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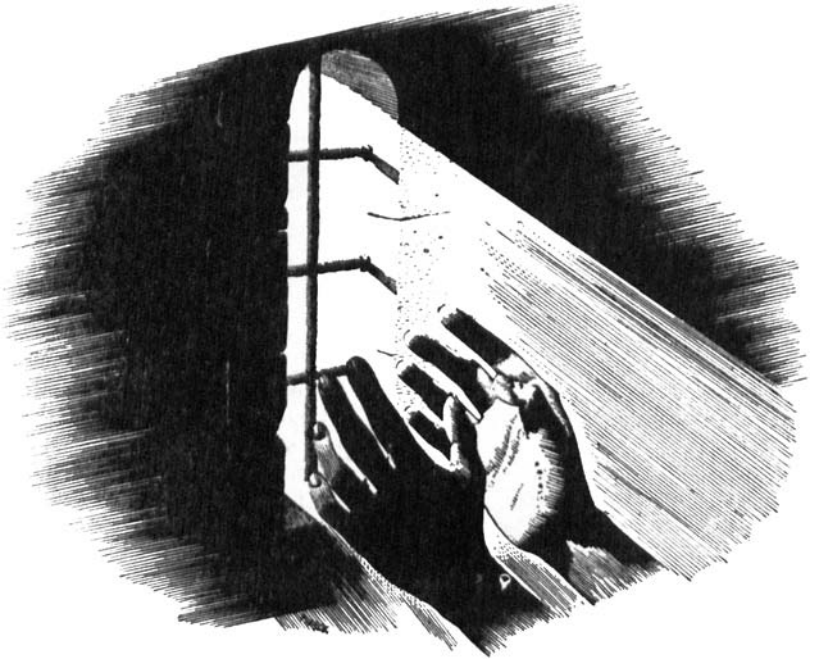

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EDITORIAL

Ever since Mitsuda, in 1916, demonstrated that certain cases of leprosy reacted positively to an intradermal injection of M.leprae from a boiled emulsion of excised nodules, what has now become known as the Lepromin Test has aroused increasing interest among leprosy workers. The work of Fernandez in S. America, and Lowe and Dharmendra and his co-workers in India, has served to elucidate many problems in connection with this. When it was announced that a positive lepromin test had a close relationship to the allergic skin reaction produced by a similar injection with tuberculin, these workers began to study in more detail the question of cross immunisation or tissue sensitisation in both diseases. In this number of the Review we are most fortunate in being able to publish a masterly and critical review of the whole subject of lepromin and tuberculin tests in relationship to B.C.G. vaccination. Little need be said further about this excellent contribution on this complicated subject, except that readers are advised to study most carefully the work of Dr. Lowe, and his sane and critical appraisement of the whole subject. In tuberculosis there is a tendency to take short cuts to the control of this most widespread disease by relying on B.C.G. vaccination on the one hand, and modern chemotherapy and antibiotic drugs on the other, bringing in the surgeon to repair the damage M. tuberculosis has done to the tissues, or to prevent further devastating trauma caused either by the organism, or by the tissue reactions produced as a result of invasion with M. tuberculosis. While well planned mass B.C.G. experimental work in connection with the anti-tuberculosis campaign is highly desirable, if the essential principles of control—the prevention of infection of the healthy community, particularly of children—are not stressed all our efforts to stop the ravages of tuberculosis may be of little avail. Dr. Lowe, while advocating further detailed study of the lepromin reaction and its relationship to immunity, quite rightly sounds a warning note which should be heeded by all, when he says ' It should be made perfectly clear to everyone concerned that B.C.G. vaccination of those exposed to infection does not remove the necessity for taking every possible step to prevent or minimise contact between open cases of leprosy and healthy persons, particularly children.'' The guiding principles which Dr. Lowe lays down in relation to the attitude of public health workers concerning B.C.G. and the lepromin test seem to us altogether admirable, and if all workers took these as their criteria when considering

B.C.G. vaccination of persons who have been, or are liable to be, exposed to leprosy, then not only much useful information should be gathered, but B.C.G. vaccination would be used in a way which is most likely to make an outstanding contribution to the control of leprosy. This article is timely and well balanced and should be heeded by all leprosy workers, particularly those responsible for the preventive side of the campaign.

We are also fortunate in securing an article from Dr. J. A. K. Brown, the founder of the famous Uzuakoli Colony in Nigeria, and now the Leprosy Specialist for Uganda. Readers are aware of the magnificent contribution of Dr. Ross Innes, the Interterritorial Leprologist attached to the East African High Commission. Dr. Brown now carries on the extensive work undertaken by Dr. Ross Innes and presents sound and well balanced views on the question of surveys in Uganda, with particular reference to the method of organisation and the interpretation of results. Extensive surveys of the type undertaken by Dr. Ross Innes are an essential preliminary to more intensive work. With the appointment of a leprologist of their own in Uganda, we anticipate not only more detailed study of the epidemiology of the disease in relationship to Uganda, but also the building up of an effective and practical leprosy control service.

It is a great pleasure to be able to reprint, by permission of the Editor of the *Annals of the Royal College of Surgeons*, Mr. Brand's Hunterian Lecture on "The Reconstruction of the Hand in Leprosy." This pioneer work undertaken by the Leprosy Research Department of the Christian Medical College, Vellore, has aroused great interest, and it is most encouraging to find that orthopaedic surgeons, both in Britain and the United States, are beginning to realise the importance of such reconstructive work. The sulphones have brought the expectation of a "cure." The work of Paul Brand has infused new hope, and the possibility, as one patient so pathetically put it, that the leprosy patient will not need for ever to carry his "visiting card"— residual deformities and disabilities —around with him wherever he goes. New hope has indeed dawned, and we rejoice with all workers throughout the world in the great possibilities ahead which this number of the Review to some extent foreshadows, and we pledge all our energies and allegiance to those who have to face the future—now much more bright but still with its haunting fear—trusting that the efforts of our colleagues the world over and our own, will hasten the dawn of the day when we, or those that come after us, shall celebrate V.L. Day—Victory over Leprosy.

TUBERCULOSIS AND LEPROSY. IMMUNOLOGICAL STUDIES.

JOHN LOWE, C.B.E., M.D., M.R.C.P., and F. MCNULTY

INTRODUCTION.

For the last twenty years and more, some leprosy workers have entertained the idea that persons who are immune to tuberculosis may show some degree of immunity to leprosy. Certain clinical, epidemiological and immunological findings pointed, rather vaguely it is true, to this conclusion. The advent of B.C.G. vaccination as a prophylactic measure in tuberculosis obviously added importance to this matter. Starting with the report of Fernandez (1) in 1939, several workers have reported that B.C.G. vaccination converts not only a negative response to tuberculin into a positive one, but also a negative response to lepromin into a positive one in the same person. Moreover Fernandez (2) later reported that lepromin-negative healthy persons could be made lepromin-positive by the injection of suspensions of the tubercle bacillus or the leprosy bacillus killed by heat. Most leprosy workers consider that a positive lepromin test indicates a degree of immunity to leprosy. Some such workers have therefore been strongly advocating the use of B.C.G. vaccination in persons, particularly young children of leprous parents, who are intimately exposed to leprous infection, and good results are already being reported from this measure.

The matter is obviously one of great interest and importance; a simple and reliable method of immunizing " contacts ' against leprosy might prove a very potent weapon in anti-leprosy work. Further, some workers, among whom Chaussinand (3) is prominent, consider that cross immunity between tuberculosis and leprosy is of great epidemiological importance. An article by Chaussinand on this subject is translated elsewhere in this issue.

So far the work on this subject has been done almost entirely by South American and French workers; a British contribution to the subject is overdue. In the present article, we attempt to review the available literature on the subject and to assess its value and significance, and at the same time to report on the early phases of a practical study of the subject, which aims at being as intensive and extensive as circumstances here in Nigeria permit.

In order to make the matter comprehensible to as many as possible, the history and development of knowledge of the im-

munology of leprosy is briefly outlined. Cross immunity between tuberculosis and leprosy is of interest to many besides leprosy workers, and particularly to tuberculosis workers who may not be familiar with the main facts regarding the lepromin test.

THE LEPROMIN TEST.

The lepromin test constitutes the results of attempts over forty years to develop in leprosy work a test similar in nature to the tuberculin test in tuberculosis.

In leprosy, the bacilli cannot be cultivated, and experimental animals are not susceptible; therefore the only source of bacillary material is the lesions of patients suffering from leprosy. In leprous nodules, the bacilli are very numerous, counts as high as one thousand million per cubic centimetre of tissues having been recorded by Hanks (4). By excising such nodules, sterilizing by heat and by grinding them up in saline, vast numbers of bacilli are liberated, and suspensions of this nodular material can be made suitable for injection. Such suspensions contain not only bacilli but tissue cells fluids and lipoids, but the antigenic material is the bacilli.

According to Hayashi (5), K. Mitsuda (6 and 7) was the first to record that the intradermic injection of a small amount (0.1 cc) of a boiled emulsion made from excised leprous nodules ground up, usually gave a positive response in healthy (adult) contacts, in non-contacts, and also in " maculo-anaesthetic " cases of leprosy, (these cases are often mild and self-limiting), and usually gave a negative response in cases of " nodular " type (usually severe and progressive).

The positive result however was peculiar, a definite small nodule developing slowly at 2 to 5 weeks and then slowly subsiding. Mitsuda interpreted this positive result seen in healthy people and in the mild self limiting forms of leprosy as indicating " resistance,' partial or complete, to leprous infection.

Numerous later workers confirmed all these main points, and also added further information. In young healthy children, the result was usually negative, but with increasing age often became positive. The frequent occurrence of positive results in healthy adults, even in countries where there was no leprosy, was confirmed. The test, often known as the Mitsuda test, became a routine procedure, not in diagnosis of leprosy, for here it was of practically no value, but in classification of cases and in prognosis.

The anomalous features of the test (a) the lateness of the reaction, (b) the positive results in persons with no contact with leprosy, and (c) the negative results in " nodular " (now called

" lepromatous ") cases, remained unexplained or only partly explained, though numerous writers suggested as the explanation of (b) infection with other acid-fast organisms, the tubercle bacillus being possibly one or the chief of these, and of (c) a specific anergy to the leprosy bacillus. This anergy is the most specific feature of the test.

THE NATURE OF THE POSITIVE RESPONSE TO LEPROMIN.

In brief, three different theories have been held by different workers. A few [e.g. Bargehr (8), Rotberg (9)] have considered a positive test as being caused by specific allergy to the leprosy bacillus and its products of disintegration. This view is no longer tenable and this position now seems to have no supporters. Rotberg himself has changed his mind on this matter.

Others have considered a positive reaction to be neither allergic nor specific, and have thought that a positive reaction was due to " resistance " of the body tissues to the bacilli, and that a negative reaction was due to lack of this " resistance." (The meaning of this term resistance was never clearly defined.) This position seems to have been undermined by more recent work reviewed later.

Most workers have regarded the positive reaction as allergic, but not specific in nature.

The work of Fernandez, and of Dharmendra has cleared up some anomalies. Fernandez (10 and 11) showed that a positive late response (2-5 weeks) was almost always preceded by a " tuberculin-like " early response at 24-48 hours, consisting of a definite area of erythema and oedema surrounding the point of injection. Others, e.g. Lowe and Dharmendra (12), soon confirmed this, and these workers also showed that, by grinding the bacilli for several hours till the bacillary forms were few or no longer found, and by suspending in saline and injecting the residue, the early response was greatly increased and the late response was much diminished. They interpreted these findings as indicating, that (a) both the early (Fernandez) and the late (Mitsuda) reaction to injection of lepromin were allergic in nature, and moreover (b) that they were both due to the same antigen, the early reaction being due to free antigen present in the lepromin, and the late reaction due to slow liberation of the same antigen from the bacilli by slow disintegration at the site of injection. The findings were supported by histological studies. Fernandez however interpreted his findings as indicating two antigens, one active at 24-48 hours and the other at 2-5 weeks.

Wade (13) expressed still another view of the mechanism of the late reaction. He thought that the test might not reveal the presence of allergy at the time of the injection of lepromin, but only

of potential allergy. In persons who were only potentially allergic, when lepromin was injected, the allergy induced by the injection showed itself 2-5 weeks later by reaction at the site of the injection, where bacilli are still present. Persons who were not even potentially allergic showed no such reaction.

[There is one serious difficulty presented by Wade's theories. If they were true, persons who had never been exposed to leprous infection, and could therefore be only potentially allergic, should show no early reaction but only the late one. Various workers have reported that this is not so; it appears that even in a person never exposed to leprous infection, a positive late reaction is usually preceded by an early (24-48 hours) reaction. Wade himself (14) realised and discussed this difficulty.]

Ideas rather similar to those of Wade in certain respects have been expressed by other workers, several having considered that some inherent constitutional factor influenced the results of the lepromin test. For example, Rotberg (9) thought that many people, probably the big majority, were potentially allergic to the leprosy bacillus, and that when infected with leprosy, they developed either no disease or else the mild " maculo-anaesthetic " form these being the lepromin-positive persons; on the other hand some, probably a minority, were inherently incapable of reacting allergically to lepromin or to leprous infection, and, if infected with leprosy, they developed the severe " nodular " or lepromatous form of the disease, the lepromin test remaining of course negative.

These ideas, if true, would have an important bearing on the question of the possibility of immunization against leprosy; they are discussed in that connection later.

There still seems to be no unanimity among leprosy workers regarding the nature and mechanism of the reaction to lepromin. All these three views however (those of Fernandez, of Lowe and Dharmendra, and of Wade) accept allergy as the basis of the reaction. We have seen no reason to abandon the view expressed by Lowe and Dharmendra that one antigen only operates, and Dharmendra's later work supports that view, for he (15) developed a method of completely separating leprosy bacilli from leprous tissue and preparing lepromin which could be standardized by weight, and moreover he (16) was able to isolate various chemical fractions of such isolated bacilli. He isolated soluble antigenic fractions (protein) from the bacillus which give a marked early reaction and no late reaction; he failed to isolate any fraction which gave a late reaction only.

Regarding specificity; the positive findings in people never exposed to leprous infection have already been mentioned and are

discussed more fully later. Dharmendra and Jaikaria (17) failed to find any fraction of the leprosy bacillus which when injected gave a response which was specific for leprous infection. They and others considered infection with the tubercle bacillus as a possible or probable cause of non-specific response to the injection of lepromin. Recent work, more fully discussed later, supports this idea.

This then is the present position of the lepromin test. It is regarded as allergic but non-specific, of value mainly in classification and prognosis. The injection of lepromin can produce two responses, an early (24-48
phenomenon) and a late (2-5 weeks) response of nodular type (the Mitsuda phenomenon); both these responses have, in the opinions of some workers, the same significance, although some other workers think that the early response indicates " sensitivity " and the late response indicates immunity. The grounds for this differentiation are not clear and it is not possible here to discuss this matter further. (In the present study both readings have been made, but the late reading alone is considered here. The two have usually agreed.)

VARIATIONS IN RESULTS OF THE LEPROMIN TEST.

It is advisable here to consider the question whether the results of the lepromin test in any individual can vary from natural causes. That lepromin-negative healthy persons can become lepromin-positive as the result of exposure to infection with leprosy bacilli is generally recognized, and most workers consider that infection with other acid-fast bacilli, particularly the tubercle bacillus, can produce the same result. This matter is discussed more fully later.

In persons with leprosy of the lepromatous type (lepromin negative) a few workers have reported that when the disease subsides under chemotherapy, the lepromin test may become positive. Such reports are few. We, personally, in an experience of several hundreds of such cases over six years, have not been able to demonstrate this change in a single case.

Regarding the possibility of lepromin-positive persons becoming lepromin-negative, opinion seems to be divided. Regarding non-leprous but lepromin-positive persons, information is scanty. Regarding persons with leprosy, a few workers have reported that lepromin-positive " maculo-anaesthetic " or " tuberculoid " cases can develop into lepromin-negative " lepromatous " cases, but even such workers do not find that this change is common; most workers find that while the degree of positivity in the lepromin test may vary at different times with varying phases of activity and quiescence of this (allergic) tuberculoid form of the disease, a change from frank lepromin positive to complete negative, and a corresponding change

in the type of the leprosy, appears extremely rare or, in the opinion of some, impossible.

Thus, on the whole, the allergic response seen in the lepromin test in some persons (presumably the result of exposure to infection with acid-fast bacilli) is very persistent; similarly the lack of response of other persons not only exposed to such infections but actually suffering from lepromatous leprosy, is also very persistent.

These findings tend to support the idea of an inherent factor influencing the results of the lepromin test.

THE RELATION BETWEEN THE LEPROMIN RESPONSE AND THE FORM OF THE DISEASE.

Finally the following question must be considered. In cases of leprosy, is it the form and the severity of the disease which determines the response seen in the lepromin test, or is it the reverse, namely is it the allergy or immunity of the body, as demonstrated by the lepromin test, which determines the form of the disease?

While a few workers seem to have adopted the first view, most appear to adopt the second, which is much more easily reconciled with the known facts, for example, that persons with no leprosy and never exposed to leprous infection are often lepromin-positive; that once a person is found positive or negative he almost always remains so; that subsided lepromatous cases nearly always remain lepromin-negative, and so on.

Thus the two main forms of leprosy, the allergic (tuberculoid) form, and the anergic (lepromatous) form, appear to represent two widely differing ways in which the body may react to leprous infection, the form of the disease being determined by the state of the body (sensitization, allergy and possibly immunity) existing at the time of infection or developing early in response to that infection, this allergy usually persisting indefinitely.

The important question whether a positive lepromin test indicates immunity to leprosy is discussed later.

THE TUBERCULIN TEST.

In almost every way this test and the significance of its results are very much simpler and easier to discuss than the lepromin test and its results. There is almost universal agreement that a positive result is an allergic phenomenon which indicates sensitization to the tubercle bacillus and its products introduced into the body in the form of a natural infection or by the procedure of B.C.G. vaccination.

It is however true that a few workers have at times questioned its specificity. For example, Cummins and Leroux (18), finding

rather an inexplicably high tuberculin-positive rate in one part of Africa, considered and investigated the possibility of some of the positive results being due to leprous infection patent or otherwise, but with negative results. Chaussinand (3) in a recent discussion of the subject does not state definitely that leprosy can cause a positive tuberculin test, but he does state that patients with tuberculoid (allergic) leprosy, free from tuberculous infection, react strongly to the intradermal injection of Koch's bacillus killed by heat, while healthy people and people with lepromatous (anergic) leprosy show no such reaction.

On the whole, the specificity of the tuberculin test remains without serious challenge. A positive result indicates tuberculous infection past or present. A negative result however does not necessarily indicate the absence of such infection. Even in severe tuberculous disease, such as miliary tuberculosis and the last stages of pulmonary tuberculosis, the tuberculin test may be negative, indicating an anergy (which recalls in some respects the anergy of lepromatous leprosy).

One further point about the tuberculin test should be mentioned. It is apparently not unusual for the result of the test to be found changing from positive to negative and vice versa. It has been suggested that the test remains positive only in the presence of infection, which is often, however, latent and inactive. After complete eradication of tuberculous infection a positive tuberculin test may slowly become negative; with reinfection it may become positive again. Further, with progressive spread of the disease, a person previously positive may become negative.

Similar findings are recorded after B.C.G. vaccination. The positive tuberculin test induced by this measure is often short-lived, and to maintain positively repeated vaccination is often necessary.

These findings contrast with the persistence of the response in the lepromin test.

METHODS OF TUBERCULIN AND LEPROMIN TESTING USED.

The best general method of making lepromin is believed to be that of Dharmendra (15); by this method a lepromin is prepared consisting of leprosy bacilli and nothing else; thus it can be standardized by weight. This method involves centrifugalizing in ether at a temperature not too high. The use of this method here in Eastern Nigeria was rendered difficult by the high temperature and the lack of refrigerators large enough to contain an electric centrifuge, though one lot of lepromin was prepared in this way. This lot was used as a standard. Further lots of lepromin were prepared by the following method. Excised nodules were sterilized in an autoclave and

ground in chloroform by Dharmendra's method till nearly all the bacilli had been extracted. The chloroform (containing the bacilli and the tissue lipoids) was evaporated on a hot water bath. The residue was very fatty; it was suspended in saline by grinding in a pestle and mortar. The result was a saline suspension of leprosy bacilli with also many fat globules. The suspension was allowed to stand and the fat globules coalesced; it was then filtered twice through fine filter paper, which removed most of the fat, leaving a fine suspension of leprosy bacilli; .5% carbolic was added.

This lepromin was standardized against the lepromin already standardized by weight prepared by the method of Dharmendra, dilutions from 1 in 5 to 1 in 20 being prepared and 0.1 c.c. being injected intradermally into patients with leprosy of the two main types, allergic and anergic; at the same time 0.1 c.c. of the standard preparation was injected. The dilution which gave the same results as the standard lepromin was adopted for routine use. The undiluted lepromin was stored, and some was diluted with normal saline on each day on which the test was used.

This lepromin has proved very satisfactory, and is maintaining its potency very well. The early (24-48 hours) response in our dark skinned Africans is often not easy to read with accuracy; but a definite early response has always been followed by a marked late (2-5 weeks) response. The late response has been the one used here in recording the patient as positive, doubtful, or negative.

In deciding what is positive the following criteria have been adopted. A positive result means a definite nodule easily palpable and usually easily visible, detectable in the third and fourth weeks. " Pin head " nodules have been ignored in this work. The nodules recorded as positive have measured 4 mm. to 10 mm. or more in diameter, the large ones often showing superficial alteration.

In a few cases only, the results have been recorded as doubtful.

The tuberculin used in this work was obtained from the Pasteur Institute, Paris. In all cases, a preliminary scratch test (cuti reaction) was done with crude tuberculin undiluted, the readings being made at 48 and 72 hours; if a definite reaction was obtained, no further test was done. Patients with doubtful and negative results were then given an intradermal injection of 50 international units of purified tuberculin. In practice, a definite raised area of erythema and oedema measuring eight or more millimetres in diameter was recorded as positive, though the nature of the reaction rather than the measurement was the deciding factor in a few doubtful cases. (In some doubtful cases a further test with 1 in 100 tuberculin was done, but these results are not here recorded.)

A. STUDIES IN HEALTHY PERSONS.

Several studies of a nature similar to the present one have been made in the past and are discussed later. The issues can easily be confused by the presence of leprosy or of tuberculosis in the persons studied. A study made in healthy persons is in many ways far more illuminating.

FINDINGS OF THE PRESENT STUDY.

We have made the following studies of the results of the lepromin and tuberculin tests in healthy Africans here in Uzuakoli, Nigeria.

(a) *Studies in children ages* 1-15.

No. tested 81.

Tuberculin positive 47 (58%)

Lepromin positive 31 (35%)

From the above data it is possible by simple calculation to find out the proportion of the cases in which the results of the two tests should agree or should disagree, and in what way they should agree and disagree, if the two tests are entirely independent.*

The figures are here given, together with the actual findings made:

	Both tests positive	Both tests negative	Tuberculin positive Lepromin negative	Tuberculin negative Lepromin positive	Disagreement
Expected ...	22%	26%	36%	16%	52%
Actual ...	(31) 38%	(34) 42%	(16) 20%	nil	20%

It will be seen that the actual results obtained were very different from those expected if the two tests are entirely independent. Moreover, these differences when examined statistically (this has been done for us by Dr. B. Nicholson) are highly significant. The two tests are not independent; the results of the two tests agree far more often than they should do if they are independent.

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* This simple calculation can best be explained by an example. A reasonable sized group of persons is tested, say 200. The following findings are made.

Tuberculin positive 60%, negative 40%

Lepromin positive 55%, negative 45%

If the two tests are independent, the one test having no influence on the other, the grouping of the 200 patients should be

Tuberculin and lepromin positive	55% of 60% = 33%	51% agreement
Tuberculin and lepromin negative	45% of 40% = 18%	
Tuberculin positive and lepromin negative	45% of 60% = 27%	49% disagreement.
Tuberculin negative and lepromin positive	55% of 40% = 22%	
	100	

(b) *Studies in adults.*

No. tested 278.
Tuberculin positive 223 (80.2%)
Lepromin positive 224 (80.5%)

A study of the results by the methods outlined above gives the following results:—

	Both tests positive	Both tests negative	Tuberculin positive Lepromin negative	Tuberculin negative Lepromin positive	Disagreement
Expected ..	64.6%	3.8%	15.6%	16.0%	31.6%
Actual ...	(201) 72.3%	(32) 11.5%	(22) 7.9%	(23) 8.3%	16.2%

In this group of adults, with both tuberculin and lepromin positive rates considerably higher than in children, the findings are less striking, and the differences between the results calculated on the basis of the two tests being independent and the actual results observed are less marked than in the children; nevertheless the differences are of the same nature, and moreover, statistical analysis shows that they are significant, and that there is a greater agreement between the results of the two tests than can possibly occur by hance.

DISCUSSION.

We now look at the figures of similar studies made by other workers in other countries and analyse them in the same way.

Dharmendra and Jaikaria (19) studied 260 healthy persons in the Punjab (India) where there **was practically no** leprosy and not much tuberculosis and gave the following figures:

260 tested. Tuberculin positive 52%
Lepromin positive 35.4%

	Both tests positive	Both tests negative	Tuberculin positive Lepromin negative	Tuberculin negative Lepromin positive	Disagreement
Expected ...	18.4%	31.0%	33.6%	17.0%	50.6%
Actual ...	28.0%	40.4%	24.2%	7.3%	31.5%

These results again show the same thing, but since the tuberculin-positive and lepromin-positive rates are lower than here in Nigeria, the differences are in some respects more marked.

The same general findings are also found in the report of Chaussinand (20) from Indo-China, where both leprosy and tuberculosis are common.

Cases tested 231 (children 4-8 years). Tuberculin positive

61.4%; lepromin positive 65.4%.

	Both tests positive	Both tests negative	Tuberculin positive Lepromin negative	Tuberculin negative Lepromin positive	Disagreement
Expected ...	40.1%	13.4%	21.2%	25.3%	46.5%
Actual	54.1%	29.3%	7.4%	11.2%	18.6%

Chaussinand's (3) report of studies of 41 children in Paris are also interesting when studied in the same way. (Three with " doubtful " results are omitted from this analysis.)

Persons tested 38 (children 10-17 years). Tuberculin positive 44.7%. Lepromin positive 47.3%.

	Both tests positive	Both tests negative	Tuberculin positive Lepromin negative	Tuberculin negative Lepromin positive	Disagreement
Expected ...	21.1%	29.1%	23.6%	26.2%	49.8%
Actual	44.7%	52.6%	nil	2.6%	2.6%

Although the group is small, the findings in Paris, where leprous infection is so rare, are very striking, and the results are undoubtedly significant.

CONCLUSIONS.

These three studies, our present study and the previous studies of Dharmendra and Jaikaria, and of Chaussinand, these studies having been made in different countries by different workers at different times, the methods used also differing, all point to the same conclusions; the two tests are not independent, and there is some factor operating strongly to make the two tests agree. What is this factor?

THE CAUSE OF AGREEMENT BETWEEN THE TWO TESTS.

Four possibilities have to be considered.

Firstly, exposure to leprous infection (in this country leprosy is highly endemic, and many if not most of the persons tested have had contact with leprosy cases) might have made persons allergic to both the leprosy and the tubercle bacillus.

If this hypothesis were true, patients with leprosy of the allergic (tuberculoid) type should be tuberculin positive. As is seen later, this is often not so. There is practically no evidence to support this hypothesis; nearly all the evidence is against it.

Secondly, it might be postulated that persons had been exposed either to both infections or else to neither, although it would not be easy to explain how this might occur, in Nigeria at any rate. But this argument is upset by the fact that in persons never exposed to

leprous infection and living in countries with no leprosy, the two tests agree in a still higher proportion of cases. This is shown in the reports of Chaussinand (3) and of Fernandez (1) on studies in Paris.

Thirdly, it might be postulated that some other factor, possibly some other acid-fast infection, is making people allergic to both the tubercle bacillus and the leprosy bacillus. This is perhaps less improbable than it might appear. Acid-fast bacilli are very common in nature, and can be found, isolated and cultivated from many natural sources. Very few of them are known to be pathogenic to man, but that does not mean that they could not infect man, and perhaps produce in man the power to react allergically to themselves and to other acid-fast bacilli, including the tubercle bacillus and the leprosy bacillus. Nevertheless there is no direct evidence to support this hypothesis.

Fourthly, much the most likely explanation is that exposure to tuberculous infection is making people allergic to the leprosy bacillus.

On this basis it is easy to explain how most healthy persons in most countries are allergic to both bacilli or to neither. In West Africa however and in other countries with much leprosy, it is more than possible that some persons have been exposed to leprous infection but not to tuberculous infection, and this would explain those cases which are lepromin-positive but tuberculin-negative. There remain however the cases that are tuberculin-positive but lepromin-negative. Analysis of the 38 such cases in our present series shows that nearly all of them are weakly positive to tuberculin, which suggests that the degree of reaction to tuberculin influences the response to lepromin. Further examination of our records supports this view. In our 278 healthy adults studied, 71 showed a definite reaction in the scratch test (cuti reaction) which indicates a high degree of sensitization to tuberculin, and 70 (98.6%) of these showed a positive lepromin test, nearly all strongly positive. (One of these was in a person who had just left by air, and for the first time, a country with no leprosy.)

The observations recorded and quoted afford strong evidence that exposure to tuberculous infection, as shown by a positive tuberculin test, can, and usually does cause the lepromin test to become positive. In fact the observations can only be reasonably explained on this basis; no other hypothesis appears able to explain the facts.

This hypothesis is strongly supported by published work other than that already quoted.

The following workers have reported a high incidence of positive lepromin tests in adults in countries where there is little

or no leprosy, and where the possibility of the positive results being due to leprosy can be ignored. Cummins and Williams (21) in England, Dubois (22) in Belgium, Boncinelli (23) in Italy, Fernandez (1) in Paris, Convit Azulay *et al.* (24) in New York, Azulay and Convit in Ohio (25), Bechelli *et al.* (26) in New York, Dharmendra and Jaikaria (19) in the Punjab, India, and Chaussinand (3) in Paris. Several of these workers have reported on the fact that tuberculin-positive persons studied were usually lepromin-positive.

Other reports are those of Fernandez (1) who stated that in tested persons from countries with no leprosy, the agreement between the tuberculin and lepromin tests was 95%, and of de Sousa Campos *et al.* (27) in Brazil, who found all Mantoux-positive isolated children of parents with leprosy studied were also lepromin-positive (although some were lepromin-positive and Mantoux-negative). Garcia Miranda (28) in Cuba reported that, of non-leprous persons, 78% were lepromin-positive, and the results of the Mantoux tuberculin test and lepromin tests coincided.

Doubtless many other reports could be traced and quoted. The literature of the subject gives ample evidence to support the idea that tuberculous infection, as shown by a positive tuberculin test, can and usually does make the lepromin test positive. The present report only confirms the reports of previous workers.

There are however some reports of other workers who have studied the matter, which are rather less definite in their findings. Such reports include those of Rotberg and Bechelli (29), and of Convit, Azulay *et al.* (24) based on work in New York; although a later report of Azulay and Convit (25), based on work in Ohio, records a more definite correlation between the results of the two tests.

A very discordant note is struck by Radna (30), who in an area without much leprosy found that of 100 tuberculin-negative (cuti reaction) persons, 94% were lepromin-positive. Such a report, quite unsupported by other workers, makes one doubt the efficiency of the methods used.

THE EFFECT OF B.C.G. VACCINATION ON THE LEPROMIN AND TUBERCULIN TESTS IN HEALTHY PERSONS.

The following published reports on this matter are available. Fernandez (1) reported that, in persons negative to both tests, B.C.G. vaccination usually made both tests positive. He studied 122 children with no contact with leprosy or tuberculosis, all being lepromin- and tuberculin-negative. After B.C.G. vaccination, 99% became tuberculin-positive and 95% became lepromin-positive.

Neyra Ramirez (31) took 53 healthy persons negative in both tests, and gave B.C.G.; 87 became lepromin-positive.

Chaussinand (3) took 30 children negative in both tests, and found that all became lepromin-positive after B.C.G. vaccination.

Azulay (32) gave B.C.G. to 15 lepromin- and tuberculin-negative children. Twelve became tuberculin- and lepromin-positive.

Gines and Poletti (33) studied 31 healthy children of leprous parents, giving B.C.G. vaccine. Twenty-five were found lepromin-positive after vaccination. Of 11 whose previous lepromin test was not done, 9 were found positive, and of 20 whose previous test was negative, 16 became positive.

Rosemberg, de Souza Campos and Aun give two reports (34 and 35). In the first they studied 39 healthy children of leprous parents, all tuberculin- and lepromin-negative. In 27, B.C.G. was given daily and orally for 28 days in increasing doses, with a total dose of 1.19 G.* In all 27, the lepromin test became positive; the tuberculin test became positive in 24 and doubtful in 3. In the other 12 children, only one dose of B.C.G. (.1 G.) was given. Nine became tuberculin-positive and 8 became lepromin-positive; 3 remained tuberculin- and lepromin-negative. In the second paper they studied 36 healthy tuberculin-negative children of healthy parents. B.C.G. was given orally for 28 days. This B.C.G. vaccine produced tuberculin conversions in 25. Ten months later, 24 of the 25 had become tuberculin negative; the lepromin test was still found positive in all the 36. Thus the lepromin test had become and remained positive after B.C.G. vaccination (a) in the 1 case becoming and remaining tuberculin-positive (b) in the 24 becoming tuberculin-positive but later reverting to negative and (c) in 11 who had never even become temporarily tuberculin-positive.

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*In Brazil, where this work was done, the routine method of giving B.C.G. in the field is by the oral route. The dose used is now 100 m.g. in a single dose. This dose is large but is tolerated extremely well. Moreover this method has one great advantage in field work, that no preliminary tuberculin testing is necessary; persons who are strongly tuberculin-positive can take 100 m.g. of B.C.G. orally with no upset whatever. The extra cost of the large dose of B.C.G. is more than neutralized by the saving in time, staff, and work caused by the elimination of the preliminary testing.

For research purposes, and where statistics of the conversion rates are needed, this oral method of administration without preliminary testing is of course useless, except in children within a few weeks of birth, when it can safely be presumed that tuberculin and lepromin tests will be negative.

For field work on a large scale, this method has obviously great advantages. A study of its use in the mass B.C.G. campaigns now in progress in several countries would appear well worth while. At present, lyophilized B.C.G. in this dosage is not available. In Brazil they make their own B.C.G. in this dosage in liquid form, and it has to be used within 25 days. There appears no reason why doses of 100 m.g. should not be lyophilized to keep up to one year. If this could be done, the wide use of B.C.G. might be greatly facilitated.

Their findings therefore indicated that by B.C.G. vaccine given orally, conversions from lepromin-negative to lepromin-positive were more common and also much more persistent than the tuberculin conversions produced by the same vaccination.

Other reports on the action of B.C.G. in converting a lepromin test from negative to positive include those of Rudianski (36) and Dauden Valls *et al.* (37).

PRESENT WORK.

B.C.G. vaccine has been given by intradermal injection of 0.1 m.g. in 63 healthy persons all of whom were tuberculin-negative, and all but seven lepromin-negative before the B.C.G. was given. The tuberculin and lepromin tests were repeated 2-3 months later.

(a) *Very young babies*—13.

B.C.G. given soon after birth. (No preliminary tuberculin and lepromin tests done, presumed negative.)

	Before B.C.G.		After B.C.G.
Tuberculin positive and lepromin positive	nil	—	9
Tuberculin positive and lepromin doubtful	nil	—	4
Tuberculin positive and lepromin negative	nil	—	nil
Tuberculin negative and lepromin positive	nil	—	nil
Tuberculin negative and lepromin negative	13	—	nil
Total	13		13

(b) *Older babies*—8.

	Before B.C.G.		After B.C.G.
Tuberculin positive and lepromin positive	nil	—	3
Tuberculin positive and lepromin doubtful	nil	—	4
Tuberculin positive and lepromin negative	nil	—	nil
Tuberculin negative and lepromin positive	nil	—	nil
Tuberculin negative and lepromin negative	8	—	1
Total	8		8

(c) *Older children*—29.

	Before B.C.G.		After B.C.G.
Tuberculin positive and lepromin positive	nil	—	20
Tuberculin positive and lepromin doubtful	nil	—	6
Tuberculin positive and lepromin negative	nil	—	3
Tuberculin negative and lepromin positive	nil	—	nil
Tuberculin negative and lepromin negative	29	—	nil
Total	29		29

Adults—15.

	Before B.C.G.		After B.C.G.
Tuberculin positive and lepromin positive	nil	—	15
Tuberculin positive and lepromin doubtful	nil	—	nil
Tuberculin positive and lepromin negative	nil	—	nil
Tuberculin negative and lepromin positive	7	—	nil
Tuberculin negative and lepromin negative	8	—	nil
Total	15		15

Totals 65.

	Before B.C.G.		After B.C.G.
Tuberculin positive and lepromin positive	nil	—	47
Tuberculin positive and lepromin doubtful	nil	—	14
Tuberculin positive and lepromin negative	nil	—	3
Tuberculin negative and lepromin positive	7	—	nil
Tuberculin negative and lepromin negative	58	—	1
Total	65		65

Conversions.

Of 65 previously tuberculin-negative, 64 became positive

Of 58 previously lepromin-negative, 40 became positive and 14 more became doubtful

Of 54 becoming lepromin-positive or doubtful, all became tuberculin-positive.

Of 64 becoming tuberculin-positive, 7 were previously lepromin-positive, and, of the rest, 40 became lepromin-positive and 14 more became doubtful. Three cases becoming tuberculin-positive did **not** become lepromin-positive.

The tuberculin conversions were thus more numerous and definite than the lepromin conversions. All the lepromin conversions also showed tuberculin conversions; the tuberculin conversions did not always show a lepromin conversion.

These findings are in accord with the previously recorded findings of the two tests in healthy adults. While it is seen that tuberculin conversions are more numerous, there is evidence (35) that the lepromin conversions are more permanent. It also seems highly probable that the doubtful lepromin tests recorded after B.C.G. are significant.

DOES A POSITIVE LEPROMIN TEST INDICATE IMMUNITY FROM LEPROSY?

The general feeling of experienced leprologists is that it does.

A person who is found lepromin-positive, even after prolonged and intimate contact with leprosy, is practically always free from signs of leprosy, or else the disease is in the mild self-limiting form.

Most workers believe that it is the power to react allergically to the leprosy bacillus, and the immunity which accompanies this phenomenon, which keep the person free from the disease, or, if the disease is acquired, keeps it in the mild form. It must be admitted that the proof of this idea is not complete. Moreover it may be that a positive lepromin test produced as a response to *leprous* infection might indicate immunity to leprosy, but one produced as a response to *tuberculous* infection or to *B.C.G.* might *not* be accompanied by and indicate the presence of immunity to leprosy. These matters are not easy to investigate, but more information is highly desirable.

The only available information bearing on this matter is contained in two reports, one by Fernandez (38) and one by Montestruc and Blaché (39).

Fernandez states " For several years I have had under observation a group of children who were inoculated with B.C.G. after birth and who have continued to live with their leprous parents. As yet, none of them has developed the lepromatous form." This statement would appear to imply that some have developed non-lepromatous forms of leprosy.

Montestruc and Blaché record a family in Martinique in which a lepromatous mother bore children in 1938, 1940 and 1941, and all three children were vaccinated with B.C.G. at birth, and revaccinated at 1, 3, 5 and 9 years. All children have remained with the mother. In 1950 their ages were 12, 10, and 9 and they were healthy, and tuberculin- and lepromin-positive. Four other similar cases are reported in children (1950) aged 12, 9, 7 and 5. All were given B.C.G. at birth and two were revaccinated at one year. All have stayed with the mother and all are healthy. In four other similar children in similar circumstances but not given B.C.G., all have developed leprosy, at the ages of 11 months, 3, 5 and 7 years; three are lepromatous cases. Montestruc and Blaché realise that their numbers are small, but suggest that B.C.G. deserves a thorough trial in the prophylaxis of leprosy.

CAN B.C.G. BE RECOMMENDED IN THE PROPHYLAXIS OF LEPROSY?

Several experienced workers have already given their answer in the affirmative. Their answer is based on the experience already outlined. B.C.G. vaccine is now being widely recommended and used in the prophylaxis of leprosy, especially by French and South American workers, and in coming years much more evidence regarding its value may be produced. Until now, the evidence is meagre and much of it is indirect; arguments are based largely on experience of tuberculosis with the tuberculin test and B.C.G.

But there are eminent tuberculosis workers who consider that the value of B.C.G. in the prophylaxis of tuberculosis is not proved, and a similar situation may be expected among leprosy workers.

Regarding B.C.G. and leprosy, one interesting and possibly vital question arises. I have already outlined the theory of certain experienced workers who postulate that there are a few persons who are inherently incapable of reacting allergically to the leprosy bacillus, and that these exposed to leprous infection become the progressive and infectious lepromatous cases. If this theory is true, and if the inability to react allergically to the leprosy bacillus is inherent and hereditary, then B.C.G. vaccination does not appear likely to overcome it. In other words it is possible that B.C.G. vaccine only " immunizes " those (the majority) who are already potentially allergic and potentially immune and do not need immunization, but fails to immunize those persons (the minority) who are inherently susceptible, and most need immunization.

We have studied four babies whose parents are both known to us as lepromatous cases under our own observation. All four babies were lepromin- and tuberculin-negative. After B.C.G., all four became tuberculin-positive and three lepromin-positive and one lepromin-doubtful. Other workers have reported similar findings to us, personally. It appears that any hypothetical inherent inability to react to lepromin is not acquired by direct heredity.

If *all* children of leprous parents *even if both parents are lepromatous cases*, can be rendered allergic to the leprosy bacillus by B.C.G., the case for the use of B.C.G. in prophylaxis will be considerably strengthened.

We have now reached the following position. A positive lepromin test is generally accepted as indicating some immunity to leprosy. A positive lepromin test is often produced by tuberculous infection as shown by the tuberculin test, and it can also be induced by B.C.G. vaccination. There is no clear indication that there are any persons who cannot be made lepromin-positive by B.C.G. vaccination, repeated and given orally if necessary (this can be done without ill effects, even if the tuberculin test is positive).

So far the position seems fairly clear.

But an important question arises. If tuberculosis immunizes against leprosy, might we not expect all cases of leprosy to be tuberculin-negative, indicating a lack of immunity conferred by previous tuberculous infection? The answer to this question is that while the mild self-limiting forms of leprosy showing immunity (positive lepromin test) might be expected to be tuberculin positive, the severe progressive cases showing no immunity (negative lepromin test) might be expected to show a negative tuberculin test.

Is this expectation fulfilled? The answer is a very definite negative. Lepromin-negative (lepromatous) cases of leprosy show a tuberculin-positive rate little lower than that of the community from which they are drawn, and also as high as or higher than the tuberculoid leprosy cases in the same area. Moreover they frequently show tuberculous infection, and not infrequently die from it. The lepromatous case thus appears to disobey all the rules.

These findings refuse to be fitted into the picture we have been outlining. There are possible explanations or partial explanations. These lepromatous cases may have acquired serious leprosy before they became infected with tuberculosis, and by then it was impossible for the immunity induced by tuberculosis to manifest itself. There is some evidence that tends to confirm this view; for example in some countries it is recorded that lepromatous leprosy usually arises early in life, and that leprosy appearing later is more often mild; but in other countries this appears not to be so. It is doubtful if these ideas explain the anomalies.

It is impossible to discuss this matter fully here. A careful study of the lepromin test, the tuberculin test and B.C.G. vaccination in actual cases of leprosy has been made here and is reported later in this paper. It may however be said that the findings in lepromatous cases are very different from, and hardly reconcilable with, those of studies of healthy persons by the same methods here recorded. Our understanding of sensitivity and immunity in leprosy and tuberculosis is far from complete, and while cross-sensitivity is proved, and cross-immunity seems to be more than possible, there are some facts which cannot yet be reconciled with these ideas.

To return then to our question " Can B.C.G. be recommended in the prophylaxis of leprosy? " The evidence is incomplete and some of it appears contradicatory. There still remains doubt in the minds of some workers whether a positive lepromin test (particularly if induced by B.C.G.) really indicates immunity. Until such doubts can be resolved or confirmed, what is the reasonable attiude to adopt towards the question of B.C.G. immunization with a view of preventing leprosy?

It appears to us that its use, even at the present time, is justified, but that certain conditions should be fulfilled (a) It must not be used indiscriminately, but generally it should be confined to those healthy persons, mainly children, who are unavoidably exposed to leprous infection. (b) In countries where mass B.C.G. vaccination against tuberculosis is being adopted, it may be difficult so to confine its use. In such countries, an attempt should be made to utilize the mass B.C.G. campaign to give evidence of the value of

B.C.G. in the prevention of leprosy. In some areas it may be possible for the B.C.G. campaign to be carried out by the leprosy staff, and to be designed specially to give evidence of its value in the control of leprosy. (c) All work with B.C.G. in countries with much leprosy should be planned, carried out and recorded in such a way that it can, in the future, give reliable evidence on the value of B.C.G. vaccination in the prevention of leprosy. (d) It should be made quite clear to every one concerned that B.C.G. vaccination of those exposed to infection does not remove the necessity for taking every possible step to prevent or minimize contact between open cases of leprosy and healthy persons, particularly children.

B. STUDIES IN PERSONS WITH LEPROSY.

Studies of the lepromin and tuberculin tests in cases of leprosy, and of the influence of B.C.G. immunization on the results of the tests in cases of leprosy, may be of interest. They might give some insight into the question of cross-immunity between the two diseases, and on the causation and significance of a positive lepromin reaction; they might give some indication whether B.C.G. immunization is likely to be of any value in the treatment of leprosy.

RESULTS IN CASES OF LEPROSY.

The results are here recorded in tabular form.

	Tuberculin+ and Lepromin+	T+ and L—	T— and L+	T— and L—
Tuberculoid cases 91	46 (50%)	4 (4.4%)	41 (45.5%)	nil

Lepromin positive 87 (95.6%)
Tuberculin positive ... 50 (55.0%)
The two tests agree in 50% of cases.

	Tuberculin+ and Lepromin+	T+ and L—	T— and L+	T— and L—
Lepromatous cases 275	1 (0.36%)	162 (58.9%)	—	112 (40.73%)

Total lepromin positive ... 1 (0.36%)
Total tuberculin positive ... 163 (59.4%)
The two tests agree in 41% of cases.

DISCUSSION.

The literature on the tuberculin reaction in leprosy is very extensive, and it has been ably reviewed by Wade (40). He found that there were no major differences between the results recorded (a) in healthy persons in the area studied (b) in cases of tuberculoid type, and (c) in cases of lepromatous type. Some reports on work with purified antigens suggested that in lepromatous leprosy there was "evidence of a tendency to a lowered frequency of reaction."

We will first consider *cases of tuberculoid type.* This is the form

of leprosy which is characterized by allergy to the leprosy bacillus and its products as demonstrated by the positive lepromin test. It is a relatively mild form of the disease, and is often self limiting. Histologically the lesions are of " tuberculoid " structure and closely resemble those of tuberculosis in its less acute forms, even in some cases to the extent of the production of caseation.

Early in this century, when what is now called the tuberculoid form of leprosy first attracted considerable attention, it was suggested that this form of leprosy was caused by leprous infection in a person who was also harbouring a tuberculous infection. More recent work already outlined has indicated (a) that this form of leprosy is associated with, and probably caused by, the power of the tissues of the infected person to react allergically to the infection, and (b) that tuberculous infection can sensitize the tissues in such a way as to enable them to react allergically to the leprosy bacillus. It thus appears that the old idea that in the aetiology of tuberculoid leprosy, both infections, leprosy and tuberculosis, may play a part, may contain a grain of truth, and that grain might possibly be quite large. Is it possible that tuberculoid leprosy really is the result of leprous infection in a person who was tuberculin-positive (and therefore usually lepromin-positive) before the leprous infection was acquired?

A study of the lepromin and tuberculin tests applied simultaneously in tuberculoid cases of leprosy should throw light on this subject. If tuberculoid leprosy were the result of leprous infection in a person harbouring and reacting allergically to a tuberculous infection, it would be reasonable to expect that all or nearly all tuberculoid leprosy cases will be not only lepromin-positive (which is so), but also tuberculin-positive. A study of our findings shows that this is not so. In fact the proportion of tuberculin-positives (55.0%) is actually slightly lower than in lepromatous cases (59.4%), and considerably lower than in healthy people in this area (75.2%).

These findings go strongly against the idea that tuberculous infection is always a contributory factor in the causation of tuberculoid leprosy. This does not mean that it is never a contributing factor, although our findings give no clear indication on this point.

The other findings in tuberculoid cases call for little comment. As usual, practically all are found lepromin-positive; moreover a large number of strong positives is found in this group, larger than in healthy persons. The degree of positivity is related to the clinical manifestations of the active disease, past or present. In most of these patients when tested, the disease had been rendered inactive by chemotherapy, but the results of the lepromin test did not appear to be modified markedly. The inactive " major " tuberculoid cases

still showed the strongest reaction, and the inactive " minor " ones a less strong but still definitely positive reaction.

The agreement between the lepromin tests and tuberculin tests is of a low order, agreement being seen in only 50% of cases, for large numbers of cases were lepromin-positive and tuberculin-negative.

The lepromatous form of leprosy, often severe, generalized and progressive, is characterized by anergy to the leprosy bacillus and its products as shown by the lepromin test. It might be (and probably has been) postulated that this anergy is due to the absence of tuberculous infection to make the person's tissues react allergically to the leprosy bacillus, and that the tuberculin-positive rate will therefore be low. A study of our findings shows that this is not so. In fact the tuberculin-positive rate (59.4%) is higher than in tuberculoid cases (55%), although not as high as in healthy persons (75.2%).

It has been stated that in the lepromatous (anergic) form of leprosy, the reaction to tuberculin may be interfered with. On this point the evidence given by our studies is contradictory. On the one hand it is true that the lepromatous cases show a lower tuberculin-positive rate than the healthy persons studied. On the other hand they show a slightly higher rate than the tuberculoid cases. Our studies indicate that complete anergy to the leprosy bacillus (negative lepromin test) may be accompanied by a high degree of sensitization to tuberculin, even the cuti reaction being strongly positive.

As in tuberculoid leprosy, the two tests (lepromin and tuberculin) show agreement in a low proportion, (only 41%), a high proportion being tuberculin-positive and lepromin-negative. These findings might be interpreted as indicating that tuberculous infection has no influence on the way a person's tissues react or fail to react to lepromin. This conclusion would not be justified by the evidence. It should be remembered that, although they predominate in this and other leprosy institutions, lepromatous cases form only a fraction of the total number of leprosy cases in the population (the size of the fraction varying widely in different countries between about 5% and 50%.) Moreover the leprosy cases in countries where leprosy is prevalent form only a fraction of the total actually infected with leprosy, infections often proving abortive. It may be that the lepromatous cases represent that small fraction of the population in whom leprous infection itself, and also tuberculous infection, for some unknown reason completely fail to elicit an allergic response to the leprosy bacillus; some inherent factor necessary to produce this response may be lacking. This is the view

of Rotberg and to some extent of Wade. Thus the fact that lepromatous (lepromin-negative) cases of leprosy may show a strongly positive tuberculin test must not be interpreted as indicating that *in normal persons* tuberculosis infection does not influence the result of the lepromin test. There are many indications that lepromatous cases are only that small fraction of the population which is immunologically abnormal in its reaction to the leprosy bacillus.

On the other hand it may be argued that in lepromatous cases with a positive tuberculin test, the lepromatous leprosy developed first, and the tuberculous infection was acquired later, too late for any allergy or immunity to leprosy to be established. This argument appears rather weak, but perhaps not impossibly so, and it is consistent with the finding often recorded that leprosy acquired early in life is more likely to appear in the lepromatous form than when acquired late in life, for early in life fewer persons have been infected with tuberculosis which may induce immunity to leprosy.

THE RESULTS AS A WHOLE.

We will last consider the results as a whole. The nature of the forms of leprosy called " lepromatous " and " tuberculoid " make pointless any analysis by the methods used above in healthy persons, for lepromatous cases are nearly all lepromin-negative, and tuberculoid cases are nearly all lepromin-positive.

One point is striking; in both the lepromatous and the tuberculoid cases, the results of the two tests agree in only 50% or less of the cases.

Further the following data appear to be of interest.

Of 88 lepromin-positive cases, 47 (53%) are tuberculin-positive while of 278 lepromin-negative cases, 166 (59.7%) are tuberculin-positive.

Of 213 tuberculin-positive cases, 47 (22.6%) are lepromin-positive while of 153 tuberculin negative cases 41 (26.6%) are lepromin-positive.

These findings, in cases of leprosy, give no evidence of any factor operating to make the results of the two tests agree; in fact the findings are consistent with the idea that the two tests are entirely independent. Thus the findings are in marked contrast with those made in healthy persons.

In lepromatous cases the characteristic anergy to the leprosy bacillus is often accompanied by allergy to tuberculin, so the fact that the two tests often give differing results is understandable. In tuberculoid cases, however, no such factor operates, and one would expect that agreement between the two tests would be as much as,

or more than in healthy persons. This expectation is not fulfilled; and there is no obvious explanation.

CONCLUSIONS.

Studies of the tuberculin and lepromin tests in cases of leprosy, in marked contrast to similar studies in healthy persons, give no evidence of any cross-allergy and possible cross-immunity between the two infections.

RESULTS OF B.C.G. VACCINATION IN TUBERCULIN-NEGATIVE CASES OF LEPROSY.

So far we have failed to trace any previous published report on this matter.

It seems possible that such a study might be of interest and practical value. In the first place it might give information on the immunology of leprosy. For example, if lepromatous cases are the result of an inherent inability to react allergically to the leprosy bacillus, and if this anergy is specific for the leprosy bacillus, the giving of B.C.G. in such cases should be expected to produce conversions from tuberculin-negative to tuberculin-positive, but not from lepromin-negative to lepromin-positive. If by any chance conversions from lepromin-negative to lepromin-positive were seen, it would be of interest to see what effect, if any, this would have on the leprosy.

In tuberculoid cases, already lepromin-positive, B.C.G. would be expected to produce conversion from tuberculin-negative to tuberculin-positive, but it would be of interest to see whether the already positive lepromin test was made more strongly positive, and whether there was any change in the leprous lesions which suggested a focal reaction.

It might be that B.C.G. has some value in improving the prognosis and the rapidity of response to treatment by inducing or increasing immunity to leprous infection.

I here summarise the data so far collected in our studies.

(a) LEPROMATOUS CASES.

104 lepromatous cases, tuberculin-negative and lepromin-negative, were given one intradermal injection of 0.1 G of B.C.G., and the tuberculin and lepromin tests were repeated after two months.

Tuberculin tests.

Of 104 previous negative 88 showed a positive reaction
10 showed a doubtful reaction
6 remained negative

104

Lepromin tests.

Of 104 previous negative 11 became definitely positive
19 showed a very slight late reaction (1+)
15 showed a slight early reaction only
59 showed no reaction whatever.

104

The Two Tests Together.

Of 88 becoming tuberculin-positive, 10 also became lepromin positive.

Of 16 not becoming tuberculin-positive, 1 became lepromin-positive.

Of 25 becoming strongly tuberculin-positive (cuti), 7 also became lepromin positive.

Of 79 not becoming strongly tuberculin-positive (cuti), 4 became lepromin-positive.

Of 11 who became lepromin-positive, 10 also became tuberculin-positive.

Of 93 who did not become lepromin-positive, 58 became tuberculin-positive.

CONCLUSIONS.

The definite tuberculin conversions were 88 out of 104, i.e., 84.6%.

The definite lepromin conversions were 11 out of 104 (10.6%), although there were another 34 (32.7%) who showed slight reaction early or late but not enough to be classed as definitely positive.

In general, lepromin conversions were seen only in those who showed tuberculin conversions, and were seen mainly in those with the strongest tuberculin response.

These results show

(a) That lepromatous cases of leprosy show no appreciable inability to be made allergic to the tubercle bacillus by B.C.G.

(b) That lepromatous cases, while they are usually not made allergic to the leprosy bacillus by B.C.G., 10.6% were and another 32.7% showed a slight tendency in that direction.

(c) The anergy of the lepromatous cases is specific for the leprosy bacillus; further it is not absolute, no less than 43.3% showing some reaction early or late, after B.C.G.

(b) TUBERCULOID CASES.

30 tuberculoid cases, all tuberculin-negative or doubtful, and 28 lepromin-positive, were vaccinated with B.C.G.

The results observed were:

Tuberculin tests.

Of 22 completely negative 17 became positive and 5 doubtful.
Of 8 previously doubtful 8 became positive.

Of 30 — 25 became positive and 5 doubtful.

Lepromin tests.

(a) Early response to lepromin.	*Before B.C.G.*	*After B.C.G.*
No response	4	1
Doubtful response ...	13	8
Definite response ...	13	21
	30	30

(b) Late response.	*Before B.C.G.*	*After B.C.G.*
1+	2	2
2+	6	5
3+	13	12
4+	9	11
	30	30

CONCLUSIONS.

(a) The tuberculin conversions were normal.

(b) B.C.G. produced no marked increase in the late response to lepromin.

(c) B.C.G. produced a slight increase in the early response to lepromin.

EFFECT OF B.C.G. VACCINATION ON THE DISEASE.

Early effects on the disease.

No changes in the leprous lesions, or in the general condition of the patient, attributable to B.C.G. vaccination, were observed.

In lepromatous cases, " reaction " might have been expected, for such procedures as small-pox vaccination or TAB inoculation often produce it. The incidence of reaction in our lepromatous cases was not increased by B.C.G. This may have been because B.C.G. has no such effect, or it may be that since our patients had nearly all had prolonged chemotherapy with thiosemicarbazone or sulphone, the relative inactivity of the disease prevented this effect.

In tuberculoid cases, some focal reaction in the lesions might

have been expected, for this is sometimes seen after the injection of lepromin or tuberculin. Such a focal reaction was seen in only one case, and that not very definite, but once again this may be because the infection had been or was being controlled by chemotherapy.

Late effects on the disease.

It is the general opinion that those few lepromatous cases that naturally show a positive lepromin test have a better prognosis than the majority which do not. It is possible that the induction of a positive lepromin test by B.C.G. might improve the prognosis. We have so far made no observations which would confirm this idea, but the time since such B.C.G. vaccination has been very short.

Similar remarks may be made about the tuberculoid cases. We have as yet seen no beneficial effect of B.C.G. vaccine, but most of the lesions had previously been rendered inactive by chemotherapy.

SUMMARY.

The hypothesis that between tuberculosis and leprosy there exists a cross-immunity which may have an important bearing on the immunology, spread, prophylaxis, and epidemiology of leprosy is examined.

The nature of the lepromin test is discussed; a report is presented of the analysis of the results of simultaneous lepromin and tuberculin tests in 359 healthy persons in East Nigeria. The degree of agreement between the results of the two tests is found to be significant; the reason for the high degree of agreement is considered to be that tuberculous infection, as shown by the tuberculin test, makes people sensitive to lepromin as shown in the lepromin test.

The reports of other similar studies of the same subject by other workers in other countries are discussed and analysed in the same way, and give similar results.

The findings are presented of the study of the effect of B.C.G. vaccination on the lepromin and tuberculin tests in healthy persons. Of 65 persons previously tuberculin-negative, 64 were made tuberculin-positive. Of 58 of the same persons previously lepromin-negative, 40 were made lepromin-positive and 14 were recorded as "doubtful." Lepromin conversions were seen only in persons who showed tuberculin conversions.

The question whether a positive lepromin test indicates immunity to leprosy is discussed, and the available evidence is presented; no definite conclusions are drawn, but the findings are considered suggestive.

The advisability of using B.C.G. vaccination of healthy people in prophylaxis in countries where leprosy is common is discussed.

Its value is regarded as not proved, for the evidence is incomplete and some of it is contradictory. Nevertheless the view of Chaussinand " that B.C.G. vaccine deserves to be widely used in areas where leprosy is common and is difficult to control, and where the future extension of tuberculosis constitutes such a terrible menace ' is endorsed, with the proviso that the work should be so planned and carried out that it affords evidence of the value or otherwise of B.C.G. vaccination in the control of leprosy and of tuberculosis, and that the use of B.C.G. shall not be regarded as rendering unnecessary the isolation of open cases from other persons, particularly children.

The findings are presented of a study of the lepromin and tuberculin tests in 366 cases of leprosy, 91 of tuberculoid type and 275 of lepromatous type.

The findings give no evidence to support the hypothesis that previous tuberculous infection renders leprosy mild because it produces some immunity to leprosy. Many tuberculoid cases were found tuberculin negative. Futher no evidence was afforded that in the absence of previous tuberculous infection, leprosy tended to be severe; most of the lepromatous cases were tuberculin-positive.

In general, the study of lepromin and tuberculin tests *in cases of leprosy* gave *no* evidence of cross-immunity between the two infections; this was in marked contrast to the studies in healthy persons. This contrast between studies in healthy persons and those in cases of leprosy is recorded; no attempt is made to explain it.

The effect of B.C.G. vaccination on the lepromin and tuberculin tests in 134 tuberculin-negative cases of leprosy has been studied.

The tuberculin conversions were about the same as in healthy persons, and were seen in both tuberculoid and lepromatous cases. The lepromin conversions (seen only in lepromatous cases for tuberculoid cases were already positive), were definite in 10% and were slight in a further 32.7%. These findings were unexpected, a lepromin-positive lepromatous case being usually regarded as hardly possible, and the term as being almost self-contradictory.

In tuberculoid cases (already lepromin positive), B.C.G. vaccination did not induce any marked increase in the response to lepromin; any increase seen was mainly in the early reaction and not in the late reaction.

B.C.G. vaccination did not produce any focal reaction in the leprous lesions. During the short period that has elapsed, there has not been any accelerated clinical improvement in the lepromatous cases that were rendered lepromin-positive. There is thus no definite indication so far that B.C.G. vaccine is likely to play any part in the treatment of leprosy.

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TUBERCULOSIS AND LEPROSY: MUTUALLY ANTAGONISTIC DISEASES.*

R. CHAUSSINAND, M.D.

"PREMUNITION" TO LEPROSY PRODUCED BY B.C.G. VACCINE.

Tuberculosis and leprosy are two infections which show numerous points in common. Before the discovery of Hansen's bacillus, certain workers, of whom Danielsen was one, had more or less openly expressed the idea that the two infections were really one. Of course there is no doubt that the two infections are quite separate; nevertheless they present so many points in common that they can be regarded as related diseases.

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*(Translation (by J. Lowe) of pp. 146-152 of "La Lèpre" by R. Chaussinand, Head of the Leprosy Department of the Pasteur Institute, Paris, and now Secretary of the Leprosy Expert Panel of the World Health Organization.

"La Lèpre" was published in 1950 by L'Expansion Scientifique Française. The views expressed in the section here translated had been outlined in at least two previous articles.

Since tuberculosis and leprosy are closely allied, the question has arisen whether there might not occur a certain degree of cross-immunity or premunition pertaining to these two infections.

By studying 1,600 cases of leprosy, we satisfied ourselves that a positive Mitsuda reaction to lepromin indicated a condition of relative immunity to leprosy, which showed itself by a marked resistance of the tissues to invasion by the bacilli. Further studies of persons not exposed to leprous infection have shown that such a person infected with tuberculosis, or given B.C.G. vaccine, generally reacts to lepromin; while such a person never infected with tuberculosis and never given B.C.G. vaccine, showed no reaction to lepromin.

These observations recorded in non-leprous persons have been supported by our experiments in animals. Forty guineapigs, 10 rabbits, 6 monkeys, and 2 dogs found tuberculin-negative were also found lepromin-negative. In a similar number of similar animals either infected with Koch's bacillus, or vaccinated with B.C.G. the lepromin reaction was positive.

We have further shown that the normal monkey and the guinea-pig, which are never lepromin-positive, become lepromin-positive after a local leprous infection has been produced by the implant of a piece of leprous nodule.

These findings have led us to the conclusion that immunity to leprosy consists in a state of relative premunition to leprosy, which is the result of a previous infection, either leprous or tuberculous. Since the body infected with tuberculosis appeared to enjoy a certain degree of premunition to leprosy, we considered whether the converse might not be true, that is to say, whether the presence of leprous infection in the human body conferred a degree of relative immunity to tuberculosis.

Rogers and Muir, basing their views on the fact frequently recorded that in advanced leprosy, tuberculosis is a common cause of death, consider that leprosy produces no immunity whatever to tuberculosis. This statement appears to us far too dogmatic. We must always keep in mind the fact that leprosy develops in two markedly contrasting forms, the benign, allergic (lepromin-positive) form and the malignant, anergic (lepromin-negative) form. Further we have found that in allergic leprosy, even in the absence of tuberculosis infection, the intradermic injection of an antigen consisting of tubercle bacilli killed by heat produces a positive reaction; the same antigen injected into healthy persons or into persons with anergic (lepromatous) leprosy produces no reaction. Animal experiments have given identical results. The normal guineapig and monkey show no local reaction to Koch's bacillus killed by heat and

injected locally. Nevertheless, 10 guineapigs and 3 monkeys, in which sensitivity to lepromin had been induced by the insertion in the tissues of a fragment of a leprous nodule, were found to have acquired the power to produce a local reaction to the intradermic injection of such killed tubercle bacilli, although the tuberculin reaction was still found negative.

To summarize; a certain degree of resistance to the tubercle bacillus (bacteria para-allergy) is found in allergic leprosy only. It therefore appears to us that it is only to be expected that persons with anergic (lepromatous) leprosy will not show any protection against tuberculosis infection which can be attributed to their leprosy. On the other hand in allergic (tuberculoid) leprosy, we believe we can postulate a state of relative premunition against the tubercle bacillus; this view is based on (a) biological findings above described and (b) on clinical observations.

In general, tuberculosis constitutes a fatal complication of leprosy only in anergic (lepromatous) cases. Allergic (tuberculoid) cases of leprosy usually manage to overcome the primary tuberculous infection, which shows itself most often only by tuberculin sensitivity or sometimes by cervical gland tuberculosis.

Of over 500 cases of allergic (tuberculoid) leprosy examined, we found only 3 cases of progressive pulmonary tuberculosis with tubercle bacilli in the sputum (as shown by culture or guineapig inoculation). In these cases the clinical and bacteriological evidence of active tuberculosis disappeared within a few months of the institution of an artificial pneumothorax. It appears from these observations that cases of allergic leprosy possess a certain degree of resistance to tuberculosis infection.

Tuberculosis and leprosy are thus mutually antagonistic diseases because one can show that there can exist a state of relative cross immunity, produced by these two infections.

Both leprosy and tuberculosis are chronic infectious diseases. Tuberculosis in man is found to be much more infectious and virulent than leprosy. In any population where these two organisms find themselves in competition, the tubercle bacillus spreads more rapidly and widely. And since a previous infection with the tubercle bacillus produces a certain degree of immunity to leprosy, those persons who have been infected with the tubercle bacillus show a state of relative premunition against a later attack by the leprosy bacillus. The gradual but progressive driving out of leprosy will be the predominant feature, and this will be due to the relative cross premunition produced by these two infections.

The truth of our theory of the driving out of leprosy by tuber-

culosis can be established only by extensive research carried out on the one hand in areas where the spread of leprosy is relatively recent or very marked, and on the other hand in areas where leprosy has declined. The tuberculin-positive rate of the population should be low in regions where leprosy has recently spread. It should be high in regions where it has disappeared. Unfortunately we cannot now produce statistics to prove our theory. All workers on tuberculosis have recognised that the best available statistics are incomplete, and for leprosy, accurate statistics can be considered as non-existent.

In 1925, Rogers thought that a population with a high incidence of tuberculosis infection might enjoy a certain degree of immunity to leprosy. This hypothesis however, based only on epidemiological findings concerning leprosy and tuberculosis, was not supported by experimental work.

Behr visited European and Asiatic countries where leprosy is found, and was able to show that there is little tuberculosis in countries where leprosy is endemic, and, conversely, that regions with widespread tuberculous infection were free from leprosy. He concluded that tuberculous infection does not favour the spread of leprosy.

The spread of leprosy apparently precedes that of tuberculosis, for tuberculosis has not yet attained its peak incidence in most countries of the world, whereas leprosy is markedly declining in many countries. The epidemiological curve of the world incidence of tuberculosis is still in the ascending phase; while that of leprosy is in the declining phase. Moreover it appears that the rise in the curve for tuberculosis has caused, after a longer or shorter interval, the fall of the curve for leprosy.

England and Germany are the two European countries which first attained the peak of the curve of the incidence of tuberculosis (Burnet).	England and Germany were the first countries in Europe in which leprosy disappeared (Rogers and Muir).
The tuberculosis curve for Norway was still rising in 1890 (Burnet).	Leprosy has persisted in Norway until the present time. But in fact it is now markedly declining; in 1856 2,850 cases compared with 16 in 1948 (Melsom).
The Japanese tuberculosis curve is at its peak, and should soon begin to fall; it has been less broad than the curve in European countries. It rose later and more quickly, and came later under the influence of civilization (Burnet). Moreover the tuberculin-positive rate is relatively low in rural areas.	Leprosy is still endemic in rural areas of Japan.

In India, the tuberculosis rate is still rising. The rate is low in rural areas. The people have a poor resistance to tuberculous infection, and the disease frequently takes a rapid course. (Lowe).	In India the leprosy rate is probably beginning to decline. The people show a considerable degree of resistance to leprosy as shown by the predominance of the mild forms of the disease in many areas. (Lowe).
In Indo-China the incidence of tuberculosis has not yet reached its peak. The tuberculin positive rate in the town of Saigon-Cholon is about 60% for children of 10-15 years and 80% in adults. In the provinces a rate of 20% has been recorded for children of 10 years, and 29% for children 10-17 years.	In Indo-China leprosy is widespread. The people show a degree of resistance to leprosy and the benign form is more frequent than the malignant form.
In Oceania tuberculosis is of relatively recent importation. Ziemann recorded that in 1909-1910 of 4,177 persons hospitalised in Nauru only five showed pulmonary tuberculosis.	In Oceania leprosy is very common. In 1920 following the influenza epidemic, a very high incidence of leprosy was recorded in Nauru (Bray).
In West and Central Africa tuberculosis is rare. The tribes without European contacts are practically free (Calmette).	West and Central Africa shows foci of leprosy which are the most active in the world (Rogers and Muir).
Civilization by the development of industries, commerce and means of communication spreads tuberculosis.	Civilization in spite of the development of industries, commerce and communications, makes leprosy disappear.
Tuberculosis spreads first in the towns and later in the countryside.	Leprosy declines first in the towns but can remain endemic for long periods in rural areas.

It follows from what has been written above that the progressive driving out of leprosy by tuberculosis constitutes the dominant phenomenon attributable to the relative cross immunity between these two infections.

Further, since B.C.G. vaccination establishes, as do primary infections with leprosy and tuberculosis, a state of allergy to the leprosy bacillus, it seems logical to utilize B.C.G. vaccine in the prophylaxis of leprosy.

In my opinion, the production of premunition by B.C.G. vaccine, which is not difficult, and can be widely applied, deserves to be widely used in areas where leprosy is common, where the fight against leprosy presents so many difficulties, and where the future extension of tuberculosis constitutes such a terrible menace.

THE TUBERCULIN REACTION

F. R. G. HEAF, M.D., F.R.C.P.

The Therapeutic Substances Act includes under the term tuberculin " preparations of fluid media on which the Bacillus Tuberculosis has been grown in artificial culture and which have been freed by filtration from the bacilli." There are other preparations consisting of bacilli, or products of their disintegration obtained by physical and chemical action, which have at times been called tuberculins, but these substances are now rarely used and by tuberculin we usually mean either Standardized Old Tuberculin (O.T.) or Purified Protein Derivative (P.P.D.) The choice between these two tuberculins lies with the physician. Most of the surveys and investigations on humans in this country have been done with Old Tuberculin and the majority of veterinary work is done with P.P.D. The relative superiority of the one tuberculin over the other is claimed by the respective enthusiasts. It is probable that P.P.D. has more advantages and fewer disadvantages than O.T. and it is possible that in the future it will be used more widely. Whichever tuberculin is used the reaction depends on the specific allergic response of the body tissues to the products of growth of the tubercle bacillus. The specificity of the reaction was in the past generally accepted but recent work has shown that non-specific reactions are not uncommon with lower dilutions of Old Tuberculin, furthermore the borderline between a positive and negative reaction is still too broad, irrespective of the technique employed. There is little difficulty in defining a definitely positive reaction. It can be said to be an induration of 5 mm. or more diameter with the Mantoux technique, induration with three or more vesicles with the Jelly patch flourpaper test, and six definitely indurated papules with the Heaf multiple puncture method. Any reaction less than these is doubtful or negative. With the Mantoux Technique we have to decide the lowest dilution that must be used to exclude a negative reaction. The World Health Organisation has agreed to use as the final test 1/2000 dilution of standardized O.T. (5 International Tuberculin Units) in all tropical countries. The Medical Research Council require 1/100 dilution O.T. (100 I.T.U.) for the final test, and in other countries 30 I.T.U. is the strength of the last test. It is important that in recording the results of the test the type and dilution of the tuberculin are stated and the technique used. The recent work of Edwards and Palmer (1953) shows

that low grade tuberculin sensitivity is associated with geographical factors. They are inclined to believe that there is an unknown non-specific factor that causes low grade sensitivity. It is more likely that the frequency or infrequency of a super-infection resulting from the degree of exposure to infection is one of the factors and that the variation in the character of the skin may be another agent influencing the results they obtained in various countries. The variation of the degree of tuberculin sensitivity with altitude can be explained by this frequent or infrequent re-infection factor as it is directly proportional to the density of population.

The tuberculin sensitivity of body tissue that has been infected with tubercle bacilli can be depressed by drugs, hormones or the products of other bacteria. D'Arcy Hart, Long and Rees (1952) noted that polyoxethylene ethers diminished sensitivity to the same degree but not in the same manner as cortizone. The action of the latter substance is dependent on dietary factors, as it is ineffective in guinea pigs fed on a cabbage diet. A similar depressant action is noted when animals on a diet deficient in ascorbic acid are given free ascorbic acid, but this depressant action is prevented by giving cabbage (Long, Miles and Perry 1951). Variation in tuberculin sensitivity may be noted in pregnancy and puerperium. Thyroxin will also reduce the sensitivity of tissues, whilst indian ink and certain dyes exert a local effect on the capillaries which reduce the inflammatory reaction following the introduction of tuberculo-protein into tuberculous tissue.

The tuberculin reaction is not a simple phenomenon that gives a clear definition on the presence or absence of tuberculous infection. The true positive reaction may be taken to indicate the presence of live tubercle bacilli in the body tissues; a negative reaction does not necessarily mean the absence of such infection. Assuming that the technique is correct a negative tuberculin reaction may occur under the following conditions:—

(a) In the absence of tuberculous infection.

(b) Where tuberculosis infection has taken place but

(1) complete sterilization of the lesion has occurred.

(2) insufficient time has elapsed since infection for allergy to have developed. The development of sensitivity usually takes from three to six weeks.

(3) The disease is so active and advanced that the tissues are saturated with tuberculo-protein.

(4) The sensitivity has been depressed by
  (a) concurrent infections, e.g. measles.
  (b) drugs or hormones.

(5) The tissue refuse to develop sensitivity for some unknown reason. That this occasionally occurs can sometimes be demonstrated after B.C.G. vaccination.

(6) The tissues may have been artificially desensitised by:—
  (a) repeated small doses of tuberculin.
  (b) a single large dose of tuberculin.

This last method of desensitising is being used experimentally as an adjunct to treatment with antibiotics; the theory being that in the absence of sensitivity the fixation of the infecting tubercle bacilli in the tissues with the accompanying inflammatory and caseous reactions will be eliminated, so allowing easier contact of the antibiotic with the bacilli. Much more work will have to be done before this form of treatment can be accepted, as it is at present not without risk of producing progressive lesions which the antibiotic may not be able to control.

Certain factors have to be borne in mind when using the tuberculin test for determining the presence of tuberculous infection. First the possibility of a non-specific reaction arising from the injection of other proteins than tuberculo-protein. The frequency of this can be reduced by using Purified Protein Derivative tuberculin. Secondly the assumption that the skin gives an accurate measure of the sensitivity of the body tissues generally, and thirdly that the skins of all infected people will react similarly to infections of tubercle-protein. The great difference in the sensitivity of the skin of the guinea pig compared with that of the cow makes it reasonable to assume that the skins of different human races and even of individuals of the same race will show varying degrees of response to tuberculin infections.

In routine work the tuberculin reaction is sufficiently specific to be of practical value, but where scientific investigations are contemplated consideration must be given to all the known factors that influence the response of the tissues to tuberculo-protein.

1. EDWARDS, L. B., PALMER, C. E. (1953) *Lancet* i 53.
2. HART, P. D., LONG, D. A., REES, R J. W. (1952) B.M.J. i 680.
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LEPROSY POLICY IN UGANDA

JAMES A. KINNEAR BROWN, M.D., B.Sc., M.R.C.S., D.T.M.

East Africa has always had a place of interest in the news but in recent months it has been unusually and unhappily prominent. In leprosy circles attention has also been focussed on East Africa, of which Uganda is a part, and it may therefore be useful to give my impressions after 12 months of fairly concentrated investigation.

Uganda lies with its southern border on the equator and embracing the northern shores of Lake Victoria. It stretches northwards to the Sudan, westwards to the Belgian Congo, and eastwards to the highlands of Kenya. It has an area of 93,000 square miles, is roughly in the shape of a square and is an undulating plateau some 4,000 feet above sea level. Rather more than one seventh of its surface is swamp or open water. Its climate is tropical but pleasant, the heat of mid-day being relieved by the comparative coolness of the evening and early forenoon. Its people are a heterogenous collection of Bantu, Hamitic and Nilotic origin and whilst the main tribes can be located geographically in well defined areas, the exact pattern is somewhat irregular, reflecting as it does the history of various migrations and the effect of the general labour pattern in the Protectorate. The population is almost the equivalent of that in Kenya, and includes some 5 million Africans, about 50,000 Asians and approximately 5,000 Europeans, the latter being mostly in Government, commerce or mission employment. The municipality of Kampala and townships such as Jinja and Mbale are modern developments indicating industrial and trading concentrations, rather than the natural residential locations of a people with urban habits. The inhabitants are dispersed fairly evenly over the countryside, each family to its plot of land; a picture more rural than England in the days of the stage coach. There are neither villages nor towns but rural parishes and rural boroughs, and these factors, which are of the utmost importance in their influence on every phase of development, must be remembered over and over again when trying to assess and understand East African problems from a distance.

The incidence of leprosy in Uganda has been reasonably estimated by Ross Innes at 80,000 with an overall average of 1·7%. The distribution however has not yet been determined, and because it may help towards an understanding of the epidemiology of the disease, extensive efforts have been made or planned during 1952 to define the incidence in different areas. Impressions of the prevalence of the disease based on those attending for treatment might

give indications, but they can be quite misleading. In one unit of 2,000 people, occupying an area of ten square miles, 19 cases were known to have gone to a settlement many miles away. As proportionately so many had travelled the long distance from this one parish, it would not have been unnatural to imagine that this pointed to an unusually high incidence . In actual fact, a survey revealed only a similar number who had not made the journey, and only three cases that had not been recognised by the chiefs, a total incidence in the parish of 2%, or little more than the general average. Elsewhere there had been some pressure for a new settlement because of the heavy local prevalence but a preliminary survey did not disclose anything more than the average; whereas 25 miles away where there had been little apparent anxiety, a survey revealed an incidence of 5%, the highest figure yet obtained. Much depends on the appreciation of the value of treatment or the degree to which public opinion is leprosy conscious. Such influences may invalidate attempts made to determine the incidence by examining large numbers of people collected at a hospital, dispensary or other convenient place, because if the people are concerned to have their own treatment centre, patients may be summoned from far and near to create an impression; whereas if it does not pay to become recognised only those will attend who are certain they are beyond suspicion.

Similarly in assessing the results of surveys great care has to be taken; as for example in one survey producing the unexpected result of 6% it was found that the area was a place of resettlement after sleeping sickness measures, and being within three miles of a settlement, all the cases were out-patients who had squatted and none were actually native to the locality. In another instance the 3% was made up half of immigrants from other tribes and half of the local populace.

Much of the years' work, as far as surveys are concerned has been spent in developing a technique whereby 100% of representative units, that is, natural parishes that can always be identified and examined again, can be examined in privacy under the best conditions. The dispersal of the population makes it quite impossible even to think of house to house visitation, but it is satisfactory that now in almost every survey it is possible to account for practically every member of the community if not at the first visit, certainly at the follow up, some days or weeks later.

It will take some time to complete the picture for the timing of the surveys depends on many factors, among which may be mentioned the weather, planting and harvesting, and other district activities, and to secure results which everyone will feel satisfied contain as little margin of error as possible, one has to be content

to make haste slowly. Explanations at every point are essential to gain the confidence that is a necessary prerequisite; this itself takes time, time that is well spent, and it may be remarked that the co-operation of the administrative and medical officers has been willingly and unsparingly given.

During 1952 upwards of thirty surveys have been attempted by different methods throughout the country, and whilst some have been preliminary or experimental, others have given results which are felt to be beyond serious doubt. Figures have been obtained as low as 0·4% some around 1%, and a few with values of 2%, 3% and one of 5%. It must be understood that these figures refer not to massive districts but to discreet parishes, occupying areas of perhaps four to ten square miles and with populations of between five and fifteen hundred. Having concentrated deliberately on areas of reputedly high incidence, it is hardly likely that in other similar sized units, in the same districts, any higher figures will be obtained; what may eventuate in districts where work has not yet been atttempted it is not wise to speculate. Side by side, where the chiefs appeared to be quite reasonably accurate with their diagnosis, attempts have been made to appoint African inspectors to the task of examining and visiting every known or suspicious case in much larger units, for checking on some convenient occasion, in order more rapidly to obtain a picture of conditions over wider areas, and to decide whether the figures obtained for the smaller parishes do in fact reflect the general situation.

Apart from the statistical evidence which has been obtained, much time has been spent in conferring both before and after the surveys with the official representatives of the people to explain what has been found and what may be necessary to introduce treatment into the district. These have been very happy occasions, when much of value has been learnt as well as taught, and simply by behaving as good listeners, inferences have been confirmed about the fluctuations of the disease. So far it may be said that there appears to be reasonable evidence that in some areas the disease may be spontaneously dying out, whilst in others the disease constitutes a problem needing greater concentration. There is a general desire to bring the disease under complete control, a desire which is growing as treatment centres are opened and as the scope of the surveys increases. The final statistical picture will take a long time to complete, but the surveys have a more immediately practical value in that they are not only a means of contact and of obtaining confidence in relation to what it is proposed to introduce, but the best method of determining the most tactical points at which to make the introduction. It is as important to establish facilities

where there are the greater concentrations of disease as to avoid being persuaded by any kind of vociferous clamour to dissipate the limited resources where the incidence hardly requires anything very ambitious.

How is the problem to be met? To put all the cases in leprosaria would be counsel of perfection which is quite impossible on the grounds of expense and of the skilled personnel required. To limit the use of leprosaria to lepromatous cases and to children would be an admirable middle course, but this unfortunately is still outside the bounds of what is economically practicable, and such a course would still leave out of account a large number of patients who might need hospitalisation during their treatment. The presence of a number of the more able bodied tuberculoid patients in properly organised leprosaria helps to a greater degree of self-support and therefore to extending the work of the settlement with the same income to a greater number of patients. The limiting factors are economic, and to recognise them and plan accordingly is not to be casual but realistic. If leprosy were the only endemic disease it would not be so necessary to talk about such limitations, but there are unfortunately others which menace the whole population, some in a greater degree, and which threaten the productivity of the people upon which depends the ability to finance the whole of the medical, educational and social programme. It was a consideration of such factors and that the accommodation of the favoured few would not lead to any regression of the disease in the country that led the writer in 1936 after pioneering and organising the Uzuakoli settlement in Southern Nigeria to look beyond settlements for the final answer, and to publish the principles of control that were later adopted. In Uganda the problem is similar, though conditions are different, and whilst its solution will hinge on the effective use of settlements, the problem in the field will require a somewhat modified orientation. From a humanitarian point of view one patient restored to health is an achievement of which one can be justly proud, but what is even more humanitarian is the spreading of all the resources of manpower and money so that the healthy are nowhere at risk and all who need it have treatment available to them. These are the principles actuating present policy by which any other considerations however admirable in themselves, are quite secondary.

Village segregation and village clinics are impossible because as has been stated villages do not exist. The dispersal of the people which may have its own value in restricting the spread of infectious disease, increases the difficulty in applying communal public health measures. To expect patients to travel ten or twenty miles once or

twice a week for months or years is quite unrealistic and to entrust them with a month's supply of tablets is definitely unsafe except perhaps in a very few isolated instances. Segregation in some form secures the rest of the population and makes continuity in treatment a possibility, but segregation must not be imposed from above, so much as induced from below. For this reason the various councils with the African leaders are of value in explaining how partial yet not inconvenient segregation will lessen the danger and make treatment possible through the ordinary medical channels. Posters illustrating the effect on parishes accepting or neglecting this first step are being prepared and it is hoped they will be shortly in wide circulation.

A rigid plan of action which might be applied to the whole of Uganda is unlikely to be fully effective. Even in a country as small as this there are many variations of a tribal and environmental nature and the result of these would be that an inflexible programme would be effective only where it happened to fit. The following are the broad principles which it is considered will allow of the necessary elasticity in application:

(a) The use of the existing settlements insofar as they are geographically convenient, as Primary Residential Centres, to serve as focal points from which will radiate area schemes and to act as training centres for African personnel; together with the establishment of new ones if such are found to be essential. It is hoped that these centres, under a qualified staff, will be able to carry out reliable therapeutic trials and routine histopathological investigations. It is equally hoped that in the course of time their own agricultural development will enable them to support a larger number of patients.

(b) The development of secondary residential centres, staffed by ex-patients and supervised by the Government medical officer with the assistance of the District Commissioner, and the Agricultural and Forestry Officers. Three of these have been begun during the year. They are financed entirely by the local governments, and have a resident chief appointed and salaried by the local government. A fourth has been accepted by the African authority in another district. They are experimental but the early stages of their development have been most encouraging. Whether a European in charge will be essential if they grow beyond their present capacity remains to be seen. So far they are a credit to the officers sponsoring them.

(c) The three centres thus established are on a district basis,

a district being analogous to one of the larger counties in Great Britain. There may be centres for smaller areas, areas which at home would be described as rural parish or borough centres. The principle of these will be that the patients (with their families if necessary) will settle in one part of the area near a dispensary outpost. In other words, this means organised and controlled squatting; but where the family moves, the patient if infectious will need to observe night segregation.

(d) The creation of treatment facilities at existing dispensaries or at specially provided outposts, where owing to land tenure, or for any other reason organised segregation is impracticable.

At every stage the advice of the responsible chiefs is being encouraged as it will be to them that one will have to look for the full implementation of the details. It is a flexible scheme and the wheels will revolve slowly in the beginning, but it is hoped they will gather momentum as experience is gained.

Leprosy work in Uganda, as in most of the Dependencies, has been hitherto very much the responsibility of the missionary societies extensively aided by the Protectorate government, the British Empire Leprosy Relief Association and philanthropically disposed individuals. The capacity of outside organisations to shoulder any more of the burden, however, is becoming severely limited by the various changes which have taken place in the external social structure. Equally the order within the colonies and protectorates has undergone vast evolutionary changes, and whilst Governments have always been anxious to reinforce as much as possible every effort by indigenous populations towards self-help, it is now becoming increasingly necessary as development proceeds to stimulate the people more and more to rely on the fruits of that development for the relief of their own social problems. In this respect the outlook in Uganda is distinctly encouraging and it is gratifying to see indications that the people will be able to appreciate this policy; it is only on this appreciaton and with the salutory discipline of self-help that the vital factor of maintenance may be safeguarded for the future.

I need only add that I am grateful to all the administrative and medical officers of the Government of Uganda and to the representatives of the missionary societies and the British Empire Leprosy Relief Association for their interest and assistance, and to the Director of Medical Services for his encouragement and permission to publish this paper.

THE RECONSTRUCTION OF THE HAND IN LEPROSY

Hunterian Lecture delivered at the
Royal College of Surgeons of England
on
24th October, 1952

by
P. W. BRAND, F.R.C.S. (Eng.)

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Leprosy is a disease which affects chiefly two tissues; skin and peripheral nerves. Through most of his life the patient with leprosy should be a relatively healthy person. His vital organs are not affected, his mind is clear, and his digestion sound. There may be bouts of fever in the acute stages, and distressing complications such as iritis, but these are now controllable by the new drugs which the physician has at his disposal.

The fact is, however, that a large proportion of leprosy patients do not live an active life, and depend entirely upon charity for their maintenance, both during the active phase of their disease and after it has become arrested.

There are two main reasons for this. One is the social stigma of leprosy, which makes employment a problem, and the other is the paralysis and deformity of the hands and feet which often make any skilled trade out of the question, and which may make it difficult for the patient even to feed or to dress himself.

Physicians have long worked to find a cure for the disease, and now, with the help of the research chemists, are able to offer the patient the prospect of the arrest of his symptoms and the probable eradication of the infection. Welfare organisations and missions are working to dispel the fear and superstition that surround the word " leper," and now it remains the obvious duty of the surgeon to see whether the crippling effects of paralysis can be overcome, and the patient thereby allowed to take his place as an active wage earner and independent citizen.

The reason that a serious attempt to reconstruct the hands of leprosy patients has not been made a long time ago is due, probably, to two popular misconceptions about the effects of this disease. One is that its paralysis is haphazardly progressive and has no well-defined limits; and therefore healthy muscles used for transplantation

might themselves later become paralysed and make the operation useless. The other is that leprosy causes fingers to fall off or become absorbed; it is not worth trying to mobilise fingers that may not long remain with the patient.

We need not discuss whether these would be valid reasons for withholding surgery, because we shall try to show that they do not represent the full facts.

The paralysis of leprosy certainly appears to be haphazard in some respects. It may be completely asymmetrical, and it may show periods of rapid progress and of complete arrest which are difficult to explain or to predict, and which seem to bear no relation to the activity of the disease. The paralysis may progress after clinical cure of the disease, and during periods of treatment with the most effective drugs.

However, we have been able to show that in one important respect the paralysis is predictable. It affects only certain nerves and these nerves only at certain anatomical levels. Therefore, when a hand is assessed at any stage in the disease, one may say with some confidence that though certain muscles may become paralysed later, certain others will almost certainly never become paralysed, however far the infection progresses.

We shall not attempt, at this time, to explain the reason for this, but simply append a list of the muscles affecting the hand which, in our experience, are commonly paralysed, and a list of the muscles which we have rarely or never seen paralysed in a series of over a thousand cases of leprosy.

COMMONLY PARALYSED.

All the intrinsic muscles of the hand, lumbricales, interossei, and of the thenar and hypothenar eminences.
Flexor carpi ulnaris.
Flexor profundus to little finger. (Less commonly.)
Flexor profundus to ring finger. (Rarely.)

SOMETIMES PARALYSED (less than 1 per cent.).

All the extensors of the wrist.
The long extensors of the fingers and thumb.
Abductor pollicus longus.

VERY RARELY PARALYSED

Flexor digitorum sublimis, all fingers.
Flexor profundus, index and long fingers.
Flexor pollicis longus.
Flexor carpi radialis.
Palmaris longus.
All upper arm and shoulder muscles.

With regard to absorption, we need only say that we have become convinced from a careful observation of a number of cases, and questioning of many others, that injuries and burns are responsible for almost all of the loss of fingers in leprosy.

The loss of the sensations of pain and temperature make the patients liable to frequent injury, and allow gross carelessness and misuse of wounded and infected fingers. This leads to osteomyelitis and gangrene and loss of digits. (Fig. 1.)

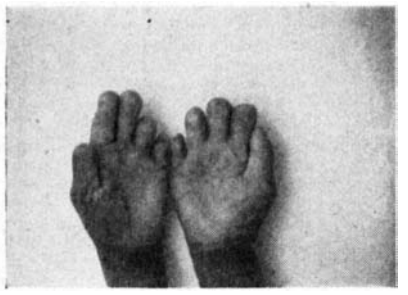


Fig. 1. The hands of an active manual worker, a coolie. These hands have loss of sensation but no paralysis, and have been exposed to repeated trauma and burns. These are still strong and useful hands.

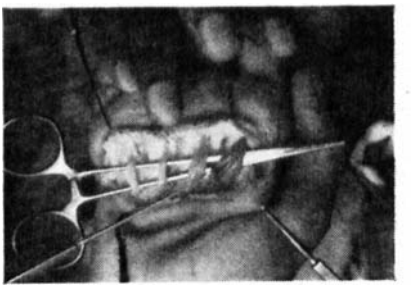
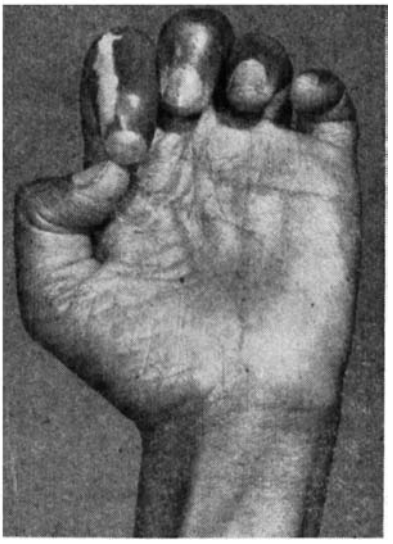


Fig. 2. The lumbrical muscles exposed at operations. The little and ring finger muscles have long been paralysed, the index finger only recently.

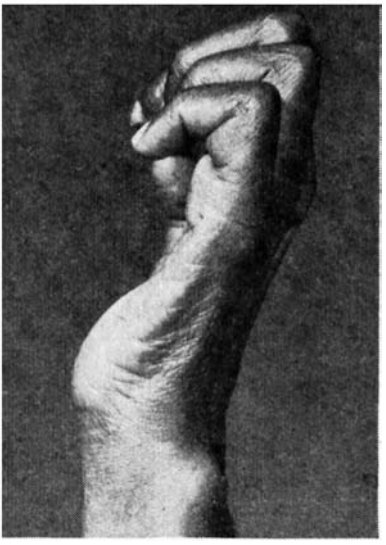
It would be going beyond our evidence to state that in the absence of injury leprosy never causes absorption of fingers, but there can be no doubt that the main causes of absorption are preventable, and that, if the patients can be trained to anticipate and avoid the commoner causes of injury and treat their slight wounds with respect and care, there is no reason why they should not keep their fingers intact.

Hand disability in leprosy begins usually with some anaesthesia to light touch and temperature sensation at or near the ulnar border of the hand. This spreads to involve the ulnar nerve area of the skin and then the median and radial nerve areas, producing an irregular glove anaesthesia extending proximally up to the elbow and beyond. This anaesthesia deepens to include loss of pin-prick and skin pain, and later some deeper sensations, but even in advanced cases patients retain some position sense in their fingers, and are able to appreciate deep pressure and deep pain.

Paralysis commonly first shows itself in the small muscles of the hand, in the ulnar nerve group. The patient becomes unable to adduct the little finger, and then loses power of abduction and adduction in all fingers, and gets clawing of the little, ring and perhaps long fingers. The pinch becomes a little unstable from

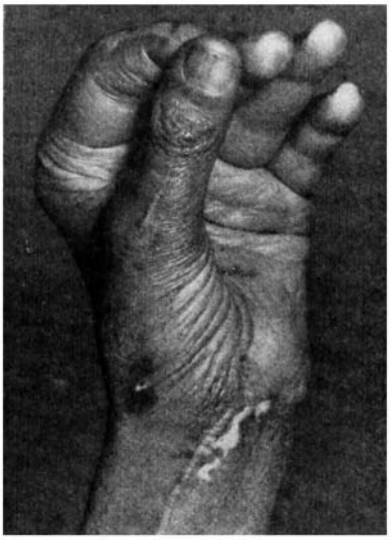


3A

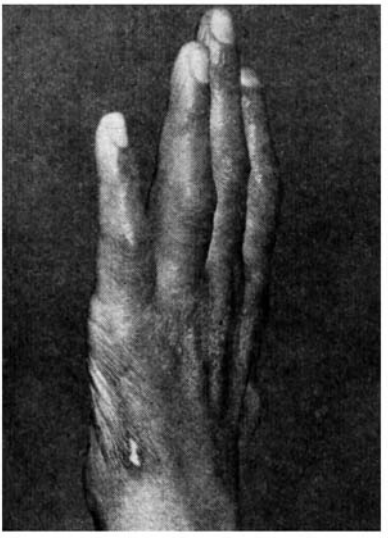


3B

Figs. 3A and 3B. Neural leprosy with complete paralysis of all small muscles of hand. Median and ulnar nerves affected. Typical attempt at pinch.



3C



3D

Figs. 3C and 3D. The same patient three months later, following Bunnell's operation on all fingers, and transplantation of flexor sublimis from ring finger to thumb, passing through pulley at pisiform bone.

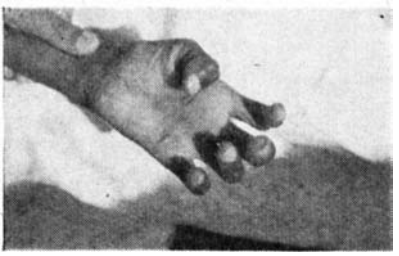


Fig. 4A. Claw hand with thenar paralysis. Attempt to extend fingers and oppose thumb.

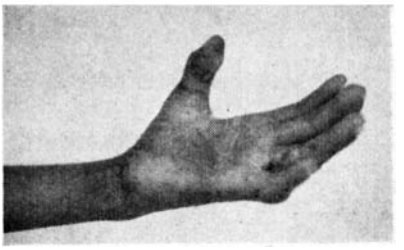


Fig. 4B. Same hand one month later after Bunnell's operation and flexor sublimis transplantation from ring finger to thumb.

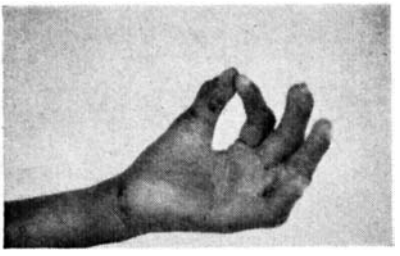


Fig. 4C. Same hand, showing post-operative pinch.

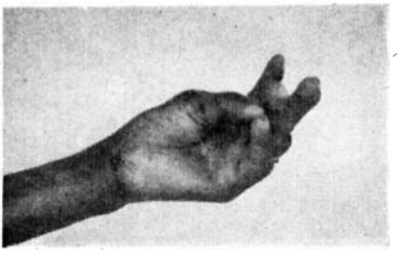


Fig. 4D. Same hand showing post-operative range of opposition.

NEURAL LEPROSY

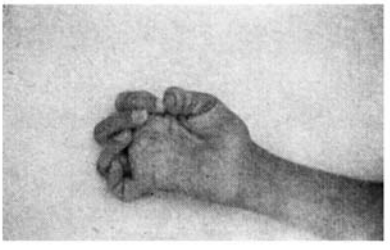


Fig. 5A. Complete claw hand and thenar paralysis of many years' standing. Attempt to extend fingers and oppose thumb.

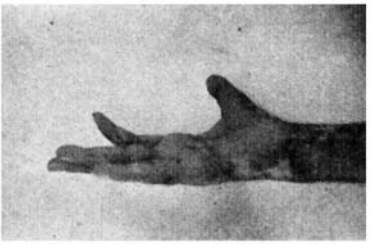


Fig. 5B. Same hand after Bunnell's operation to all fingers and flexor sublimis transplantation from ring finger to thumb.

Fig. 5C. Same hand in grasp position, post-operative.

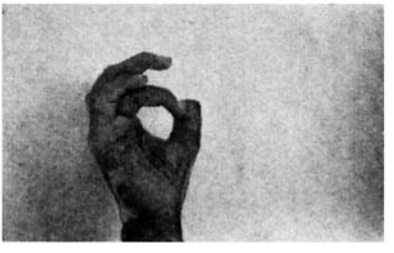


Fig. 5D. Same hand showing pinch, post-operative. Note the interphalangeal joint of the thumb has not been arthrodesed.

loss of the first dorsal interosseus and adductor pollicis and flexor pollicis brevis. When the median nerve becomes affected, the clawing becomes complete in all fingers. The thumb falls back as the thenar muscles are paralysed, and it becomes impossible to oppose the thumb to the fingers in grasp or pinch.

Ultimately there are only three useful functions left to the hand. The first is the closed hook. If some object such as a bucket has to be carried, its handle can be pushed into the curve of the clawed fingers, and the strong flexors will easily maintain the hook position and carry the object. The second is the interdigital squeeze. Small objects like pencils are pushed into interdigital clefts, usually the index-long cleft, and when the fist is clenched, the pencil is held firmly by the adduction that accompanies flexion. The third useful movement is a sideways pinch between the proximal segment of the thumb and the second (index) metacarpal. This is powered by the simultaneous contraction of the flexor pollicis longus and the extensor pollicis longus, and is the most useful movement left to the patient.

The chief disability is thus the loss of the grasp, due to the inability to extend the interphalangeal joints, and the loss of pinch owing to the loss of abduction and opposition of the thumb.

Following paralysis, in the absence of treatment, there develops an increasing stiffness of interphalangeal joints, due to disuse. Chronic sores also develop due to misuse and burns, and to wear and tear of dorsal and interdigital skin which has had to take strains normal to palmar skin.

Once the natural history and pathology of the deformity of leprosy is understood, its surgical treatment may follow the well defined lines that have been worked out by the pioneers of modern hand surgery, such as Sterling Bunnell.

First the superficial sores and ulcers must be soundly healed.

Then the hand must be mobilised as far as possible by a programme of active exercise and physiotherapy, designed to limber up the joints.

Next an operation must be performed for the restoration of lumbrical action, using transplanted long flexors or long extensors; and then an operation for the restoration of opposition to the thumb.

Finally a programme of rehabilitation is necessary.

At the Christian Medical College, Vellore, we have operated upon over 250 clawed fingers, and on 45 thumbs that have lost the power of opposition. Our first cases were done in 1948, and have been followed for four years. As a result of this experience we have reached a few conclusions about the best technique for these leprosy cases.

PRELIMINARY MOBILISATION OF JOINTS.

Metacarpophalangeal joints are nearly always mobile and active already. It is only the interphalangeal joints that give trouble as a rule, and these are often stiff in flexion and may be very obstinate. Active exercise is most valuable, and is best done with the metacarpophalangeal joints stablised in flexion, using the other hand for this purpose, or a knuckleduster type of splint. Passive stretching is especially dangerous in leprosy, because violence may easily be used, even by the patient himself, since pain is not a restraining factor. Elastic traction may be used, provided care is taken that too much pressure is not placed on the pulps of the fingers. We have found it useful to apply a light plaster splint (two layers of Gypsona) to each finger in maximum gentle extension. This is removed in one or two days, the finger exercised, and a new splint applied in what will probably be a few degrees more extension. This may be repeated every two days for a few weeks, as long as improvement is being maintained, and regular exercise continued.

Wax baths and oil rubbed into the fingers at exercise times are probably of value.

PREPARATION FOR OPERATION.

Skin preparation is important, as cracks, sores, and scabies are common when the hands are first seen. These must all be soundly healed before surgery is attempted. We have sometimes operated on the hands of a patient who still has unhealed ulceration on the soles of his feet, provided that the latter are clean and healing. In these cases the feet are covered with occlusive dressings, and not exposed during the days of hand preparation, and penicillin is given to cover the operation and post-operative period.

We have not found that operations cause any flare-up of leprosy, except in a few cases where there has been prolonged general anaesthesia, and even in these cases the reaction has not been severe. It is probably wise to continue the routine sulphone or other therapy throughout the operative period. We have operated on lepromatous as well as on neural cases, but have avoided operations during acute phases of the disease.

A pre- and post-operative vitamin supplement, at least of B complex and ascorbic acid has been given.

ANAESTHESIA.

Brachial plexus block anaesthesia has been used in nearly all cases. The partial loss of pain sensation that most patients already have has probably contributed to the uniform success which we have had with this method. The only complaint that patients make is of tourniquet discomfort, and if this becomes severe a gas and oxygen or pentothal supplement has to be given.

GENERAL SURGICAL TECHNIQUE.

A bloodless field is, of course, essential, and a pneumatic tourniquet should be used. It is probably wise to keep the pressure below 225 mm. and to release it at the end of an hour or hour and a quarter, as the nerves in leprosy are harmed by prolonged ischaemia. The tourniquet may be reapplied for a second period if necessary. The importance of fine instruments and an atraumatic technique has often been stressed by hand surgeons, and is not less important in leprosy cases. It is also important that all parts of the operation should be carefully planned and that a fairly speedy technique be developed, because the average leprosy hand requires five tendon transfers, and often an arthrodesis as well. The only alternatives are a rather prolonged operation or else repeated operations on the same hand, with increased scarring and long hospitalisation. For any but an experienced hand surgeon it would be wise to operate on two fingers at a time, and on the thumb at a separate session. With increasing experience all five digits can conveniently be operated at one session.

Healing is probably rather slower in leprosy cases and skin stitches may be left in for 14 days. If Bunnell's pull-out wire technique is used the wires should be left in for longer than is advised for healthy patients. Most of our patients are mal-nourished, and part of the delay in healing may be due to this.

Great care should be taken in applying any sort of pressure bandages after operation. Superficial skin necrosis has occurred in some of our cases, under ace bandages that would not have been considered too tightly applied for healthy orthopaedic cases. We have now given up pressure dressings, and use only light plaster splints over gauze dressings, and depend on continuous high elevation of the limb to prevent oedema.

Plaster and other splints must be moulded with extra care because of the patient's inability to appreciate pain or discomfort on excessive pressure. For this reason we prefer light plaster splinting even to the most malleable of metal splints, as only the former can be moulded with finger tip gentleness and precision.

CHOICE OF OPERATION.

1. *For clawed fingers.* We have used two operations for these fingers; Bunnell's sublimis transplantation is the operation of choice for suitable cases, and interphalangeal arthrodesis for the fingers with stiff joints.

Patients are usually offered operation as soon as they themselves feel the need for it, that is when they find that their fingers will not open far enough to grasp the objects which they commonly use.

Nothing is lost by waiting and exercising, but there is always the fear that exercises will be discontinued, and then stiffness may begin and soon become irreversible.

There is a simple test that decides whether Bunnell's operation will benefit a finger. The metacarpophalangeal joint is passively flexed by pressing the proximal phalanx forwards from the dorsal surface and then the patient is instructed to extend the inter-phalangeal joints. The extent to which he then succeeds in straightening his finger is about the extent to which Bunnell's operation will enable him to do it without help.' If he makes a strong attempt, but does not get very far, it is worth sending him back for further exercises, and physiotherapy, and then a second test may be made. It is very important to keep records of the range of joint movement at each stage of progress, measured with a protractor which has a swinging arm. Even very good guesswork on angles can be quite a long way out, especially if a different surgeon makes the second assessment.'

Bunnell's operation is well worth doing even if the best that a patient can do is well short of a straight finger, because the chief disability of clawing is not so much the failure of the finger to become straight, but that it begins its flexion movement by closing its interphalangeal joints before its metacarpophalangeals, i.e, it curls up into the palm already clenched. This feature of the clawed finger is completely cured by Bunnell's operation even when absolute straightness is not achieved.

We have found, however, that, if the patient is not able to extend his finger beyond 90 degrees at the proximal interphalangeal joint, even when his metacarpophalangeal joint is stabilised, then Bunnell's operation is usually a failure. It is in these cases that we advise inter-phalangeal arthrodesis.

In a few cases the impression may be gained that the skin is the chief obstacle to extension, and then a Z-plasty may give a better extension, or a flap of dorsal skin may be turned volarwards, but our results in these cases have been disappointing. Arthrodesis gives a strong useful hand, so is really the operation of choice for flexion contractures.

The angle for arthrodesis depends upon the trade which the patient is to follow, but for carpenters and most manual workers we like an angle of 90 degrees for long, ring, and little fingers to give a grasp against the palm, and a wider angle for the index finger to meet the pulp of the thumb in a pinch. This angle should be decided after the thumb has been reconstructed and may be about 130 degrees.

The proximal interphalangeal joint is the only one that usually

needs to be arthrodesed, but if the terminal joint is too sharply flexed that may be fused as well.

In Bunnell's operation a midlateral incision is made on each side of each finger, from the web down to the proximal interphalangeal joint and the edge of the extensor expansion is defined. The lumbrical tendon is exposed and its canal identified. The flexor sheath is then opened near the interphalangeal joint and the flexor sublimis tendon divided near its insertion. It is split back to where it surrounds the profundus tendon, and released.

The palm is opened by a transverse incision just proximal to the distal crease, and the sublimis tendons withdrawn into the palm, and the two halves split back for about 2½ inches. The lumbrical canals are opened up from the palmar end and each strand of sublimis tendon is passed down a canal to one side of a finger. Each half is pulled into the finger incision, passed through a slit in the lumbrical tendon and sutured to the dorsum and edge of the extensor expansion, just proximal to the joint.

Bunnell advises that each half of each tendon should be inserted into the same side of two adjacent fingers, that is, the index finger sublimis should go to the lateral side of the index and to the lateral side of the long finger, while the sublimis from the long finger might go to the medial side of the index and the medial side of the long finger. This is so that a certain amount of side to side movement may be obtained.

Details of anatomy and operative technique are fully described in Bunnell's " Surgery of the Hand " and it is not our purpose here to discuss any operative procedures in detail, but simply to establish the principle that such procedures are applicable to patients with leprosy.

We have introduced a few minor modifications of technique into this operation, the most useful of which was suggested to us by Dr. William White when he visited us. We now operate on only one side of each finger and attach the tendon transplants only to the radial side of each finger. We find that it gives us the following advantages: (1) A saving of tendons for transplantation. We use the index finger tendon for the radial side of the index finger, the long finger tendon is split and used half for the long finger and half for the ring finger, and the little finger tendon is used only for the little finger. This leaves the ring finger sublimis for use on the thumb for the restoration of opposition. (2) A great saving of time. Four incisions are eliminated. (3) A better stabilisation of the index finger against adduction strains in pinching. The loss of side to side movement does not seem to be important, as we had not been very successful in educating our patients in lateral movements of the fingers even with the original technique. The loss of fine movements

is in any case not so serious when there is loss of sensation in the hands, because the patients are unable to use fine varied movements in their trades owing to the clumsiness that comes from loss of touch. They do most of their work through the medium of tools, and therefore we concentrate on the production of a strong simple grasp and pinch. The radial deviation that might be expected to result from this one sided operation has not, in fact, been observed, whereas there were one or two cases of ulnar deviation seen among the earlier cases that had the original procedure.

2. *For restoration of opposition to thumb.* In the operation to restore opposition to the thumb it is important that the following of Bunnell's rules should be followed. The new tendon should run from the base of the proximal phalanx towards the pisiform bone or to a point about half an inch to its radial side. The new tendon should run in a sub-cutaneous tunnel. It should cross the summit of the metacarpophalangeal joint, or at least a point dorsal to the fulcrum of the joint (the tendon of insertion of the abductor pollicis brevis is a good landmark of this fulcrum). With regard to the choice of tendon and the point of its insertion, and other matters, Littler has given a fine exposition. We are in full agreement with him that the flexor sublimis to the ring finger gives a far better result than any wrist flexor, or palmaris longus, both because of its better range of excursion and because a tendon suture at the wrist level is avoided. The point of insertion may be into the bone on the ulnar side of the base of the phalanx, or into the extensor longus tendon just distal to the joint. It is probably an advantage to suture this tendon under somewhat greater tension than normal.

We have no new contribution to make on the subject of the shrinkage of the thumb web in long-standing cases, and the transposition of the extensor longus pollicis tendon when it restricts opposition. These matters are dealt with fully in the literature.

It is well known that in complete small muscle paralysis of the hand the power of extending the terminal joint of the thumb becomes lost, following the loss of the stabilizers of the proximal joint. We do not think it has been sufficiently emphasised how disabling this can be. The position of function of the thumb is usually pictured as making an O between thumb and index finger. In actual fact the O position is rarely used except in picking up small objects off a flat surface. The normal position of function of the thumb is with the terminal joint in extension for pinch and very slight flexion for grasp. The pinch with the terminal joint flexed is not strong, and is particularly unstable when sensation is imperfect. It is finger-tip pinch instead of a pulp pinch.

In early cases some power of extension seems to return to the terminal joint after an operation for opponens replacement, but in

later cases it does not return, even if the new tendon is inserted into the extensor longus tendon. In these cases we find the thumb is much more useful if the terminal joint is arthrodesed in extension.

In the exceptional cases in which the extensors of the wrist and fingers are paralysed, the radiocarpal joint should certainly be arthrodesed and wrist flexors used for finger extension.

Partial loss of digits from previous injuries need not deter the surgeon from reconstruction of the rest of the hand. In fact hands that have suffered some absorption will often be found to belong to the most keen and active patients, with fairly good forearm muscles. It is their strength and activity that has exposed them to the hazards of injury. The grossly paralysed hand often has intact digits, because the paralysis has prevented any active use and exposure to trauma.

It is quite exceptional to find a hand so damaged or paralysed by leprosy that it is not possible to restore some useful grasp and pinch, and it has been encouraging to find that, in cases in which attempts have been made to reconstruct very bad hands, subsequent use has resulted in still further improvement, and has well justified the intervention.

REHABILITATION.

When all tendon transfers are completed a leprosy patient is left with a fairly mobile, active hand, with fair strength in grasp and pinch, and with position sense, but without cutaneous sensation.

Such a hand is clumsy in fine movements, and easily damaged, especially by burns.

Patients on discharge are liable to get quickly discouraged finding that they cannot even now compete with healthy workers, and soon return to their old occupation of begging.

It is of great importance that in the post-operative phase the patients should be shown how to make the best use of their hands and be taught trades in which their skill and dexterity may compete on equal terms with others with normal hands.

We have studied this matter with some care, and our experience is that these patients do well in a trade or craft in which all the work is done with tools and handles, and none or very little with direct finger manipulation. Basket making, at which blind people excel, is an example of a completely unsuitable trade, as so much of the weaving depends upon touch reflexes.

Simple carpentry is quite within the power of most patients, provided some care is taken to see that the handles of all tools are adjusted where necessary to fit the strongest part of the grasp. Handles of a diameter of one to one and a half inches are usually good for chisels and screwdrivers. Pliers and forceps should be

fitted with springs to keep the handles open about three inches apart, and be about an inch or an inch and a half apart when closed. Scissors, similarly, should have the ring handles removed and simple spring-open grasp handles fitted. All tools should be kept on a rack above the bench with the handles projecting, so that time is not lost in fumbling to pick up tools from a flat surface.' Nails and screws should be kept in racks, and handled with forceps rather than fingers. If small machines such as jig-saws can also be supplied to do tedious parts of the work, then these men are well able to produce good work at a speed which will enable them to earn their living.

There are many other trades which may be similarly studied and adjusted to become suitable for hands without sensation.

At the same time that the trade is being taught, the patient must also be helped to understand the need for care of his hands.

Every day his hands should be inspected for small cuts or abrasions. If any are found, their cause must be sought, and explained, and their recurrence avoided. A simple first aid dressing box, preferably using ready cut adhesive dressings should be kept in the homes and workshops of all patients, and the danger of continuing to use an infected finger emphasised.

If the rehabilitation team enters with sympathy and enthusiasm into this matter of care of the hands, and regards with real horror and distress the small injuries that the patients tend to ignore, then it will be found that the patients themselves will soon develop a new respect for their hands. They will begin to take a pride in the fingers which they had previously tried to hide, and will take trouble to avoid the trauma which previously had not bothered them because it did not hurt.

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SIXTH INTERNATIONAL CONGRESS OF LEPROSY

Under the patronage of the Government of Spain and the International Leprosy Association, the Sixth International Congress of Leprosy will be held from 3rd to 10th October, 1953, in Madrid. The meetings will take place in the *Esquela de Estomatologia* (School for Ear, Nose and Throat) situated in the University City. His Excellency the Head of the State has accepted the Honorary Presidency of the Congress. A national Organisation Commission has been constituted, of which His Excellency, Sr. Dr. José A. Palanca is the President, Dr. D. Felix Contreras Dueñas, the Secretary, and Sr. D. Manuel Ambles Pipo, the Treasurer. The Foreign Ministry has sent, through its embassies, official invitations to all Governments with which it has diplomatic relations, asking them to appoint official delegates to the Congress.

Apart from these official invitations, the National Commission is inviting all who are interested in a practical way in the study of leprosy, and sending with the invitations a form for completion and return to the office of the Congress (Esquela Nacional de Sanidad, Ciudad Universitaria, Madrid) before the 30th of June.

The great importance of this Congress is shown by the official subjects which will be debated, the most important of which are: *Revision of Classification; Treatment of Leprosy; Immunology in Leprosy; Control of Leprosy.* The last of these will include any communications which deal with *Epidemiology* and *Social Organisation.*

Before the opening of the Congress an Executive Committee will be formed, which will include members of the International Leprosy Association and of the National Commission. It will plan and explain the arrangements before the beginning of the meetings, and at the first session will ask for confirmation or modification as may be agreed upon. During the course of the Congress various committees will be created to study and formulate the different problems which arise at the combined sessions.

Likewise there will be an Exhibition to which all members of the Congress are invited to send exhibits, such as drawings and cinematograph films. All such exhibitors should communicate with the local Secretary before 30th June, mentioning the nature and size of their exhibits.

All scientific works which are to be presented at the Congress should include a resumé of 200—300 words, which should give a clear understanding of the matter dealt with. The resumé should be sent before the 30th of June to the Secretary of the National Commission, Dr. Felix Contreras Duenas. Those resumés received after that date cannot be published. Complete copies of each work should be delivered at the Secretary's office before the beginning of the Congress on October 3rd.

So that the scientific sessions may function as well as possible, it has been agreed that 10 minutes should be allowed for the reading of each paper, and 5 minutes for each member who desires to take part in the discussions. Five minutes will also be allowed for a reply by the reader of the paper. To facilitate the understanding of the works presented in different languages, the Congress has arranged for the service of a number of interpreters and the instalation of a modern simultaneous translation service. Spanish, French, English and Portuguese have been adopted as the official languages of the Congress.

The definite programme of the Congress has not yet been drawn up, but it will be published in sufficient time before the inauguration. We can say beforehand, however, that in addition to the working sessions there will be various social functions arranged by the Foreign Office, the Municipal and Provincial authorities of Madrid, the Institute of Spanish Culture and the *Patronato Social Antileproso* etc.

The Administration of Spanish Railways has made a concession of 20% to all members of Congress, and the French Railways have similarly made a rebate of 20% in their communicating lines. It is necessary for all members of Congress who wish to make hotel reservations to pay a deposit of one day's charge. Also at the time of registering as a member of Congress, the registration fee must be paid. The National Commission has appointed as official travelling agencies The American Express Company for America, Canada and the Philippines, and Wagon-Lits Cook for the rest of the world.

All persons who wish to attend the VIth International Congress of Leprosy, and have not yet received a registration bulletin, should communicate with the General Secretary, Dr. Felix Contreras, Esquela Nacional de Sanidad, Ciudad Universitaria, Madrid.

REVIEWS.

International Journal of Leprosy, Vol. 20 (1952) July-Sept.

Tratamiento de la Reaccion Leprotica (Lepro-reaccion Lepromatosa) con Plasma by F. Contreras and others.

In the English summary the writers state:—

' In other diseases of a serious nature for which also no effective treatment has been found, treatment with blood plasma or other fractions of denatured blood has been employed. Of the blood fractions it seems that the gamma globulin is the richest in immune bodies and it might be useful in the treatment of the reactions in leprosy. Twenty-two patients with advanced lepromatous leprosy who had frequent lepra reactions were given 85 transfusions of " iso plasma " (plasma from disanaphylactisized calf blood). Tolerance to this treatment was found to be fairly good. Twelve of the patients tolerated the heterologous plasma perfectly. Six had slight side effects of no importance. In four cases there were serious although shortlived ill effects of allergic nature. All patients treated showed improvement. The best results were seen in patients who had nausea, vomiting and intolerance of all kinds of food, which condition yielded rapidly. Persistent and repeated epistaxis also ceased quickly. Great improvement was seen with respect to neuritis, manifestations in the skin and mucous membranes, the general condition, and the fever, which in some instances subsided after the first transfusions while in others its subsidence occurred after the other symptoms disappeared.

Changes in the Anterior Nasal Spine and the Alveolar Process of the Maxillary Bone in Leprosy by V. Møller Christensen and others.

The first writer noticed a marked atrophy of the alveolar process of the maxillary bone and also atrophy of the anterior nasal spine in 110 of 150 skulls of leprous patients buried in the Naestved, Sct. Jorgensgaard between 1260 and 1540 A.D. in addition to the typical changes in the hands and feet. He assumes that this atrophy is typical of leprosy and calls it " Facies Leprosa ". Seven living patients with leprosy were studied and in five X-rays showed atrophy of the ant. nasal spine and all seven showed atrophy of the alveolar process of the maxillary bone but this was probably due to earlier loss of teeth. No changes of sensitivity were found which might indicate that the atrophy was due to neurotrophic disturbance of the bone. They consider that atrophy of the ant, nasal spine may be an early manifestation of leprosy and may be demonstrated by X-ray or palpation.

Changes in the Lepromin and Tuberculin Reactions of Lepromin-Negative Patients after Vaccination with B.C.G. by J. Convit and others.

The writers believe that the prognosis in persistently lepromin negative lepromatous cases can be improved by the previous vaccination with B.C.G. A group of 113 patients with lepromatous leprosy whose lesions had disappeared under diasone or promin treatment were given B.C.G. vaccine. Of these patients 51 were negative to tuberculin and 62 weakly positive. Of the 51 cases negative to both tests 25.4% became positive to lepromin after B.C.G. vaccination, and of the 62 who were negative to lepromin but weakly positive to tuberculin 53.2% became lepromin positive.

In a group of 40 patients with the indeterminate form of leprosy who were negative to both tests the lepromin reaction became ositive in 87.5%.

A Nonchromogenic culture of an Acid-fast bacillus isolated from the nasal mucus of a leprosy patient; Its virulence for laboratory animals by H. C. de Souza-Araujo.

This paper describes the isolation and cultivation of an acid-fast coccobacillus obtained from the nasal mucus of a young Brazilian woman leprosy patient. The culture called " Dalva " strain after her produced generalised infection and considerable lesions in guinea-pigs, black mice and cebus monkeys. In the original culture on Loewenstein's medium the germs were predominantly coccobacilli but became bacillary in the lesions in the laboratory animals. The bacilli were strongly positive to the Dubos test, as strongly as the Koch bacillus, but did not produce tuberculous lesions in guinea pigs. At first the culture could not be recovered from the experimental lesions but in a addendum to the paper the writer says that in further experimentation a cebus monkey was reinoculated on Jan. 15, 1952 with a suspension of a two-month-old culture grown on 5% glycerin-agar and nodules developed which were very rich in acid-fast bacilli. From these growths were obtained on Loewenstein's media similar to the original Dalva strain.

The Mechanism of action of the Sulphone derivatives in Lepromatous Leprosy by Paulo Rath de Souza and M. de Souza Lima.

This is a very interesting and provocative paper. In their descriptions of the fundamental lesions of lepromatous infiltration and lepromata they state that both are formed essentially by variable numbers of histiocytic (Virchow) cells assembled together and sometimes forming tumour like masses. Within these cells are found the agent of the disease, Hansen's bacillus. These lesions do not last indefinitely but undergo regression either after treatment or spontaneously and when complete leave only scars. The Virchow cells in regression are definitely swollen with a pycnotic nucleus and a cytoplasm with a great number of rounded vacuoles of various sizes which give them a foamy appearance. After staining with scarlet red these vacuoles are seen to be filled with lipids. These cells in regression contain few of rare acid-fast bacilli of granular appearance and they may contain no bacilli whatever. Virchow cells which are not in regression are smaller than those in regression. They have a vesicular nucleus and their cytoplasm is contrary to what is currently believed, is not vacuolated and still less is it foamy. They are fairly simple macrophages of a wide variety of shapes and forms. They are seen teeming with typical bacilli forming globi. The quantity of lipids found is in general inversely proportional to the number of bacill. G. O. TEICHMANN.