LEPROSY AND TUBERCULOSIS[1]

A COMPARATIVE STUDY WITH THE AID OF SKIN TESTS WITH TUBERCULIN, KILLED BCG, AND THE DHARMENDRA LEPROMIN IN SOUTH AFRICAN BANTUS[2]

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INTRODUCTION

The aim of this study was to investigate the immunological relationship between leprosy and tuberculosis, with a view to ascertaining the possible value of BCG vaccination in leprosy prophylaxis. The problem of the use of BCG for this purpose is dealt with in so many publications that we find it unnecessary to discuss the subject again, mentioning only certain important publications: by Fernandez ([11-13]), who found that BCG vaccination could convert negative lepromin reactors to positive, indicating that perhaps resistance against leprosy could be enhanced by BCG vaccination; and by Chaussinand ([3]) who concluded that leprosy and tuberculosis are antagonistic diseases and that there exists a bacterial parallergy and relative cross immunity between tuberculoid leprosy and tuberculosis.

To study the immunological relationship between leprosy and tuberculosis we carried out skin tests with tuberculin, killed BCG, and the Dharmendra lepromin in patients with leprosy, in patients with tuberculosis, in leprosy contacts, and in healthy people.

It has been pointed out by Floch ([15]) that tuberculin and lepromin are completely different kinds of antigens, tuberculin being a protein substance extracted from the culture medium whereas lepromin contains whole bacilli. We concur with Floch's opinion that in immunological studies the antigens should be as similar as possible. Therefore we compared the reactions to killed tubercle bacilli and killed leprosy bacilli. As it is assumed that the antigenic properties of human tubercle bacilli and bovine Calmette-Guérin bacilli do not differ much, we used killed BCG bacilli.

The BCG test.—In recent years skin tests with killed BCG have been

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[1] This paper is drawn from the thesis by A. W. F. Rutgers on Leprosy and Tuberculosis, Free University of Amsterdam, Zaandijk, J. Heijnis Tsz., 1956, 217 pp. (See THE JOURNAL **25** (1957) 78.)

[2] Because the Dharmendra antigen is so very different from classical lepromin, the bacilli being extracted to nonacid-fastness and intended only for the early reaction, the term lepromin is customarily not applied to it in THE JOURNAL when it is avoidable, in order not to compound confusion in the literature. In this case its use is not avoidable, this article being in effect a summarization of a published monograph.—EDITOR.

more and more frequently used for diagnostic purposes in tuberculosis. As this test is not widely known it will be discussed briefly. For more information we refer to Ustvedt ([29]), who has done much important work on the BCG test.

There has been a great lack of uniformity in the execution of the BCG test. Not only are the modes of administration and the amounts of living or dead BCG antigen very different, but the time of reading and the interpretation of results also vary with almost every investigator. Theoretically, three kinds of reactions following the injection of BCG into the skin are distinguished:

1. The late reaction, or vaccination reaction, appearing 2-4 weeks after the injection, characterized by a nodule which generally reaches its greatest diameter after 6 weeks. This late reaction is seen in people who have not had any previous contact with the tubercle bacillus. The injection of BCG acts in these cases as a vaccination, and reaction sets in as soon as allergy is established.

2. The early or accelerated reaction, appearing before the 10th day, indicating—as an attenuated Koch's phenomenon—the presence of tuberculous allergy evoked by previous contact with the tubercle bacillus. According to Ustvedt ([29]) and Heaf ([21]) the question whether a positive result of the BCG test indicates immunity is not at all settled. Results of experiments performed by Raffel ([26]) showed that a positive phenomenon can occur without resistance against reinfection. Ustvedt proposed to call this accelerated reaction a "positive diagnostic BCG test." When in the following presentation we speak of a positive BCG test this accelerated reaction within 10 days after the injection is meant.

3. The immediate reaction, appearing after 12-24 hours, considered nonspecific ("traumatic") by most investigators, as it is usually seen in persons without tuberculous allergy, who also show a typical late reaction.

The BCG test is especially of practical value in those people in whom the tuberculin reaction is negative or has become negative in spite of previous contact with the tubercle bacillus, but in whom the BCG test frequently remain positive as a sign of still-existing tuberculous allergy (bacillary hypersensitivity). Probably tuberculin hypersensitivity and bacillary hypersensitivity are phenomenon independent of each other, although they often run parallel.

Tests with killed tubercle bacilli in leprosy patients.—Fernandez ([14]) carried out a small comparative investigation with killed human tubercle bacilli and tuberculin in 14 patients with lepromatous and 10 with "neural" leprosy. He concluded that tuberculin only gave early reactions but that the killed tubercle bacilli evoked early and late (3rd week) reactions. The late reactions always had been preceded by early reactions, therefore one should rather say that the early reactions were frequently still present in the third week.

Chaussinand (2) performed intracutaneous BCG tests in patients with tuberculoid leprosy. He found that these patients showed positive reactions with the BCG test even when the tuberculin reaction was negative. In guinea-pigs and monkeys "infected" with leprosy by means of the implantation of a leproma, and in consequence showing a positive Mitsuda reaction, the BCG test was also positive, although the reaction to 10 mgm. of tuberculin (1000 TU) remained negative. From these results Chaussinand concluded that there exists a parallergy between the leprosy and tubercle bacilli.

Floch (15) compared the reactions obtained with lepromin and killed BCG in 46 patients with tuberculoid leprosy, 58 with the indeterminate form, and 40 with the lepromatous type. He chose the dilution in such a way that both suspensions contained about the same number of bacilli. He found the concordance between the results of the lepromin and BCG tests substantially greater than that between the lepromin and tuberculin tests of a former investigation (16). The results of Floch's investigation are difficult to evaluate, because his criteria of positivity of the BCG test are not mentioned and doubtful reactions are interpreted as positive. Floch's arguments for reading the lepromin test and the BCG test both on the 22nd day are debatable. Moreover, since his investigations were completed the opinion on the BCG test has changed considerably.

Various investigators have carried out skin tests with killed tubercle bacilli and so-called paratuberculosis bacilli in patients with leprosy. They will not be mentioned here separately. Generally, they obtained strong reactions also in the lepromatous type.

The articles dealing with skin testing with lepromin and tuberculin of patients suffering from leprosy or tuberculosis and of healthy people are so abundant and conflicting that we refrain from mentioning them. With respect to our own results we will discuss only the more relevant items.

One thing is very obvious, i.e., that much of the value of the articles is wasted because the results of the reactions are published only as positive or negative, sometimes even without mentioning further particulars of the material and method used. It seems advisable to give reading in millimeters in scientific articles. The use of different antigens by the various investigators, especially with regard to lepromin, is a great handicap. The need for a standardized lepromin cannot be overemphasized.

MATERIAL AND METHODS

The investigation was carried out in June-September 1955 in the Westfort Leprosy Institution near Pretoria (Medical Superintendent, Dr. A. R. Davison), and in the Rietfontain Hospital near Johannesburg (Medical Superintendent, Dr. J. H. Loots). Five groups were examined:

Group 1: 62 patients with lepromatous leprosy.
Group 2: 54 patients with tuberculoid leprosy.
Group 3: 92 healthy leprosy contacts (personnel of the institution).
Group 4: 101 patients with active pulmonary tuberculosis.
Group 5: 150 healthy controls (garbage collectors).

All subjects were male Bantus from various parts of the Union of South Africa, their ages varying from 18 to 65 years. X-ray examination of the lungs was carried out in all of them. The following antigens and doses were used:

1. Tuberculin, PPD, 5 TU. The reaction was considered positive when the induration measured 6 mm. or more;

2. BCG from the Institut Pasteur, Paris, killed by heat, 1/20th standard strength, i.e., 0.005 mgm. per injection; after analysis of the frequency histograms results were considered positive when the induration was 6 mm. or more on the 7th day;

3. Lepromin prepared by Dharmendra's method, 0.01 mgm. per injection.[3]

The three injections were given simultaneously; all reactions were read in millimeters after 2, 7, 14, 21, 28 and 42 days.

RESULTS

1. *Tuberculin test.*—The percentages of positive tuberculin reactions in the different groups were as follows:

Group 1:	62 lepromatous leprosy patients	82% positive
Group 2:	54 tuberculoid leprosy patients	76% "
Group 3:	88 leprosy contacts	89% "
Group 4:	104 tuberculosis patients	97% "
Group 5:	145 healthy controls	70% "

It will be noticed that the frequency was approximately the same in leprosy patients and healthy controls. Of the leprosy patients, tuberculoid and lepromatous, 12 per cent showed no reaction at all to either tuberculin or killed BCG, although calcified foci in the lungs had been detected by X-ray examination. In the other groups there were hardly any nonreactors. Among the lepromatous patients 45 per cent showed a marked hypersensitivity to tuberculin (reactions >20 mm.).

2. *Lepromin test.*—No statistically significant difference was found in the positive percentages of the Mitsuda reaction (>4 mm. 28th day) in Groups 2-5, according to the criteria laid down at the Madrid Congress in 1953:

Group 2:	54 tuberculoid leprosy patients	50% positive
Group 3:	88 leprosy contacts	56% "
Group 4:	103 tuberculosis patients	44% "
Group 5:	137 healthy controls	41% "

The lepromatous patients showed no positive Mitsuda reactions. From these results one could conclude that there was no influence from leprosy or tuberculosis on the incidence of positive lepromin reactions according to the usual criteria. The low frequency of positive Mitsuda reactions in tuberculoid leprosy patients (50%) is ascribed to the use of the weak Dharmendra lepromin.

However, on further meticulous statistical analysis, comparing the lepromin reaction in millimeters at different intervals, there appeared to be statistically significant differences in the intensity and the acceleration of the lepromin reactions among Groups 2-5. The term "acceleration" means that the highest reading of the reaction or of the average readings falls on an

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[3] See Footnote 2.—EDITOR.

earlier day, a matter which will be explained further. These differences can be seen by putting the results in the form of Table 1.

TABLE 1.—*Lepromin reaction after 14 days.*

Size of reaction lesion	Group[a]				
	1	2	3	4	5
Unknown			2	5	59
0 mm.	57	12		3	13
1 mm.	3	6	4	4	10
2 mm.	1	5	7	13	23
3 mm.		8	17	19	18
4 mm.		3	17	20	13
5 mm.	1	3	15	8	17
6 mm.		1	15	8	4
7 mm.		3	8	8	1
8 mm.			1	3	
9 mm.		1	2	4	
10 mm.		1	1	5	
11 mm.		2		3	
12 mm.		2		1	
16 mm.		3			
17 mm.		1			
18 mm.		2			
22 mm.		1			

a The groups were: 1, lepromatous; 2 tuberculoid; 3, leprosy contacts; 4, tuberculous; 5, healthy controls.

These small differences appeared to exist in a greater or lesser degree in the results after 48 hours and 7, 14, 21 and 28 days.

Tabulated in another way, these differences between the results of the Groups 2 to 5 appeared to be statistically significant to a high degree. For this purpose 4 classes were made: 0-1 mm., 2-3 mm., 4-5 mm. and 6 mm. or more as shown in Table 2.

By means of the X^2 test, the difference between the different groups at 7 days is shown to be strongly significant ($P<0.001$). Also for the lepromin reaction after 14 and 21 days there was a strongly significant difference between these groups.

Summing up, there was a significant difference between the lepromin reactions in the different groups, consisting chiefly of the occurrence of increasingly stronger reactions in the following order: Group 5 (healthy people), Group 3 (leprosy contacts), Group 4 (tuberculosis patients) and Group 2 (tuberculoid leprosy), but after different intervals.

TABLE 2.—*Lepromin reaction after 7 days.*

Class of reaction	Group			
	2	3	4	5
0-1 mm.	27	26	15	53
2-3 mm.	6	24	34	28
4-5 mm.	4	20	25	9
6 mm.	17	18	26	2

3. *BCG test.*—With the aid of the results from a few other investigations it was found that the immediate reaction had subsided before the 7th day. Over and above that it turned out that the accelerated reactions, which appeared as early as after 48 hours, always increased to strongly positive reactions with a tendency to a maximum on the 7th day. By means of frequency histograms it was found that a limit of 6 mm. of induration for positivity of this accelerated reaction is reasonable. Generally the reaction can be read easily because the induration is well defined. Erythema was not taken into account because of the dark skin of our patients. Probably for the same reason the central dark red discoloration mentioned by Felber ([10]) was not observed in our Bantu patients, but one of us (R.) has seen it in Europe. The results with the BCG test are shown in Table 3.

TABLE 3.—*Reaction to 0.005 mgm. killed BCG on the 7th day.*[a]

Group	Number of tests	Negative		Positive	
		Total	Nil	No.	%
1	62	9	6	53	85.5
2	54	15	7	39	72.2
3	89	2	1	87	97.6
4	101	0	0	101	100.0
5	82	9	0	73	89.0

a Less than 6 mm. on the 7th day, negative; more than 6 mm. on that day, positive.

The percentage of positive reactions with the BCG test in the lepromatous group was not lower than in the tuberculoid group, but on the contrary. However, in this group there was a high incidence of strong reactions (>20

mm.), namely, in 24 per cent. Again, as with the negative tuberculin reactors, about 10 per cent of the total of leprosy patients who gave negative results to the BCG test showed calcified foci in the lungs.

Attention must be drawn to the great number of negative accelerated reactions in Group 2 (the tuberculoid patients), a total of 15 patients of whom 7 had no reactions at all. In these 7 complete nonreactors the BCG test was repeated after two months with living BCG, standard strength. Six of the 7 again showed negative early reactions and clear late (vaccination) reactions.

CORRELATIONS

1. *Tuberculin and BCG tests.*—A strong correlation was found between the tuberculin reaction after 48 hours and the BCG reaction after 7 days, i.e., the stronger the hypersensitivity to tuberculin, the bigger was the reaction

TABLE 4.—*Correlation table of results of the BCG test after 7 days and lepromin reactions after 28 days in Group 5 (healthy persons).*

BCG test 7 days[a]	Lepromin test, 28 days (mm.)[a]									Total
	II	0	1	2	3	4	5	6	7	
---	11	6	1	12	13	15	12	4	2	76
2		1								1
3		1		1		1			1	4
4	1	2	1							4
6	1	3		1						5
7				2						2
8	1			1	2	1		2		7
9				1		2	2			5
10	3			2	4	2		1		12
11					2	1		2		5
12	1		1	1	1	1	3	1		9
13			1	1	1	3		1		7
14	1	1			2	2	1	1	1	9
15	1				1	2	1	1		6
16			1	2	1	1				5
17								1		1
Total	20	14	5	24	27	31	19	14	4	158

a .. and II = unknown.

to killed BCG. With the above mentioned criteria for positivity the correlations were as follows:

Tuberculin negative, BCG negative, 41, or 10.9%
Tuberculin positive, BCG positive, 299, or 79.5%
Tuberculin negative, BCG positive, 30, or 8.0%
Tuberculin positive, BCG negative, 6, or 1.6%

2. *Tuberculin and lepromin tests.*—No correlation whatsoever was found between the tuberculin reactions after 48 hours and the lepromin reactions after 28 days, using correlation tables. A correlation to a certain extent was found only in patients with active tuberculosis between the tuberculin reaction after 48 hours and the *stronger* lepromin reaction after 14 days.

3. *BCG and lepromin tests.*—No correlation whatsoever was found be-

TABLE 5—*Correlation table of BCG results of the BCG test after 7 days and lepromin reactions after 14 days in Group 4 (tuberculosis patients).*

BCG test after 7 days[a]	Lepromin reaction after 14 days (mm.)[a]														Total
	II	0	1	2	3	4	5	6	7	8	9	10	11	12	
---			1	1		1		1							4
6					1										1
7	1				2				1						4
9						1									1
10				1		1	2								4
11				3	1			3							7
12		1		1	2	4	1	1	1						11
13	1		2	1	2	2					1				9
14				1	1	4		1	1		1	1	1		11
15		1	1	1		1	5	1	1						11
16	1			2	8	2			2	1		2			18
17		1		1		2				1		1			6
18	1					1			1		1				4
19				1	1										2
20	1					1		1	1		1		1	1	7
21					1					1					2
22													1		1
24												1			1
Total	5	3	4	13	19	20	8	8	8	3	4	5	3	1	104

a . . and II = unknown.

tween the reactions to BCG after 7 days and the lepromin reactions after 28 days. Only the correlation table for Group 5 is given, in Table 4.

Looking for correlation on other reading days, to a certain extent this was found only in patients with active tuberculosis between the BCG test after 7 days and the *stronger* lepromin reactions after 14 days, as shown in Table 5.

AVERAGE VALUES OF THE REACTIONS

An average alone of a number of reactions is not very reliable because a few extremely strong reactions or many nil reactions affect the average considerably. The spreading of our lepromin reactions at the very least was not regular according to Gauss. Nevertheless, the average value can give some indication, especially when the number of the average calculated is not too small.

1. *Average tuberculin induration.*—In Table 6 the average tuberculin indurations for the total groups are assembled, and also for the groups after the people with negative (<6 mm.) reactions were left out. A striking feature is the high average (21.28 mm.) in Group 1, the patients with lepromatous leprosy, in contrast with the averages of the other groups (10.85-12.96 mm.).

TABLE 6.—*Average tuberculin induration after 48 hours (in mm.).*

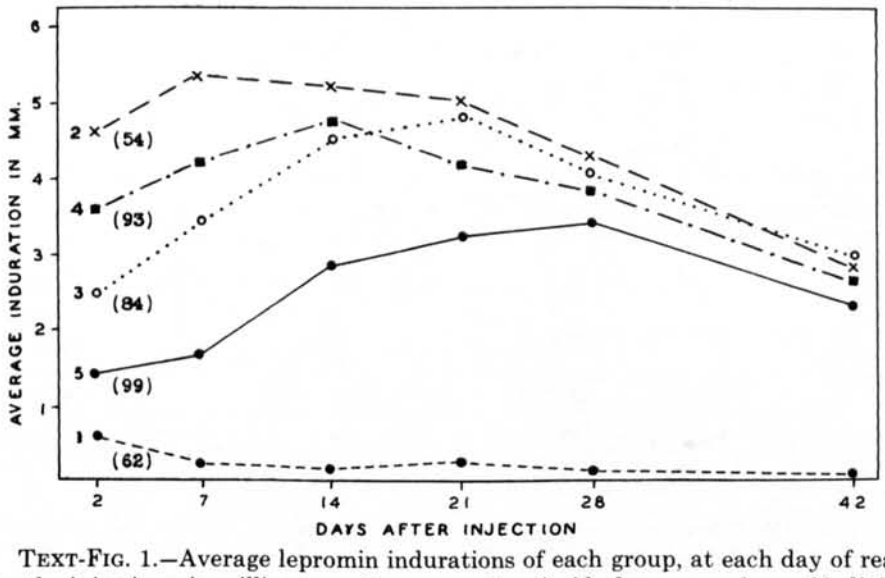
Group	Total group		Tuberculin positives[a]	
	Cases	Average	Cases	Average
1	62	17.56	50	21.28
2	54	9.85	40	12.68
3	88	11.30	66	12.27
4	101	12.64	81	12.96
5	136	8.98	48	10.85

2. *Average lepromin induration.*—The average lepromin induration for each group was calculated. These average values on the days read are presented graphically in Text-fig. 1.

This graph reveals the remarkable fact that the highest point of the curve for each group fell on a different reading day. In Group 2, tuberculoid leprosy patients, the highest was on the 7th day (5.30 mm.); in Group 3, leprosy contacts, the highest was on the 21st day (4.77 mm.); in Group 4, tuberculosis patients, the highest was on the 14th day (4.71 mm.); and in Group 5, healthy controls, the highest was on the 28th day (3.37 mm.).

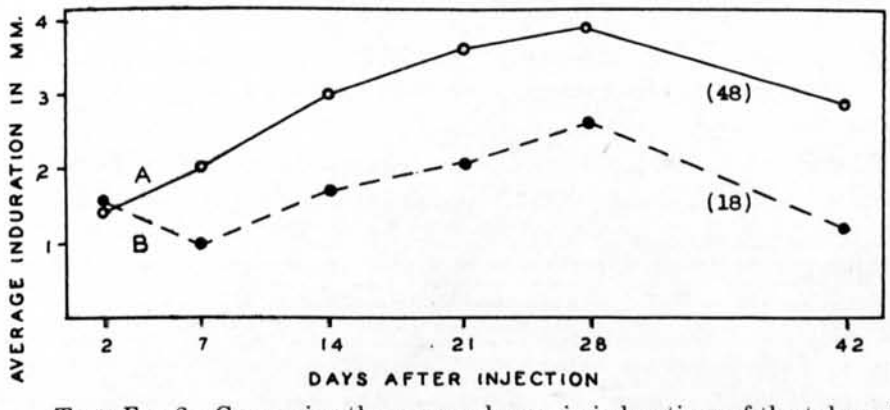
In addition, it appears that the 48-hour readings and the highest point of the curve differed in the same order as the above maxima.

Group 2. Measurement at 48 hours: 4.56 mm.
Group 3. Measurement at 48 hours: 2.47 mm.
Group 4. Measurement at 48 hours: 3.57 mm.
Group 5. Measurement at 48 hours: 1.41 mm.



TEXT-FIG. 1.—Average lepromin indurations of each group, at each day of reading after the injections, in millimeters. Group numbers inside frame; numbers of individuals in parentheses.

Summing up, there seems to exist in the order Group 5, Group 3, Group 4, and Group 2 an increasing higher 48-hour reading, a continually higher curve, a continually earlier-occurring maximum.[4]



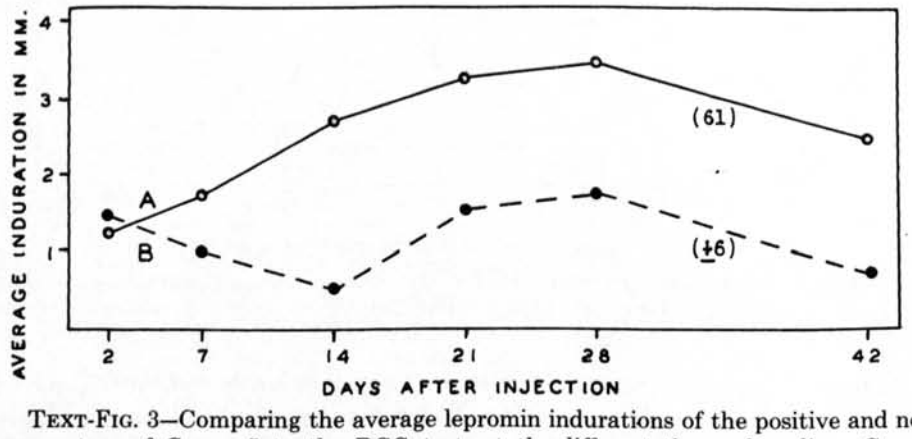
TEXT-FIG. 2.—Comparing the average lepromin indurations of the tuberculin positives and negatives in Group 5 (healthy controls), at the different times of reading. Curve A (solid line), tuberculin positives; Curve B (broken line) tuberculin negatives.

[4] The difference between Groups 3 and 4 is not as clear as between the other groups.

From these findings it seems justified to draw the conclusion that there are indications that the lepromin reaction is affected in increasing degree by contact with leprosy patients, tuberculosis and tuberculoid leprosy. This influence is shown by an acceleration and intensification of the reaction.

To study the influence of tuberculous infection on the course of the lepromin reaction, the average lepromin indurations of the tuberculin negatives and tuberculin positives of the different groups were calculated for each of the reading days. We give in Text-fig. 2 only the results in Group 5 (healthy controls), in which the average lepromin induration in the tuberculin positives was significantly greater than in the tuberculin negatives.

The same was done for the BCG test. Here also the average lepromin induration in Group 5 was greater in the BCG positives, as shown in Text-fig. 3.



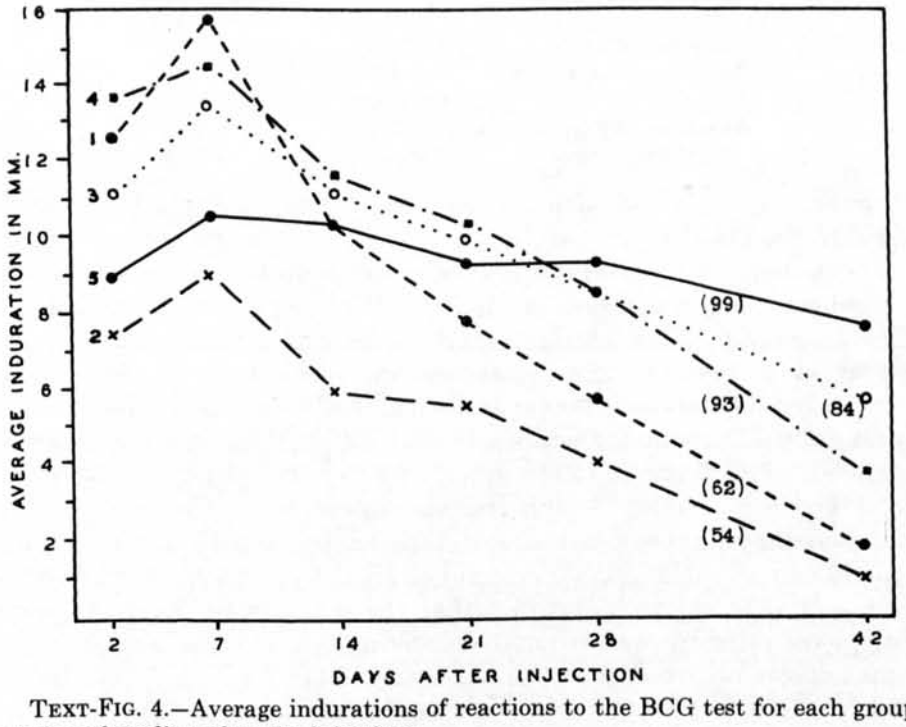
TEXT-FIG. 3—Comparing the average lepromin indurations of the positive and negative reactors of Group 5 to the BCG test, at the different times of reading. Curve A (solid line), positive BCG reactors; Curve B (broken line) negative BCG reactors.

From the results just presented it can be concluded that a tuberculous infection, as represented by tuberculin or BCG-test positivity, intensifies the reaction to lepromin.

3. *Average induration of the BCG-test reactions.*—Just as was done with the lepromin reaction, the average BCG indurations were calculated for the different groups and are presented in Text-fig. 4. The differences between the various groups are significant to a high degree. Again the course of the BCG reaction was intensified and accelerated by contact with leprosy or tuberculosis. The order of the groups was again 5, 3, 4. With regard to leprosy, Group 1 (lepromatous leprosy) has taken the place of Group 2 (tuberculoid leprosy). Why Group 2 shows smaller BCG reactions is not clear. One would have expected the opposite, because in those patients, active leprosy should accelerate the reaction still more than leprosy contact (Group 3).

SIDE-EFFECTS

The lepromin reactions did not give rise to unpleasant local reactions. This was not the case with the injection with tuberculin and killed BCG. Four patients of Group 1 (lepromatous leprosy) showed large and painful infiltrations on the forearms. Probably there exists in patients of the lepromatous type a strong sensitivity to tuberculin and tubercle bacilli. Furthermore, in that group there was an increase in the frequency of erythema nodosum leprosum (ENL, which only occurs in lepromatous leprosy), after the injection of tuberculin as well as killed BCG. Most of the patients who showed ENL after injection had shown also strong local reactions to the BCG and the tuberculin injections. However, ENL occurred also in patients with completely negative reactions to the tuberculin and BCG tests, in two of them even very strongly.



TEXT-FIG. 4.—Average indurations of reactions to the BCG test for each group, at each day of reading after the injections.

DISCUSSION

Tuberculin test.—The frequency of positive tuberculin reactions (6 mm. or larger) was approximately the same in the leprosy patients and the healthy controls. Of the leprosy patients 12 per cent showed no reaction at all to tuberculin and killed BCG, although calcified foci in the lungs were detected by X-ray. Remarkable was the observation of leprosy patients, both tuberculoid and lepromatous (6 and 8 respectively), with negative

tuberculin and BCG reactions together with calcified foci in the lungs. These calcifications were probably not due to histoplasmosis, as the percentage of positive histoplasmin reactions in Bantus is about 0.25 per cent (Kuper, personal communication). In the other groups scarcely any nil reactions occurred, but small reactions did.

The percentage of positive tuberculin reactions in the lepromatous group was not lower than in the other groups, in contrast with findings of Austin [1], Hale and associates [19, 20], Kooij [22] and Wade [30], but in keeping with those of Kuper [25]. The reason for this discrepancy may be the fact that this investigation was carried out in males only. Tuberculin negativity is much more frequent among female than among male leprosy patients in Westfort Institution, as shown by the following data obtained in 1955.

Type and results	*Males*	*Females*
Lepromatous	(91 cases)	(37 cases)
Mantous negative	60.4%	78.4%
Mantoux positive	39.6%	21.6%
Tuberculoid	(177 cases)	(105 cases)
Mantoux negative	25.9%	52.4%
Mantoux positive	70.4%	47.6%

Lepromin test.—No statistically significant difference was found in the percentages of positive Mitsuda reactions between the tuberculoid leprosy patients (Group 2) and the leprosy contacts (Group 5). From these results one could conclude that there is no influence from leprosy or tuberculosis on the incidence of positive lepromin reaction according to the usual criteria. However on further meticulous statistical analysis, comparing the lepromin reaction in millimeters at different intervals, there was found significant differences in the lepromin reactions in the different groups. Increasingly stronger reactions occurred in the order: Group 5 (healthy people), Group 3 (leprosy contacts), Group 4 (tuberculosis patients) and Group 2 (patients with tuberculoid leprosy), but after different intervals. From these results one could conclude there exists a slight degree of cross sensitivity between leprosy and tuberculosis. The fact that the reaction to the BCG test is slightly accelerated by leprosy and tuberculosis also indicates a slight degree of cross hypersensitivity. That this cross-sensitivity is only slight can be concluded from the fact that it only could be revealed after detailed statistical analysis of average reactions of whole groups, and not individual reactions. The fact that tuberculous infection was found to intensify the lepromin reaction is in agreement with the above conclusion. Since it has long since been established that hypersensitivity does not necessarily signify immunity [28], it is doubtful if cross-sensitivity also means cross-immunity. According to Gispen (personal communication) our findings could be more easily explained by the so-called adjuvant or Dienes effect of tubercle bacilli [6, 7, 18]. Dienes and associates reported that guinea-pigs showed an increased antigen response during a tuberculous infection. This effect was demonstrated by a

stronger allergic skin reaction to an arbitrary antigen in tuberculous animals compared with normal animals. This effect is considered to be nonspecific.

From our results it seems that the influence of tuberculosis on the lepromin reaction is only slight, a fact which may be ascribable to the antigens used. The Dharmendra antigen used produced decidedly smaller reactions than a Wade-Mitsuda lepromin used later in comparison. Secondly, we used killed bovine tubercle bacilli (BCG) instead of human bacilli. A part of the experiments will be repeated with a Wade-Mitsuda lepromin and killed human tubercle bacilli (strain H37).

BCG test.—By means of skin tests with killed and living bovine tubercle bacilli (BCG) we could not confirm the observations of Chaussinand ([2, 4, 5]) that patients with tuberculoid leprosy always showed positive skin reactions to killed tubercle bacilli even if the tuberculin reactions are negative. In 6 of our patients with tuberculoid leprosy we found a negative reaction to killed BCG, although they showed calcified foci in the lungs. There is no doubt about the classification of these patients, or about the negativity of the BCG test. The latter was confirmed by another test with living BCG.

Correlations.—A strong correlation was found between the tuberculin reaction after 48 hours and the BCG-test reactions after 7 days, i.e., the stronger the hypersensitivity to tuberculin, the stronger was the reaction to killed BCG.

No correlation was found between the tuberculin reaction after 48 hours, the BCG-test reaction after 7 days, and the late lepromin reaction after 28 days. A correlation to a certain extent existed between the BCG-reaction after 7 days and the larger lepromin reactions after only 14 days in patients with active tuberculosis. This is in agreement with the results obtained with the tuberculin and lepromin by Kuper ([25]) in patients with tuberculosis.

From the absence of any correlation in healthy controls between the readings of the tuberculin and the BCG tests on the one hand and the lepromin test on the other, the conclusion is drawn that in healthy individuals in South Africa the positive lepromin reaction is not caused by tuberculosis. Swerts ([27]) recently came to the same conclusion after performing tuberculin and lepromin tests in a certain population of the Belgian Congo. He found that the lepromin reaction converted earlier than the tuberculin reaction.

Positive Mitsuda-type reactions can be obtained with suspensions of normal tissue particles, as has been demonstrated by de Faria ([8, 9]), Kooij and Gerritsen ([23]) and by Floch ([17]). The late lepromin (Mitsuda) reaction particularly is considered a nonspecific reaction. This reaction can be enhanced by contact with tuberculosis and leprosy. The same might probably apply for sarcoidosis, as the lepromin and Kveim antigen are very similar ([24]).

SUMMARY AND CONCLUSIONS

The purpose of this study was to acquire information on the immunological relationship between leprosy and tuberculosis, with respect to the theory that tuberculosis protects against leprosy. The results indicated that the late reaction to lepromin, produced in some tuberculin-negative healthy people, was slightly intensified and accelerated in patients with tuberculosis and tuberculoid leprosy, which could be explained by the nonspecific Dienes effect. Gross hypersensitivity cannot be ruled out as an explanation. If cross hypersensitivity in our study were identical with cross-immunity, which is not certain, it would mean that BCG has a protective influence against leprosy. Because the cross hypersensitivity revealed in this study was slight, one would expect the possible cross immunity also to be slight. However, it is difficult to draw conclusions on the degree of protection by BCG from this study. We used killed bovine tubercle bacilli and a weak Dharmendra antigen in our skin tests. Perhaps skin tests with killed human tubercle bacilli and a Wade-Mitsuda lepromin might show a stronger cross hypersensitivity. The nonspecific Dienes effect could also have a protective influence on leprosy.

With skin tests with killed and living bovine tubercle bacilli (BCG), we could not confirm the observations of Chaussinand that patients with tuberculoid leprosy always showed positive skin reactions to killed tubercle bacilli even if the tuberculin reactions are negative.

RESUMEN Y CONCLUSIONES

Este estudio tenía por objeto adquirir información acerca de la relación inmunológica entre la lepra y la tuberculosis, con respecto a la teoría de que la tuberculosis protege contra la lepra. Los resultados indicaron que la reacción tardía a la lepromina, producida e en algunos sujetos sanos tuberculino-negativos, se intensificaba y aceleraba ligeramente en enfermos que tenían tuberculosis y lepra tuberculoidea, lo cual podía explicarse a base del efecto anespecífico de Dienes. No cabe excluir como explicación la hipersensibilidad cruzada. Si la hipersensibilidad cruzada fuera en este estudio idéntica a inmunidad cruzada, lo cual no es seguro, esto denotaría que el BCG ejerce un influjo protector contra la lepra. Por ser ligera la higersensibilidad cruzada revelada en el estudio actual, sería de esperar que también lo fuera la posible inmunidad cruzada. Sin embargo, es difícil sacar de este estudio conclusiones relativas a la intensidad de la protección otorgada por BCG. En las cutirreacciones se usaron bacilos tuberculosos bovinos matados y un antígeno de Dharmendra débil. Las cutirreacciones ejecutadas con bacilos tuberculosos humanos matados y con una lepromina de Wade-Mitsuda tal vez revelaran una hipersensibilidad cruzada más intensa. El efecto anespecífico de Dienes también podría ejercer un influjo protector sobre la lepra.

Con cutirreaciones ejecutadas con bacilos tuberculosos bovinos muertos y vivos (BCG) no pudieron confirmarse las observaciones de Chaussinand en el sentido de que los enfermos de lepra tuberculoidea muestran siempre cutirreacciones positivas a los bacilos tuberculosos muertos, aun siendo negativas las reacciones a la tuberculina.

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