was originally used for complement-fixation tests in tuberculosis, with inconstant results. When used in leprosy it gave strongly positive results in practically every bacteriologically-positive case, and weaker positive results in some of the others.

Complement fixation tests are notoriously non-specific. There is the Wasserman test itself, which, as well as the Kahn and other such tests, is usually positive in severe lepromatous leprosy. The WKK antigen gave positive results not only in tuberculosis and leprosy but also sometimes in syphilis, and always in kala-azar, in the early diagnosis of which the test is very useful. Further, the same fraction of some non-pathogenic acid-fast bacilli gives identical results (Dharmendra; personal communication). In general, in cases of leprosy, if this test is negative, ordinary bacteriological examination gives negative results, and also the lepromin test is positive; if the complement-fixation test is positive, ordinary bacteriological examination, which is much easier, shows leprosy bacilli, and the lepromin test is negative. The test is therefore of little practical value. It is of theoretical interest in that it shows that in lepromatous leprosy there is in the serum something which acts as an antibody to a fraction common to mycobacteria.

(*b*) *Precipitin tests.*

Certain polysaccharide fractions of the tubercle bacillus have given positive precipitin tests, sometimes with the sera from persons with tuberculosis, and often in very high dilution with anti-tuberculous sera of animals. (Siebert, Stacey, and Kent, 1949; Iland, 1951; Haworth, Kent and Stacey, 1948 and 1948a; Aselineau and Lederer, 1950; Choucroun, 1949). With the same fraction, Choucroun obtained positive results in lepromatous leprosy. This matter appears to have been little studied.

(*c*) *Agglutination tests.*

The heat-stable component present in the polysaccharide fraction of the tubercle bacillus, isolated by Middlebrook and Dubos (1949) and used by them to sensitize sheep's red cells to agglutinins present in tuberculous sera, has, with the modification of Scott and Smith (1950) been used in studies of sera of leprosy cases, mainly by French workers, with striking results, [Gernez-Rieux and Tacquet (1950); Gernez-Rieux, Montestruc and Tacquet (1951 and 1952); Montestruc (1952); Montestruc, Gernez-Rieux and Tacquet (1953); Floch and Sohier (1950); Levine (1950 and 1951)]. Over 80% of lepromatous cases have given positive results, usually in far higher titre than in tuberculosis; the titre may be as

high as 1 in 2000. In non-lepromatous cases the positives are fewer and the titres lower.

Basset and Bougna (1953) have used the lipo-polysaccharide fraction of Choucroun (1946 and 1947) in the same way, with similar results.

Thus, here again is evidence that in lepromatous leprosy there are circulating antibodies to a component of the tubercle bacillus. But here again, if there is a positive agglutination test, there is usually a negative lepromin test.

(*d*) *The tuberculin test.*

The tuberculin test in leprosy, with either old tuberculin or purified protein derivative, has been much studied in leprosy, both in lepromatous (lepromin-negative) cases and in tuberculoid (lepromin-positive) cases. The matter has recently been reviewed by Wade (1950) and by Lowe and McNulty (1953). The tuberculin test is little influenced by the presence or absence of leprosy, or by the form of leprosy; the findings are about the same as in healthy people in the same environment.

LEPROSY BACILLUS ANTIGENS IN TUBERCULOSIS.

Many workers in different countries, including countries in which there is practically no leprosy, have done lepromin tests in persons suffering from tuberculosis, frequently with positive results. Moreover, when lepromin and tuberculin tests are done in healthy persons in such countries, the two tests agree too often for the agreement to be caused by chance. There is strong evidence that tuberculous infection can make a person lepromin positive. Moreover B.C.G. vaccination has the same effect; it can and usually does produce lepromin conversion. This whole matter has recently been reviewed and studied by Lowe and McNulty (1953 and 1953a).

These facts mean that in a person who is tuberculin positive, the tissues can react to the leprosy bacillus by tubercle formation (for that is what a positive late lepromin reaction means) and this is a more definite indication of immunity than mere protein sensitivity. This finding, backed up by clinical observations that lepromin-positive persons rarely develop leprosy, and that if they do, it is usually mild, provides the basis for the advocacy, particularly by French and South American workers, of the use of B.C.G. to immunize contacts or potential contacts of open cases of leprosy,

There is thus some evidence that tuberculous infection and B.C.G. vaccination can sensitize a person to, and possibly produce a degree of immunity to, the leprosy bacillus. (It may here be interpolated that the evidence that leprous infection can produce

sensitization and immunity to tuberculous infection is scanty and not strong.)

DISCUSSION AND CONCLUSIONS.

I want first to stress the point that most cases of leprosy belong to either of two quite markedly contrasting types, and that changes from one type to the other are rare, or, in the opinion of some workers, impossible. (This generalization is not invalidated by the fact that there are certain cases that do not fit well into either of the two main types, and that in these atypical cases marked variations may be seen.) The differences between these two main types are striking, and are summarised later, but they seem to indicate sensitization and immunity on the one hand, and complete lack of these on the other.

Is such a phenomenon seen in tuberculosis? I do not think so. In most cases of tuberculosis you have an interplay of findings, some indicating the invasive powers of the infection, and some indicating sensitization and resistance of the host tissues.

In leprosy it is usually quite different.

On the one hand there is the lepromatous case, with extensive lesions and abundant bacilli but no cellular reaction to them, with circulating antibodies easily demonstrated, but no sensitization and no cellular antibodies revealed by the lepromin test, and no resistance to the infection.

On the other hand there is the tuberculoid case, with only local lesions, which contain very few bacilli, but which show intense cellular reaction to them in the form of tubercle formation; circulating antibodies are difficult to demonstrate, but the lepromin test is strongly positive, and there is apparently a high degree of sensitization and immunity to the infection.

There is this curious dichotomy in the manifestations of leprous infection. How can it be explained?

It cannot be that in lepromatous cases the bacilli are not antigenic, for it is from these cases that we get our lepromin. A few workers have thought that in lepromatous cases there is an inherent constitutional factor preventing any effective host response to leprous infection. This theory might explain some facts but not others.

One could surmise that with the marked infiltration of the reticulo-endothelial system which is characteristic of lepromatous leprosy, the normal production of protective antibodies by this system might be upset; such findings have been recorded in other affections of this system, for example in Hodgkins disease and in sarcoidosis, in which tuberculin sensitivity may be suppressed

(Hoyle, Dewson and Mather, 1954). But in lepromatous leprosy, there is little or no suppression of tuberculin sensitivity or of other forms of sensitivity or immunity, although lepromin sensitivity is completely absent. No, the anergy, insensitivity, lack of effective response, or whatever name one likes to give to this strange phenomenon, is specific for the leprous bacillus and its antigens. It might be that in lepromatous leprosy, the protective antibodies to the bacillus are produced, but that they are blocked or inactivated in some way, probably by some mechanism associated with the infection. An attempt to study this idea seems worth while.

The other apparent anomaly in leprosy cases, the frequent absence of, or the low titre of, the circulating antibodies in tuberculoid leprosy in which immunity is high, presents no great difficulty. It is apparently associated with the low level of infection. In such cases, temporary phases of increased activity of the disease, with an increase of the number of bacilli in the lesions, are sometimes seen, and, during these phases, circulating antibodies as shown by complement-fixation tests and Middlebrook-Dubos tests increase.

This dichotomy of leprosy, as I have called it, is a most interesting and baffling phenomenon, which appears to have no real parallel in tuberculosis. It does seem to me that a study of this matter might illuminate the question of immunity in leprosy and possibly in other mycobacterial diseases.

There is some factor or group of factors operating in the tuberculoid case which is absent or inactivated in the lepromatous case, and this absence renders the patient susceptible and the disease progressive.

Observations of the host reaction to the leprosy bacillus as seen in the two main types of leprosy suggest the following points:

1. Resistance to leprous infection bears no relation to the presence of circulating antibodies to polysaccharide or lipid fractions of mycobacteria.
2. Resistance to infection is accompanied by evidence of sensitization of the host cells to the leprosy bacillus as a whole, and to its protein components.
3. Protein desensitization may be effected without impairing cellular response to the whole bacillus.
4. Thus cellular response to the whole bacillus appears to be the main factor in immunity.
5. Sensitization of the tissues to whole bacilli can be induced only by whole bacilli, living or possibly killed, and not by any component of the bacilli.

6. The tubercle bacillus as well as the leprosy bacillus can induce this sensitization of the cells to the bacilli, which accompanies resistance to the infection and which appears to constitute the main factor in resistance to leprosy.

Have these ideas any bearing on the question of resistance to tuberculosis? I leave that question to the tuberculosis worker.

SOME CLOSING REMARKS.

We students of leprosy can learn much from students of tuberculosis. For example, our chemotherapy of leprosy is built up on studies of possible treatments for tuberculosis, and in fact, on agents, mainly the sulphones, which tuberculosis workers seem to have discarded.

I wonder if I might suggest that tuberculosis workers might gain from, as well as contribute to, a study of leprosy; that a study of mycobacteria and of mycobacterial disease as a whole is worth while; and that we should all do well to broaden our horizons.

I spoke to begin with, of leprosy research being a poor relation of tuberculosis research, and in some ways we do seem to benefit from the crumbs which fall from the rich man's table.

But I think that I should express the relationship much more truly if I said that tuberculosis research is the benevolent rich uncle to whom leprosy research is very grateful, for all he has done, and, we hope, will do for us; and that we hope that the day will soon come when we shall be able to do something for him.

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REVIEWS

MARTINEZ DOMINGUEZ, VICTOR.

Estudio epidemiologico y clinico de la endemia de lepra en la Guinea espanola. (An Epidemiological and Clinical Study of the Endemic Disease of leprosy in Spanish Guinea.) 113 pp. 15 graphs (one coloured on pl.) and 105 figs. on 32 pls., 1954. Madrid: Instituto de Estudios Africanos, Consejo Superior de Investgaciones Cientificas. (60 pesetas.)

This small colony, situated in the Gulf of Guinea, consists of two islands, Fernando Po and Annobon, and a district on the African mainland 26,000 square kilometres in area. The population of Fernanda Po is 14,735, that of Annobon 1,396, and that of the mainland 129,039. The leprosy rate is higher in the continental area than in the islands, calculated during the last 15 years at about 4,621 cases, and varying in different districts from 71.1 to 2.9 per thousand. The incidence is highest in the interior land especially in the north-east, indicating that infection originally spread with the Bantu invaders from that direction. In the islands the population is much denser and partly urbanised, and the incidence of leprosy is much less.

Under "Incidence in Relation to the Clinical Form," the cause of the greater incidence on the mainland as compared to that in Annobon is discussed. In the former the relation of tuberculoid to lepromatous types is 5.7 to 1; in the latter it is 1.8 to 1, that is, on the mainland the proportion of tuberculoid cases is 3.1 times as great. On the other hand, on the mainland the general incidence is 35 per thousand and only 7.8 per thousand in Annobon. The larger proportion of resistant form cases on the mainland is easily explained by the fact that the disease has been there for a much longer time. But the higher total incidence on the mainland is more difficult to explain on the supposition that leprosy infection goes on producing an increasing resistance to the disease.

The author explains the phenomenon by concluding that the lepromin reaction indicates sensitisation to Myco. leprae, and only indirectly a degree of immunity. Hypersensitivity does not necessarily imply high immunity. Lack of sensitivity (anergy) does not indicate complete lack of immunity in all cases. In Spanish Guinea the population is strongly sensitised by exposure to Myco. leprae (100 per cent); yet the high incidence appears to indicate a low index of immunity. To explain the want of relationship between the high incidence and the comparatively small

number of sources of infection (open lepromatous cases) it is necessary to suppose that there is hypersensitivity which increases liability to infection, and at the same time determines a great predominance of hyperergic forms (tuberculoid and intermediate).

Of the extraneous factors influencing the spread and control of leprosy the most important are considered to be density of population and the arrival of people of a more civilised race. It is found, as it has also been found elsewhere, that though leprosy is less common in the more sanitary conditions of an urbanised area, in spite of the denser population, yet in rural areas where the population is dense the incidence of leprosy is particularly high. The fact that the advent of a higher civilisation lowers the incidence of leprosy is explained by the better sanitation which results, and possibly by the spread of tuberculosis which often accompanies the white races, the latter infection bringing about a degree of resistance to leprosy.

Regarding the examination of contacts, generally considered an important part of control methods, the author says that promiscuity is so rife, the people wander about so much, and divorce is so common that it would be necessary to consider every member of the territory as a contact, or at least all those living in the mainland territory. The mortality is not dissimilar from that of the general population, which shows that leprosy is not a killing disease.

The introduction of sulphone treatment had a phenomenal result: instead of avoiding the doctors as before, there was a " veritable avalanche " of patients coming from every corner of the colony, and 1,638 new patients were registered voluntarily within a year. In the campaign against leprosy a new standing order has been issued, according to which everyone, of whatever race, has to have a passport with a special visa stating that he is not suffering from leprosy.

Anyone suspected of having leprosy can, if it is considered necessary, be kept under observation for a period of up to five years. According to the form and condition of the patient he can be kept under observation without or with treatment, but if the disease is open and active he must be isolated.

This brochure is illustrated with numerous photographs and a number of charts and diagrams.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin*.)

Leprosy—A Survey of Recent Legislation. *International Digest of Health Legislation,* (WHO) 1954, 5 p. 3-36.

This booklet of 29 pages, plus some appendices, deals for the most part with leprosy control legislation enacted since 1940 in about thirty different countries. While it realises that a uniform system throughout the world would be impracticable, it thinks that the differences between different countries are very marked, particularly in the criteria for isolation and release from isolation. The introduction quotes the report of the League of Nations and World Health Organisation Committees on leprosy regarding the necessity for making a legislation on leprosy which corresponds to the modern ideas and experience of the disease. Also commenting on legal power to enforce isolation and treatment, to prohibit certain trades and callings and marriage, and to forcibly remove children from the care of parents, it states:—" It would not only appear to be difficult to justify some existing practices in the light of our present knowledge of the disease but also, in some instances, they would appear to be in contradiction to the facts regarding its communicability, which show that it is much less than, for example, tuberculosis."

The report deals with the matter under four heads:— ' Detection of lepers ' , ' Measures relating to lepers ' , ' Measures relating to household contacts ' , and ' Miscellaneous ' .

Under " Detection " is discussed notification, which is usually compulsory, but it is interesting to see that in some countries it is the medical staff, in some countries it is the patient himself, in some countries it is any person who knows, or has reason to believe, that someone else has leprosy, who is responsible for reporting the matter. Under " Examination of suspects and contacts ", practice varies widely; some countries provide for the compulsory examination of contacts and known cases—sometimes for a period of several years and sometimes as often as every four months. Sometimes these rules also apply to suspects. Leprosy surveys and censuses are mentioned, usually by the Public Health Services.

" Measures relating to lepers " include isolation and release from isolation. The limitations of isolation are now widely recognised, and in some countries its use is being reduced or abandoned, although this is often not reflected in legislation. The legislative provisions for isolation in different countries and for release from isolation vary very widely, and this report discusses this matter at considerable length.

In some countries treatment is compulsory. In the Philippines, for example, only patients who are isolated may refuse treatment.

In some countries, doctors are allowed to prescribe only treatment that has been approved by the Ministry of Health.

The widely differing practices regarding trades and callings which may be followed by patients with leprosy are outlined. Laws regarding marriages are also quoted. In some countries, pre-marital examination for leprosy is compulsory. Leprosy is sometimes legal ground for annulment of marriage.

The immigration of persons with leprosy into a country is usually forbidden by law.

The measures relating to household contacts legally provided for in different countries are usually concerned with healthy children of lepromatous parents. The removal of such children is frequently laid down. In some countries, laws provide for assistance to patients and their families in the form of family allowances or maintenance for children.

REPORTS

The Seventy-ninth Annual Report of the Mission to Lepers, London. This report discusses the International Leprosy Conference held in India in November, 1953, sponsored jointly by the Mission to Lepers and the American Leprosy Missions, which was attended by delegates from many countries; the extended tour of the General Secretary to India, Ceylon, Malaya, Hong Kong, Formosa, Japan, Korea, U.S.A. and Canada; the opening of a children's sanatorium in North India and a Research Sanatorium in South India, or developments in other centres in India, and in Hong Kong; the great increase in outpatients being treated—17,000 in-patients and 17,000 out-patients in 1952, compared with 15,600 in-patients and 38,400 out-patients in 1953, out-patients having more than doubled in a year; the use of prophylactic treatment for healthy persons living with infective patients in villages; the use of surgery to mitigate deformities and disabilities of hands; the religious work which is an essential part of the mission's activities.

The income for the year was a new record, £320,000, and the expenditure £303,000.

World Health Organisation Technical Report Series, No. 88. Vaccination against Tuberculosis. (Sixth Report of the Expert Committee on Tuberculosis.) October, 1954.

This report is short but of such interest that we here reprint the report in full.

BASIC PRINCIPLES.

Before starting a detailed discussion, the committee wished to express its opinion that enough convincing evidence was available for it to agree on the following fundamental points:—

(1) A specific resistance develops following a natural primary tuberculosis infection.

(2) A specific resistance to tuberculosis can be induced by artificial means (vaccination).

VACCINATION WITH BCG.

VACCINES.

The committee considered the problem whether real differences in fact exist between strains of BCG used for vaccines in different parts of the world. Experience with vaccines produced in various laboratories makes it evident that there are appreciable differences in the allergy-producing qualities of vaccines and in the degree of regional glandular reactions which they provoke. These variations are particularly evident in oral vaccination when results obtained

with the strain of BCG used for the vaccine which is now being prepared in a number of laboratories in Latin America are compared with those obtained with strains used in some other laboratories. The committee felt that further studies were necessary to determine whether these differences in results are due to variations in methods of production and administration of the vaccine and to the characteristics of vaccinated populations or whether strains actually differ biologically. The committee recommended that the multiplication of BCG vaccine production centres should be discouraged.

The importance was stressed of producing vaccines with good keeping qualities, i.e. vaccines which could be kept for a considerable period of time and still be used with good effect. In this regard the committee felt that the freeze-drying process offered great hopes. However, it was recognized that there were appreciable variations between freeze-dried vaccines prepared in different laboratories using different methods. On the basis of evidence which is available at present and until further investigations are carried out, the committee did not feel able to recommend a more general use of freeze-dried vaccines even though these may offer certain advantages.

The committee considered studies made on the keeping qualities of liquid vaccines. There was suggestive evidence that liquid vaccine might maintain its allergy-producing power for a considerably longer period than was hitherto believed, particularly if it was adequately protected from light, even during the process of manufacture, and kept at a low temperature. In this connexion, the committee felt that it was important to carry out further laboratory investigations on the fundamental qualities of vaccines (with particular reference to methods for viable counts, and the relation of the survival of the bacilli to the protective value in animals), and that the results of such experimental work be correlated with the effects of vaccination in man.

The final appreciation of the value of a vaccine should be based on its ability to produce increased resistance—and not only allergy—in laboratory animals as well as in man.

TECHNIQUES OF ADMINISTRATION.

Extensive discussion took place concerning oral BCG vaccination.

Dr. de Assis presented data derived from his wide experience of oral vaccination by large repeated doses, including that in children exposed to heavy risk of environmental infection (" vaccinacao concorrente "). The opinion of the committee was favourably influenced by his report that this type of oral vaccination could be carried out without inconvenience even in tuberculin

reactors. There is, however, evidence that not every vaccine is suitable for this purpose. The committee felt that, on the basis of present evidence, it would be premature for it to recommend that this method be generally adopted. In view, however, of the apparent practical advantages of oral vaccination by large doses, the committee wished to make a strong recommendation that this procedure be carefully investigated further. Such studies should include comparisons in animals between this and other methods of vaccination. Although the committee realized that comparative studies between this form of oral vaccination and intradermal methods of vaccination in man would be most difficult and expensive, it wished to recommend that the WHO Tuberculosis Research Office (TRO) be requested to undertake the responsibility for these studies and that adequate financial support be given to this Office for this purpose.

The committee felt that, meantime, parenteral methods should be preferred for general use, but that, in situations where vaccination of the newborn and infants is desirable because the risk of infection is high and where for practical reasons the parenteral route cannot be used, oral vaccination should be recommended, provided that the particular vaccine and method chosen in each case have been shown not to give undue complications.

Reviewing previous recommendations for mass vaccination campaigns, the committee reaffirmed that intradermal vaccination was a satisfactory method.

The committee believed that when a mass vaccination campaign was carried out in a country, only one method of vaccination should be used, so as to avoid possible confusion among vaccines of different concentrations. It recognized that in some cases it might be desirable to carry out individual vaccination by more than one method for experimental or other purposes. In such instances, adequate security precautions must be taken—for example, by using markedly different containers for the different strengths of vaccine.

EFFECTS OF VACCINATION.

Complications. It was accepted that any method and any vaccine may give a certain percentage of complications, including suppurative adenitis. One should aim at using a vaccine which would give the smallest number of complications and yet produce satisfactory allergy. The committee wished to stress that small abscesses at the site of vaccination healing within two months, or non-suppurative regional adenitis of moderate degree, should not be considered as complications.

Tuberculin allergy. Testing after vaccination should be carried out with the same test that is used for selection of subjects

to be vaccinated. In order to see in mass vaccination programmes whether satisfactorily high and constant levels of allergy are maintained, periodic quantitative tests should be carried out in samples of vaccinated subjects. Such post-vaccination testing should be expressed not merely by stating the percentage of reactors but by using a quantitative method of measurement such as, for example, that adopted by the WHO Tuberculosis Research Office (frequency distribution of the diameter of induration measures in millimetres).

Since these sample checks might be affected by possible variations among batches of vaccine produced in a given laboratory, the committee felt that regular tests should also be performed on each batch, whenever practicable or else periodically, to assess the level of allergy conferred by the vaccine when properly handled and administered. In this connexion, the committee felt that satisfactory periodic checks of mass vaccination work could be achieved by the use of special assessment teams such as those now working for WHO in several areas.

The committee stressed again the importance of using standardized preparations of tuberculin, and, since the biological assay of newly prepared tuberculins against the International Standard presents great difficulties the committee strongly recommended that a single large batch of PPD of standard potency be prepared, which would be sufficient to meet the need for a considerable number of years and which should be made internationally available for the purpose of Mantoux testing.

Protection. The committee was provided with information on the large-scale control trials at present being undertaken in the U.S.A. and Great Britain designed to assess the degree of protection given by BCG vaccination in different sections of the population in these two countries. The committee was also informed by Dr. Palmer of two studies designed to obtain from mass vaccination campaigns some information on the protective value of BCG (the national vaccination roster in Finland and the tuberculosis index in Denmark). The committee looked forward to the results that might be achieved through these studies.

The committee felt that for the assessment of the protective value of BCG vaccination in man there was, more than ever, a need for studies of morbidity. The present apparent dissociation between tuberculosis mortality and morbidity gave support to this view.

The committee also stressed the necessity of reaching international agreement on a definition of tuberculosis morbidity, and the importance of having bacteriological evidence in the diagnosis of tuberculosis disease.

The committee felt that, where conditions are favourable, countries should be encouraged to maintain central or regional vaccination rosters so that records might be kept of cases of tuberculosis occurring in vaccinated individuals.

SELECTION FOR VACCINATION.

Tuberculin and tuberculin tests. The Expert Committee on Tuberculosis at its fifth session had recommended " that the WHO Tuberculosis Research Office be requested to investigate the question of which dosage of tuberculin should be used in surveys for determining the level of tuberculosis infection in the country."[1]

Dr. Palmer summarized for the committee the results of studies which had been carried out in this connexion. These supported the view that the use of a single test of 5 tuberculin units (TU) was satisfactory and practical for selecting individuals for vaccination. Moreover, much experience that had now been accumulated in the field on the use of a single 5-TU screening test had shown that this dose could be used without inconvenience in mass programmes. The committee therefore recommended that in mass vaccination programmes a single Mantoux test of 5 TU continue to be used, and that the arbitrary definition of a tuberculin reactor continue to be based on the presence of an induration of 5 mm or more in diameter at the end of three days.

Selection of groups. The committee recommended that, before undertaking a mass BCG programme in an area, preliminary surveys should be made. In most cases in would be necessary to determine the levels of natural tuberculin sensitivity and the prevalence of tuberculosis in a particular area; in some it might be important also to study more general social and demographic aspects, such as stability or movement of population, industrial development, etc.

In areas with a stable population and low incidence of tuberculosis infection, the relative needs of different public-health programmes should be considered, and priorities established, before embarking upon a mass vaccination campaign.

The committee recommended that, in areas with a high prevalence of tuberculosis, mass vaccination should cover all age-groups from 1 year to that in which 80%-90% reactors to tuberculin are found. Although in such areas vaccination of the newborn would be highly desirable, it was believed that this group would usually best be dealt with outside the mass vaccination programme.

In areas with a low and decreasing tuberculosis prevalence,

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[1] Wld. Hlth. Org. techn. Rep. Ser. 1951, 32, 10.

where mass vaccination of the whole population is not carried out, the selection of age-groups for vaccination should be determined in accordance with the epidemiology (including age distribution) of the disease in those areas.

REVACCINATION.

For individuals and groups especially exposed to tuberculosis, the committee considered it important that the vaccination be controlled by a tuberculin test 2-3 months after the vaccination had been made, and that individuals found to be non-reactors to tuberculin at this time have the vaccination repeated. Period retesting should be made later on and every individual found to be a non-reactor should be revaccinated.

For the mass campaigns, retesting should be made of sample groups to establish the effect of vaccination in terms of degree of allergy induced. The results of these " spot checks " should permit a decision as to whether or not the whole vaccinated population should be retested and non-reactors revaccinated.

VACCINATION WITH THE VOLE BACILLUS.

The committee heard with great interest a statement by Dr. Wells, who summarized the experience available to date, and described control trials in man which were being carried out to determine the possible advantages of the vole bacillus compared with other available antigens. Dr. Wells expressed the opinion that it was premature at this stage to recommend wide application of this vaccine.

The committee felt that these trials and further experimental work should be followed with close attention.

VACCINATION WITH KILLED BACILLI.

Dr. Giovanardi presented the experiments and experience in Italy with the formalin-killed tubercle bacilli (" anatubercolina "). The experimental work included a comparison with BCG in animals and in humans and showed that the degree of resistance and allergy produced by this vaccine in animals and the allergy produced in man were inferior to those produced by BCG.

It was felt that the general application of this method could not be recommended at this stage, but the committee would follow with interest further experimental work on killed tubercle bacilli.

PLACE OF VACCINATION IN THE PUBLIC-HEALTH PROGRAMME.

The committee discussed the integration of BCG vaccination into the tuberculosis-control programme and into the general public-health services of a country.

It was felt that in countries where a large-scale BCG-vaccination campaign was envisaged, its organization should not be left to tuberculosis centres but should be co-ordinated centrally or regionally and made part of the general public-health programme. The mass campaign should make use of all appropriate public-health facilities and institutions, while the tuberculosis centres would concentrate their efforts on the vaccination of particularly exposed individuals and groups.

THE WORK OF WHO.

The committee heard a statement from the Secretary, who outlined the principles which were at the basis of WHO's work in BCG vaccination and tuberculosis control. The Secretary described to the committee how WHO was attempting to stimulate, lead and co-ordinate international co-operative efforts. In carrying out this task, WHO was trying to build its programme on a solid and scientific foundation, and in this connexion the guidance and help of the Tuberculosis Research Office was essential. Without basic and field research it would not be possible for materials, procedures, and methods to be critically assessed and compared before being put into general use. Moreover, with TRO's help in the planning of field work, a high degree of comparability of data could be achieved, which would permit of sound evaluation of programmes.

The committee fully agreed that research was most necessary if satisfactory field work were to be carried out. Among the important problems needing elucidation were: the comparison of oral vaccination by large repeated doses with other methods; the value of freeze-dried vaccines (in this regard the committee understood that studies were being carried out by the BCG Pilot Station in Paris); and the effectiveness of BCG vaccination, especially in areas of high tuberculosis prevalence.

The committee was much impressed by the value and the amount of work which had already been achieved by the Tuberculosis Research Office, and expressed the hope that the activities of this Office would continue and expand and that it would be given all possible support. Some of the problems mentioned above might suitably be undertaken by the Tuberculosis Research Office.

The committee heard with interest and appreciation that the United Nations Children's Fund, which had given so much assistance already to mass vaccination work, had extended its support to research activities.

BCG AND LEPROSY.

Dr. de Assis presented his views to the committee on the role of BCG vaccination in the prevention of leprosy. The committee

also considered the report of the Joint Meeting of Leprologists and Phthisiologists held in September 1953 under the auspices of the British Tuberculosis Association's Research Committee. The committee also noted with interest the opinions expressed by the WHO Expert Committee on Leprosy in its first report.[2]

The committee did not feel qualified to take a decision in this matter which, it felt, was not within its field of competence. It believed, however, that the mass BCG-vaccination campaigns, conducted against tuberculosis with the assistance of WHO in countries where leprosy is endemic, might perhaps be used by leprologists to study the possible value of BCG vaccination in the prophylaxis of leprosy. The committee did not know whether the conditions under which BCG programmes are conducted at present would allow any valid conclusions to be drawn regarding leprosy. Were it not possible to do so, and should certain changes in the organization of BCG campaigns permit that data be more easily obtained, the committee felt that such changes might be considered, provided that they did not interfere with the correct execution of a mass campaign against tuberculosis.

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[2] See Wld. Hlth. Org. techn. Rep. Ser. 1953, 71, 13.

ABSTRACTS

SAGHER, F., LIBAN, E. and KOSCARD, E.

Specific Tissue Alteration in Leprous Skin. VI. " Isopathic Phenomenon " following B.C.G. vaccination in leprous patients. A.M.A. Archives of Dermatology and Syphilology.

Twenty-one patients with lepromatous leprosy who were receiving chemotherapy were inoculated intradermally in the left deltoid region with 0.1 mil. B.C.G. vaccine. 13 of these patients had active lesions and 8 inactive (in 4 no bacilli were found). 12 were tuberculin negative before vaccination but became positive afterwards. All were lepromin negative, but 6 gave positive Fernandez reactions, and 5 positive Mitsuda reactions after 2-3 months. All however, became lepromin negative again after 1-2 years.

Tuberculin negative patients developed clinically a lesion at the vaccination site, similar to healthy persons without tuberculosis. Tuberculin positive cases showed an accelerated reaction (Koch phenomenon) and 3 had lepra reactions.

Biopsy specimens taken from the site of inoculation at intervals of from 4 days—10 months later, however, showed histological reactions characteristic of lepromatous leprosy, whereas similar specimens taken from controls showed reactions characteristic of tuberculosis. This reaction in leprosy the authors call an " isopathic phenomenon ". (A similar isopathic phenomenon is only found in one other disease, i.e. sarcoidosis.) In 17 specimens a 3-plus reaction showed masses of granuloma composed chiefly of foam cells. In three milder reactions only a few foam cells were seen and were described as prelepromatous. Clinically the reaction is tuberculous in that the tuberculin reaction becomes positive, but histologically it is lepromatous. The writers ask " Does B.C.G. produce tuberculosis in leprosy patients, or merely activate leprosy at the site of the lesion? " They suggest that this isopathic phenomenon may be useful in detecting early doubtful cases of leprosy, and of testing the effectiveness of chemotherapy.

The writers state that in an earlier series of experiments the injection of tuberculin, leishmanin, milk and peptone also elicited a lepromatous or prelepromatous reaction in leprosy cases. This rather suggests that any foreign proteins reactivate leprosy locally.

It is well known that vaccination against smallpox and anti-typhoid inoculations are apt to precipitate lepra reactions in patients with leprosy.

The reviewer regrets that no cases of tuberculoid leprosy were

included in the series to show the histological reaction to B.C.G. in this type of leprosy.

G. O. TEICHMANN.

RIDLEY, D. S.

The Significance of Antibody in the Pathogenesis of Leprosy. Transactions of the Royal Society of Tropical Medicine and Hygiene, **48**, No. 5, 1954, pp. 400-405.

This paper is concerned with " the immunological pattern which appears in established infections " (with leprosy). The author studied the bacteriological status, the Wassermann reaction, complement fixation with lepromin, the lepromin reaction, the tuberculin reaction, and complement fixation with tuberculin, in 24 patients in England, nearly all being lepromatous cases. With lepromin, but not with tuberculin, complement fixation was obtained in most of the lepromatous sera, while the lepromin test was negative in these cases. In the two tuberculoid cases, the lepromin test was positive, and the complement fixation test was negative. In these two cases he gave intradermal injections of (a) lepromin, (b) lepromin mixed with normal serum and incubated for 24 hours, (c) and (d) lepromin mixed with lepromatous serum and incubated for 24 hours. He found the lepromatous serum reduced or removed the reaction (48 hrs.) to lepromin.

He concludes. " The experiments reported in this paper, which need confirming and extending, would seem to indicate that in many lepromatous sera there is present an antibody which reacts with lepromin to fix complement; and that some lepromatous sera are capable of neutralizing lepromin so that a mixture of the two does not elicit a response in the skin in tuberculoid cases.'

He discusses the possible bearing of these ideas on the clinical and other manifestations of leprosy.

(This paper is discussed in an editorial.)

FLOCH, H., and SUREAU, P.

Resultats d'essais de traitement de la lepre par l'I.N.H. (Results of Experimental Treatment of Leprosy with Isoniazid.) Arch. Inst. Pasteur de la Guyane et due Territoire de l'Inini. Publication No. 292. 1953, Aug., 10 pp.

The author has treated 23 leprosy patients for periods of 2 to 15 months with daily doses of 300 to 500 mgm. of isoniazid. Except in one patient who made remarkable clinical and bacteriological improvement within 11 months, this drug did not prove itself of much real value. There was some clinical improvement in some lepromatous cases, but this did not carry corresponding bacteriological amelioration. There was some reason for hope that

a combination of DDS and isoniazid would give better tolerance and avoid the danger of drug resistance, but no ground for such hope is given. Isoniazid does not appear to prevent reactions.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

FLOCH, H. (1954).

Colchicoside in the treatment of reaction in leprosy. Therapie, 9, No. 4, p. 440.

Colchicoside is an extract of colchicum, one hundred times less toxic than colchicum in mice, but possessing marked " A.C.T.H. like " properties (reduction of eosinophils, protection against anaphylactic shock caused by sensitisation of horse serum). It has been found effective in various allergic conditions. It has been well tolerated when given daily by intravenous injection in doses of 10 milligrams. Its trial in leprous reaction appeared worth while, for the immediate action of A.C.T.H. and cortisone in the condition is very beneficial, although doubts exist regarding the late results.

The use of colchicoside is reported in five cases of severe ' reaction ' arising during, or preventing the use of, sulphone treatment. In one case, given three intravenous injections 10 mg., reactions apparently of an allergic nature occurred and the drug was stopped.

In the other four cases, started on 5 mg. daily, given intravenously for 3-5 days, and then 10 mg. for 5 more days, the results are recorded as very beneficial. The reaction rapidly subsided and the general condition markedly improved.

LEITE, A. S., DA LUZ, J. V. B., and NOGUEIRA, J. P.

Relatorio da Missao de Combate a Lepra na Provincia Ultramarina da Guine. (Report of a Mission for Combating Leprosy in Portuguese Guinea.) Anais Inst. Med. Trop. Lisbon. 1953, Mar., v. 10, No. 1, 79-163 2 diagrams, 18 figs. and 2 coloured folding maps.

This is a report of a party of medical specialists sent from Portugal to investigate the extent and other particulars of leprosy in Portuguese Guinea, and to formulate a policy for its control. The itinerary followed is shown in a map. The method used was that of Dr. Ross Innes in East Africa. The 1950 census gave the total population of the province as 499,770. The number of people examined was 94,389, among whom 2,429 were found suffering from leprosy (2.57 per cent). It was roughly calculated

that 10 per cent of these were open infectious cases. It is calculated further that in the whole province there are about 12,861 cases of leprosy. It is proposed to treat the closed cases as out-patients at various centres, giving DDS orally, and to admit the open cases to the agricultural leprosy colony at Cumura near Bissau, and possibly later to a second colony in the inland region of Bafata. Cumura will be able to hold between 1,500 and 2,000 patients. The incidence varies among the different tribes, being highest among the Fula (3.5 per cent) and the Manjaca (4 per cent). The number examined in each tribe, and the numbers of cases found, are shown in a map, and further details are given in several tables. There are 18 photographs showing types of cases and buildings. ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

ARQUIVOS MINEIROS DE LEPROLOGIA.

1952, Oct., v. 12, No. 4, 279-426. XI Curos de Leprologia. (The Minas Gerais Archives of Leprology. XI Course of Leprology.)

This volume is principally composed of an account of a conference of Brazilian leprologists, who had before them for discussion two subjects: Experience with Sulphone Therapy in Brazil, and The Rights and Aspirations of Brazilian Leprologists (abstracter's translation).

The first of these took the form of a symposium, answers being made by those present to questions which had been circulated beforehand. There was much discussion on the method of administration of sulphones, whether it should be continuous or intermittent, and the length of time that sulphones remained in the tissues. The criteria of discharge from leprosaria received attention, as did also the frequency of relapse, and the frequency with which the lepromin reaction was converted from negative to positive in lepromatous cases which had become bacteriologically negative. The chairman in summing up spoke of the dispensary as the prophylactic unit par excellence, where the disease could be eliminated in its basic forms, although a long time might elapse before we might enjoy the full benefit of the new weapon (sulphones). It would be possible for lepromatous patients who after treatment had only a few vacilli left to continue their treatment at dispensaries. The phenomenon, described by Sousa Lima, of the negative lepromin reaction being converted to positive in recovered lepromatous cases had not yet been confirmed by many workers. He spoke of lepromatous cases subjected to sulphone treatment that they " frequently behave like the syndrome of tuberculinic hyper-

sensibility," and suggested cross desensitising with tuberculin or BCG. We need more ample and accurate knowledge regarding sulphone-resistance and the time and form of relapses, and more accurate control of symptomatic cures and their possible transformation into biological cures.

The discussion on the rights and aspirations of leprologists revealed a rather disquieting condition. The disease appears to be increasing, but it is difficult to get the personnel necessary to combat it adequately. Dr. Diniz ascribed this difficulty to the conditions under which work had to be undertaken, and put forward eight suggestions for improving the circumstances of leprologists, including adequate remuneration, reduced time away from home, better conditions for work, and more facilities for study. Dr. Fonte made a plea for more disinterestedness. Leprosy could not be conquered by sanitation, engineering or immunisation. Everything depended on systematic examination of the contacts of the new cases found. In spite of all that might be said to the contrary leprosy was increasing; the returns showed a proportion of 60 per cent of infectious cases, and 50 per cent of known cases were not under effective control of the sanitary authorities. ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

TOUZIN, R., and MERLAND, R.

Traitement de la lepre par une nouvelle sulfone disubstitutée. Son elimination dans les milieux biologiques. (Treatment of Leprosy with New Disubstituted Sulfone. Its Elimination in the Body Fluids.) Med. Trop. Marseilles, 1953, Nov.-Dec., v. 13, No. 6, 1002-24, 8 charts. (15 refs.)

This disubstituted derivatives of DDS is diethyl-4 4/diamino-diphenyl sulphone-disulphonate of soda (M2196), produced by Rose in 1942 but never before used therapeutically. The blood concentration rises rapidly after injection, and then falls to a low level which is maintained almost equal from the 24th to the 48th hour. The concentration produced, after different degrees of dosage, in the blood, urine and milk are shown by means of many graphs and tables. Trials were made on 49 patients, 43 of whom continued the treatment. Of these, 22 were lepromatous, most of them very advanced in the disease. The results were very striking in 11 of the lepromatous cases, as regards both clinical and bacteriological improvement. The product is very soluble and its intramuscular injection causes little or no pain. Injections were given thrice weekly in doses up to 800 mgm., corresponding to 400 mgm. of DDS. It is considered that M2196 is tolerated better

than DDS and its other derivatives, and that a constant level of blood concentration is not necessary for efficient results. After only 12 to 18 months' treatment it is still too soon to assess the full results, but it is considered that so far these are promising.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

DE MESQUITA, S. J. B.

Die Lepromin-Reaktion bei 80 Marine-Infanteristen aus Holland. (The Lepromin Reaction in 80 Marines from Holland.) Ztschr. f. Tropenmed u. Parasit. Stuttgart. 1954, July, v. 5, No. 3, 376-8.

Of 80 marines staying temporarily in Surinam, seven had previously been in Indonesia, but the rest had come direct from Holland. The lepromin test showed a positive early reading (Fernandez) in 10, and a later reading (Mitsuda) in 31. The author considered that this proportion of positive results is below the average obtained in healthy persons elsewhere.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

LAVIRON, P., and LAURET, L.

Resultats de'ensemble, apres cinq ans du traitement de la lepre par le 3668 R.P. (Cimedone). (The Average Results after 5 Years of Treatment with 3668 R.P. (Cimedone).) Med. Trop. Marseilles. 1954, Jan.-Feb., v. 14, No. 1, 65-8.

This is a report on results after treatment of 71 lepromatous, seven tuberculoid and seven undifferentiated cases of leprosy for periods up to five years, with Cimedone, the French equivalent of sulphetrone. The degree of improvement is graded into 1, 2 and 3-plus.

Of the lepromatous patients there was 3-plus clinical improvement of 44, 42, 80 and 90 per cent, respectively, in those with treatment up to 2, 3, 4 and 5 years, and 39 became bacteriologically negative. There was some amelioration in 98 per cent of those treated.

Cimedone was given at first intravenously, but this was soon abandoned because of the many reactions and the difficulty of giving daily injections. Oral treatment was substituted, patients being given 2 tablets of 0.5 gm. daily for the first week, 4 for the second, and then 6 tablets (3 gm.) continuously with a break of one week after every four weeks. There was intolerance only in two cases; reactions which were numerous at first became less as treatment proceeded. In none of the lepromatous cases did the negative lepromin reaction become positive.

The results in tuberculoid and undifferentiated cases were not as good as in the lepromatous. Compared with treatment with DDS, that with Cimedone gave, if not more rapid, at least more appreciable results. The inconvenience of Cimedone is that it is necessary to give large quantities daily, which makes it unsuitable for mass treatment.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

LAVIRON, P., LAURET, L., and JARDIN, G.

Resultats apres trois ans du traitement de la lepre par des injections espacees de DDS. dans le chaulmoograte d'ethyle. (Results after 3 Years of Leprosy Treatment with Spaced Injections of DDS in Chaulmoogra Esters.) Med. Trop. Marseilles. 1954, Jan.-Feb., v. 14, No. 1, 69-71.

Ninety-one patients were treated at the Marchoux Institute in the French Sudan and 1,134 at bush centres. Injections were given intramuscularly of 5 cc. of chaulmoogra ethyl esters suspending 1.25 gm. of DDS twice a month. This was found sufficient to maintain an adequate level of sulphone concentration in the blood for 15 days. Tolerance was good, treatment having to be interrupted only in six cases. There were four deaths from intercurrent diseases during the course of treatment. Lepra reactions were frequent during the first few months, but became exceptional after the second year of treatment. Improvement was most marked in the lepromatous cases and less in the other forms. In the first year, of 56 lepromatous patients three became bacteriologically negative, seven in the second year and 17 in the third. The first few injections sometimes gave local pain with accompanying fever for two or three days, but after a few injections this pain did not occur.

This form of treatment is liked by the patients, and is convenient for the 22 doctors who carry out the treatment over wide areas.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

GUSSENHOVEN, G. A.

Behandeling van lepra met isonicotinezuurhydrazide. (Treatment of Leprosy Patients with Isonicotinic Acid Hydrazide (INH).) Nederl. Tijdschr. v. Geneesk. 1954, Sept. 4, v. 98 (iii), No. 36, 2481-7.

The English summary appended to the paper is as follows:

" Eleven leprosy patients in South Sumatra (Indonesia) were treated with INH. In one patient a serious leprosy reaction was

interrupted; a second showed repeatedly serious reactions by the drug. Of the other nine none showed any improvement, neither clinically, bacterioscopically or histopathologically. A daily dose of 6 to 8 mg. per kg. body weight caused in the majority of patients serious toxic reactions.'

AZULAY, R. D.

O papel protetor do B.C.G. na lepra murina. (The Protective Property of BCG in Rat Leprosy.) Rev. Brasileira Leprologia, St. Paulo. 1953, Dec., v. 21, No. 4, 285-91 (19 refs.). English Summary.

Fifty-seven rats were inoculated each with 20 mgm. of BCG, 20 other rats being left as uninoculated controls. Both groups inoculated with Myco. Leprae murium 115 days later. In the group inoculated with BCG the lesions appeared later and were smaller in size. There was no difference in the morphology or staining of the bacilli in the two groups, but the percentage of infection in the internal organs was greater in the unprotected group, and the lesions were more extensive. Because of the similarity between rat and human leprosy it is considered that these experiments confirm the viewpoint that BCG is useful in the prophylaxis of human leprosy.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

MONTEL, M. L. R.

Un cas de lepre contractee en France. Contagion familiale. (A Case of Familial Leprosy Infection Contracted in France.) Bull. Soc. Path. Exot. 1954, v. 47, No. 2, 201-2.

This note records the case of a woman of 37 in France who developed a tuberculoid leprous lesion in the right popliteal space. Later a biopsy suggested that this had all the potential cellular elements of " a future leproma (see above). No acid-fast baccilli were found in the lesion or in the nasal mucus. The Mitsuda test was strongly positive. The lesion disappeared completely in seven months after treatment with thiosemicarbazone.

The patient had had close contact with her daughter who had contracted lepromatous leprosy in French Sudan, and this had become generalised a year before her mother's lesion developed. The daughter's nasal mucus was bacteriologically positive.

H. J. O'D. BURKE-GAFFNEY.

(Abstracted in *Tropical Diseases Bulletin.*)

MONTESTRUC, E., and MARTIN DE MIRANDOL, P.

Sur la fixation des bacilles de Hansen au point di'inoculation d'une injection d'anatoxine antitetanique. (On the Fixation of Myco. leprae at the Point of Innoculation after an Injection of Antitetanic Serum.) Bull. Soc. Path. Exot. 1954, v. 47, No. 2, 196-8.

A patient, who during his military service had been wounded by a rusty nail in the sole of the foot, was given an antitetanic injection in the left forearm. Round the point of inoculation a smooth light-coloured macule developed with changes in sensibility. This gradually spread, became infiltrated and then formed nodules. When he was examined three years later there was a widespread lesion of the forearm with flattening round the point of inoculation. Many lepra bacilli were found in globi in the nodules. The question is discussed whether the bacilli were injected along with antitetanic serum or were already in the body and were fixed by the substance injected at the point of the inoculation, as sometimes occurs with the tubercle bacillus. The authors, while acknowledging both possibilities, are in favour of the latter explanation.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

ROSEMBERG, J., SOUZA CAMPOS, N., and AUN, J. N.

Estado actual do conhecimento da inversao da reacao de Mitsuda por efeito do BCG oral. (Present State of our Knowledge regarding the Inversion of Mitsuda's Reaction by means of Oral BCG.) Hospital, Rio de Janeiro. 1953, July, v. 44, No. 1, 33-73, 11 figs. (45 refs.).

First the technique employed in performing the lepromin test and reading the results is described. A list is given in tabular form of 18 experiments in which BCG has been administered by various workers and the results obtained in reversing the reaction to lepromin from negative to positive. After oral administration of BCG not only does the negative lepromin reaction become positive in about 100 per cent of patients, but in course of time the reaction tends to become stronger and it remains positive for at least three years. Orally administered BCG also increases the positivity of the lepromin reaction in those originally positive.

To a certain number of children who had not reacted to lepromin, BCG was administered 41 days after the lepromin injection, and in some of these a remote reaction was produced, a nodule appearing 30 days after the vacination at the site of the previous lepromin injection. In many cases, in spite of BCG not producing a positive tuberculin reaction, the lepromin reaction becomes positive. BCG administered in repeated doses to persons positive to tuberculin may gradually desensitise them until their

tuberculin reaction becomes negative. Oral BCG administered to lepromatous patients with frequent reactions may make these reactions become less frequent and severe; if this is followed by the injection of tuberculin a reaction of the erythema nodosum type occurs. (This is a very full and clearly argued article which will repay careful study in the original.)

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

FERRAND, B.

La ponction biopsie due foie dans la lepre. (Puncture Biopsy of the Liver in Leprosy.) Bull. Soc. Path. Exot. 1954, v. 47, No. 2, 203-7, 1 fig. on pl.

Five lepromatous cases are described in which a liver puncture was done and the material recovered examined microscopically. The author was surprised to find leprous nodules in the hepatic parenchyma. Masses of bacilli were found in the usual nodular formation, with Virchow's cells and a more or less dense infiltration of histiocytes. The nodules were often numerous and sometimes in the region of the intralobular vein, occasionally the size of 20 liver cells. The Kupffer cells were often parasitised, but bacilli were not observed in the liver cells, which were pushed aside by the nodules. There was also a diffuse infiltration of lymphocytes and monocytes, but this inflammatory appearance was inconstant and moderate in degree. The author considers this method of examination safe if precautions are taken, and preferable to puncture of the sternum or testicle. It might with profit accompany skin biopsy or gland puncture.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

MARIANO, J.

Consideracoes sobre os aspectos clinicos e localizacao da nevrite leprosa. (Considerations of the Clinical Aspects and the Locality of Leprous Neuritis.) Arquivos Mineiros de Leprologia. 1953, Apr., v. 13, No. 2, 136-9. English summary (9 lines).

Leprous neuritis is unique in being the only neuritis caused by an ascending bacillary infection. In 300 cases examined the ulnar nerve was the most affected, being found in 223. The external popliteal was next in frequency, occurring in 96. Only in leprous neuritis are the volume and consistency both of the nerve trunks and the slender nerve filaments modified by the infection.

ERNEST MUIR.

(Abstracted in *Tropical Diseases Bulletin.*)

CONTRERAS, F.

Profilaxis de la lepra. (The Prophylaxis of Leprosy.) Rev. Sanidad e. Hig. Publica. Madrid. 1953, Mar.-Apr., v. 27, Nos. 3/4, 226-47.

This is a very thorough history of means that have been taken to control leprosy from the earliest times. Four stages of evolution are described: (1) the period of terror of leprosy; (2) the period when all leprosy patients were compulsorily segregated; it is difficult to understand the attitude of Danielssen and Boeck, who insisted on this segregation, yet declared that leprosy was spread by heredity; (3) prophylaxis by isolating infectious cases and treatment of all, which was recommended at the second international congress held at Bergen in 1909; (4) early diagnosis by examination of contacts of known cases, and the treatment of all cases found. This last method as now followed in Spain is fully described.

ERNEST MUIR.

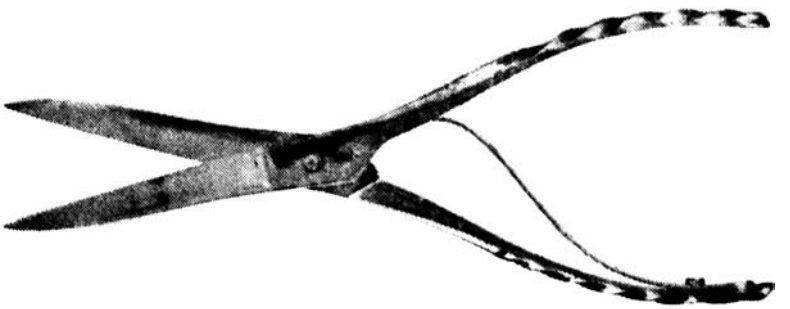
(Abstracted in *Tropical Diseases Bulletin.*)

CORRESPONDENCE

The Editor,
Leprosy Review.

Dear Sir,

I enclose a photograph of some scissors which we are now using in this settlement, in case you might like to put a note about them in the Leprosy Review. The idea is not original; it came to me when I saw the specially adapted tools used by the patients in the Vellore Rehabilitation Centre in Dr. Brand's film. I had six pairs made as an experiment, and the patients are very pleased



with them. Some with severe deformities and wasting of muscles can use them with comparative ease, where ordinary scissors are useless to them. Even those with fairly strong hands find them much simpler than the ordinary type. I chose a large size, ours are 8 ins. long, as they were needed mainly for cutting dressings, but the same principle can be used for any size.

They were kindly made for me, in stainless steel, by Messrs. Ferris & Co. of Bristol, England, at the very reasonable price of 22s. 6d. per pair.

Yours sincerely,

F. G. Priestman,
Medical Officer.

Bornu Leprosy Settlement,
P.O. Maiduguri, Nigeria.