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TUBERCULOSIS AND LEPROSY: IMMUNOLOGICAL STUDIES IN HEALTHY PERSONS

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For more than 20 years some leprosy workers have entertained the idea that persons who, as the result of an abortive primary infection, 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 paper by Fernandez (1939a), several workers have reported that B.C.G. vaccination of healthy persons 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 (1943) 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 from this measure are already being reported.

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 the chief is Chaussinand (1950), think that this cross-immunity between leprosy and tuberculosis is of profound epidemiological importance. This cross-immunity is believed to make leprosy and tuberculosis act as antagonistic diseases. A study of the history of leprosy and of tuberculosis in the world as a whole, and in individual countries, shows that leprosy is the earlier disease to spread, that tuberculosis appears later and spreads, and that leprosy then declines and finally disappears. This decline and disappearance of leprosy is thought by Chaussinand to be caused by the spread of tuberculous infection, making the population relatively immune to leprosy. Chaussinand quotes a large number of reports from different countries that the spread of tuberculosis is accompanied or followed by a decline in leprosy. He, and others, think that B.C.G. vaccination should in the future have the same effect in causing a decline in leprosy as he believes the spread of tuberculosis to have had in the past. He advocates the use of B.C.G. in the control of leprosy and of tuberculosis in countries where leprosy is still common "and the future extension of tuberculosis constitutes such a terrible menace." Such countries include most of Africa and much of Asia and South America.

These theories of Chaussinand seem so revolutionary as to provoke an immediate reaction of scepticism and adverse criticism. Careful consideration, however, is justified. The evidence Chaussinand quotes is, as he realizes, not conclusive, but it is strong. These theories, if confirmed, would throw a flood of light on the epidemiology of leprosy, which is very obscure, and would help to explain facts hitherto quite inexplicable—for example, the marked decline of leprosy in Europe between A.D. 1400 and 1800, the difficulty with which leprosy now spreads in European countries where it used to flourish, and so on.

This matter cannot be pursued here; it is mentioned to make it clear that we are discussing matters of great theoretical and practical interest and importance.

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, 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.

The Lepromin Test

The lepromin test constitutes the results of attempts of many workers over many years to develop in leprosy 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 the disease. In leprous nodules the bacilli are very numerous, counts as high as 1,000 million per

cubic centimetre of tissue having been recorded by Hanks (1945). 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 in addition to bacilli tissue cells, fluids, and lipoids; but the antigenic material is the bacilli.

The lepromin test was originated by Mitsuda (1916, 1924), who in 1916 found that when a suspension of leprosy bacilli was injected intradermally a nodule developed in two to four weeks and then slowly subsided. In many healthy children the result was negative; with increasing age many healthy persons became positive, even in the absence of exposure to leprous infection; in the benign ("tuberculoid") forms of leprosy the test was almost invariably positive; in the malignant ("lepromatous") forms of leprosy the test was almost invariably negative. A positive test has long been accepted as indicating a degree of immunity to leprosy, the nature of that immunity, however, not being clear. The test is of very little value in diagnosis, but is useful in prognosis.

The nature of the reaction and the anomalous features of the reaction—(1) the lateness of the result, (2) the positive results in non-contact adults, and (3) the negative results in malignant (lepromatous) leprosy—have been the subjects of special studies.

Nature of the Positive Response to Lepromin

In brief, three different theories have been held by different workers. A few—for example, Bargehr (1926) and Rotberg (1937)—have regarded a positive test as being caused by specific allergy to the leprosy bacillus and its products of disintegration. This view appears no longer tenable and now seems to have few, if any, supporters. Rotberg himself has changed his mind on this matter.

Others have considered a positive reaction to be neither allergic nor specific, but think that a positive reaction is 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 (1939b, 1940) showed that a positive late response (two to five 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—for example, Lowe and Dharmendra (1941)—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 caused by free antigen present in the lepromin and the late reaction by slow liberation of the same antigen from the bacilli by slow disintegration at the site of injection. These findings were supported by histological studies. Fernandez, however, interpreted his findings as indicating two antigens, one active at 24 to 48 hours, and the other at two to five weeks.

Wade (1941, 1950) expressed still another view of the mechanism of the late reaction. He thought that in some persons—for example, non-contacts—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 two to five weeks later by reaction at the site of injection, where bacilli were still present. Persons who were not even potentially allergic showed no such reaction.

Ideas rather similar to those of Wade in certain respects have been expressed by other workers, several, including Fernandez (1943), having considered that some inherent constitutional factor influenced the results of the lepromin test. For example, Rotberg (1937) thought that many people, probably the 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; in that connexion they are discussed below.

There still seems to be no unanimity of view among leprosy workers regarding the nature and mechanism of the reaction to lepromin. Fernandez, Lowe and Dharmendra, and 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 in 1942 he developed a method of completely separating leprosy bacilli from leprous tissue, and preparing lepromin which could be standardized by weight. Moreover, he (1941) 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; and 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 (1943) failed to find any fraction of the leprosy bacillus which when injected gave a response only in cases of leprosy and in contacts. They and others regarded 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 below, supports this idea.

This, then, is the present position of the lepromin test. It is regarded as allergic, but non-specific or rather group-specific, and of value mainly in classification and prognosis. The injection of lepromin can produce two responses—an early (24 to 48 hours) response of tuberculin type (the Fernandez phenomenon) and a late (two to five weeks) response of nodular type (the Mitsuda phenomenon); both these responses have, in the opinion 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.

Finally, it should be stated that in lepromin-positive persons the results of the test are usually very constant over many years. While there may be some variation in the degree of positivity, changes from positive to negative are rare.

The Tuberculin Test

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.

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—for example, in miliary tuberculosis and in the last stages of pulmonary tuberculosis—the tuberculin test may be, or become, negative, indicating an anergy (which recalls in some respects the anergy of lepromatous leprosy).

This brings us to one point about the tuberculin test which should be mentioned. It is apparently not unusual for the results of the test to change 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 in the patient, a positive may become negative. Similar findings are recorded after B.C.G. vaccination. The positive tuberculin reaction induced by this measure is often short-lived, and to maintain positivity repeated vaccination is often necessary.

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

Methods of Testing Used in the Present Study

The lepromin was prepared by a modification (necessitated by local conditions) of the method of Dharmendra (1942), and it was standardized biologically by comparison with a lepromin prepared by Dharmendra's (unmodified) method of preparing lepromin standardized by weight.

This lepromin has proved very satisfactory, and is maintaining its potency very well. The early (24 to 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 (two to five weeks) response. The late response has been one used here in recording the result 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 and often earlier and later. "Pinhead" nodules have been ignored in this work. The nodules recorded as positive have measured 4 to 10 mm. or more in diameter in the third and fourth weeks, the large ones often showing superficial alteration. In only a few cases have the results 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 in whom results were doubtful and negative were then given an intradermal injection of 50 international units of purified tuberculin. In practice a definite raised area of erythema and oedema measuring 8 or more mm. 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 recorded here.)

Findings of the Present Study

The following are the results of the lepromin and tuberculin tests in healthy Africans here in Uzuakoli.

Children Aged 1–15.—Of the 81 tested, 47 (58%) were tuberculin-positive and 31 (35%) lepromin-positive. From these data it is possible by simple calculation to find the proportion of cases in which the results of the two tests should agree or disagree, and in what way they should agree and disagree, if the two tests are entirely independent. The expected and actual figures are shown in Table I. It will be seen that the actual results obtained were very different

TABLE I

	Both Tests Pos.	Both Tests Neg.	Tuberculin-pos. Lepromin-neg.	Tuberculin-neg. Lepromin-pos.	Dis-agreement
Expected	22%	26%	36%	16%	52%
Actual ..	(31) 38%	(34) 42%	(16) 20%	Nil	20%

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 were independent.

Adults.—Of the 278 tested, 223 (80.2%) were tuberculin-positive and 224 (80.5%) lepromin-positive.

The results by the methods outlined above are shown in Table II. In this group of adults, with both tuberculin- and lepromin-positive rates much higher than those in

TABLE II

	Both Tests Pos.	Both Tests Neg.	Tuberculin-pos. Lepromin-neg.	Tuberculin-neg. Lepromin-pos.	Dis-agreement
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%

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 occur by chance.

Findings of Other Workers

We now look at the results of similar studies made by workers in other countries, and analyse them in the same way. Dharmendra and Jaikaria (1941) studied 260 healthy persons in the Punjab, where there was practically no leprosy and very little tuberculosis. The expected figure was 50.6%, and the actual 31.5%. In Indo-China Chaussinand (1949) tested 231 children of 4 to 8 years. Here the expected figure was 46.5% and the actual 18.6%. The same worker (Chaussinand, 1950) examined 38 children in Paris, and the figures were 49.8% expected and 2.6% actual.

All three studies—our present study, the previous studies of Dharmendra and Jaikaria, and those of Chaussinand—made in different countries by different workers at different times, the methods used also differing, 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?

Cause of Agreement between the Two Tests

Four possibilities have to be considered.

1. Exposure to leprous infection (in Nigeria 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 bacilli. If this hypothesis were true, patients with leprosy of the allergic (tuberculoid) type should be tuberculin-positive. As is recorded elsewhere, this is often not so. There is practically no evidence to support this hypothesis; nearly all the evidence is against it.

2. 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 (1950) and of Fernandez (1939a) on studies in Paris.

3. 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.

4. It seems that 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 unexplained, however, the cases that are tuberculin-positive but lepromin-negative. Analysis of the 38 such cases in our present two 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 all except one of these showed a positive lepromin reaction, nearly all strongly positive. (Incidentally, one may record that 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 above 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 be reasonably explained only 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 (1934) in England; Dubois (1936) in Belgium; Boncinelli (1937) in Italy; Fernandez (1939a) in Paris; Convit et al. (1944) in New York; Azulay and Convit (1947) in Ohio; Bechelli *et al.* (1945) in New York; Dharmendra and Jaikaria (1941) in the Punjab; and Chaussinand (1950) in Paris. Several of these workers have commented on the fact that tuberculin-positive persons studied were usually lepromin-positive.

Effect of B.C.G. Vaccination on Lepromin and Tuberculin Tests in Healthy Persons

The following published reports on this matter are available. Fernandez (1939a) 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 (1951) took 53 healthy persons negative to both tests, and gave B.C.G.; 87% became lepromin-positive.

Chaussinand (1950) took 30 children negative to both tests, and found that all became lepromin-positive after B.C.G. vaccination.

Azulay (1948) gave B.C.G. to 15 lepromin- and tuberculin-negative children; 12 became tuberculin- and lepromin-positive.

Gines and Poletti (1946) studied 31 healthy children of leprous parents, giving B.C.G. vaccine: 25 were found lepromin-positive after vaccination. Of 11 in whom a previous lepromin test was not done, 9 were found positive; and of 20 in whom a previous test was negative, 16 became positive.

Rosemberg *et al.* (1950a) 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 dosage 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. (0.1 g.) was given. Nine became tuberculin-positive and eight became lepromin-positive; three remained tuberculin- and lepromin-negative. Rosemberg *et al.* (1950b) 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 one 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. 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 Budiansky (1949) and Dauden Valls *et al.* (1951).

Present Work

B.C.G. vaccine has been given by intradermal injection of 0.1 mg. in 65 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 two to three months later.

Very Young Babies (13).—B.C.G. was given soon after birth. No preliminary tuberculin and lepromin tests were done, and they were presumed negative. After B.C.G. nine became tuberculin- and lepromin-positive, and four became doubtful lepromin-positive.

Older Babies (8).—Before B.C.G. all were negative to both tests. After B.C.G. three became positive to both, and four became tuberculin-positive and lepromin-doubtful.

Older Children (29).—Before B.C.G. all were negative to both tests. After B.C.G. 20 became positive to both tests. six became tuberculin-positive and lepromin-doubtful, and three were tuberculin-positive and lepromin-negative.

*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 mg. 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 mg. 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 obviously has 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 seems to be no reason why doses of 100 mg. 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.

Adults (15).—Before B.C.G. all were tuberculin-negative and seven were lepromin-positive. After B.C.G. all were positive for both tests.

Conversions.—Of 65 previously tuberculin-negative, 64 became positive. Of 58 previously lepromin-negative, 40 became positive and 14 became doubtful. Of 54 becoming lepromin-positive or doubtful, all became tuberculin-positive. Of 64 becoming tuberculin-positive, seven 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 (Rosenberg *et al.*, 1950b) 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 Reaction Indicate Immunity to 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 the disease is in the mild self-limiting form. Most workers believe that it is the power to react allergically to leprosy bacillus, and the immunity which accompanies this phenomenon, which keep the person free from the disease, or if the disease is acquired, keep 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 reaction produced as a response to *leprous* infection might indicate immunity to leprosy, but one produced as 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 reports by Fernandez (1951) and by Montestruc and Blaché (1950).

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. They reported four other similar cases in children aged 12, 9, 7, and 5. All were given B.C.G. at birth and two were revaccinated at 1 year. All have stayed with the mother and all are healthy. Four other similar children in similar circumstances but not given B.C.G. have developed leprosy, at the ages of 11 months, 3, 5, and 7 years; three are lepromatous cases. Montestruc and Blaché realize 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. We 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 "immunizes" only 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, three lepromin-positive, and one lepromin-doubtful. Other workers have reported to us personally similar findings. 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 reaction is generally accepted as indicating some immunity to leprosy. A positive lepromin reaction 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 approximately equal to 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 seems 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, and will shortly be published. 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 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 to be contradictory. There still remains doubt in the minds of some workers whether a positive lepromin reaction (particularly if induced by B.C.G.) really indicates immunity. Until such doubts can be resolved or confirmed, what is the reasonable attitude to adopt towards the question of B.C.G. immunization of persons with a view to preventing leprosy?

It seems to us that its use even at the present time is justified, but that certain conditions should be fulfilled: (1) 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. (2) 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. (3) 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. (4) It should be made quite 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 minimize contact between open cases of leprosy and healthy persons, particularly children.

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. In 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 thought to be suggestive.

The advisability of using B.C.G. vaccination of healthy people 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 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.

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ADDENDUM.—I have received from Dr. H. W. Wade, Editor of the *International Leprosy Journal*, further information about the results of B.C.G. vaccination in the prevention of leprosy in Brazil. Dr. Nelson de Souza Campos has sent to Dr. Wade a letter on this subject for publication the main facts of which are as follows:

B.C.G. has been given orally to some "contacts" of leprosy cases at the Central Leprosy Dispensary in São Paulo. Of nearly 1,700 such contacts given B.C.G., 10 (0.6%) developed leprous lesions, all tuberculoid (mild). Of over 3,300 similar contacts not given B.C.G. 179 (5.4%) developed leprous lesions—some lepromatous (severe), some indeterminate, and some tuberculoid. No details are yet available.

REFERENCES

Azulay, R. D. (1948). *Hospital, Rio de J.*, **34**, 853.
—— and Convit, J. (1947). *Int. J. Leprosy*, **15**, 264.
Bargehr, P. (1926). *Z. ImmunForsch.*, **47**, 529.
Bechelli, L. M., Keil, H., and Rotberg, A. (1945). *Rev. brasil. Leprol.*, **13**, 21.
Boncinelli, U. (1937). *C. ital. Derm. Sif.*, **23**, 425.
Budiansky, E. (1949). *Rev. brasil. Leprol.*, **17**, 27.
Chaussinand, R. (1949). *Rev. colon. méd. Chir.*, **21**, 170. (Abstracted in *Int. J. Leprosy*, 1950, **18**, 441.)
—— (1950). *La Lèpre*, p. 148. Expansion Scientifique Française, Paris. Also *Int. J. Leprosy*, 1948, **16**, 431.
Convit, J., Azulay, R. D., Bermudez, D., and Salgado, P. (1944). *Int. J. Leprosy*, **12**, 60.
Cummins, S. L., and Williams, E. M. (1934). *British Medical Journal*, **1**, 702.
Dauden Valls, F., Moray Comas, J., and Dauden Sala, C. (1951). *Acta dermo-sifiliogr., Madr.*, **42**, 505.
Dharmendra (1941). *Leprosy in India*, **13**, 89.
—— (1942). Ibid., **14**, 122.
—— and Jaikaria, S. S. (1941). Ibid., **13**, 40.
—— —— (1943). Ibid., **15**, 40.
Dubois, A. (1936). *Bull. Soc. Path. exot.*, **29**, 649.
Fernandez, J. M. M. (1939a). *Rev. argent. Dermatosif.*, **23**, 425.
—— (1939b). *Ann. paulist. Med. Cirurg.*, **37**, 308.
—— (1940). *Int. J. Leprosy*, **8**, 1.
—— (1943). Ibid., **11**, 15.
—— (1951). Ibid., **19**, 474.
Gines, A. R., and Poletti, J. G. (1946). *Bol. Ofic. sanit. pan-amer.*, **25**, 884.
Hanks, J. H. (1945). *Int. J. Leprosy*, **13**, 25.
Lowe, J., and Dharmendra (1941). *Leprosy in India*, **13**, 81.
Mitsuda, K. (1916). Quoted by F. Hayashi, *Int. J. Leprosy*, 1933, **1**, 31.
—— (1924). *Proc. 3rd. Int. Leprosy Conf., Strasbourg.*, p. 219. Baillière, Paris.
Montestruc. E., and Blaché, R. (1950). *Rev. colon. méd. Chir.*, **15**, 358.
Neyra Ramirez, J. (1951). *Rev. Sanid. Policia*, **11**, 519.
Rosemberg, J., Campos, N. de S., and Aun, J. N. (1950a). *Rev. brasil. Leprol.*, **18**, 3.
—— —— —— (1950b). Ibid., **18**, 128.
Rotberg, A. (1937). Ibid., **5**, Spec. No. 45.
Wade, H. W. (1941). *Int. J. Leprosy*, **9**, 39.
—— (1950). Ibid., **18**, 487.