REACTIONS TO TUBERCULINS IN LEPROSY

A REVIEW

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The tuberculin testing of leprosy patients is not given a great deal of attention in practical work, for in most circumstances tuberculosis is accepted as a common complication about which not much can be done. There are, however, certain questions—academic, perhaps, but none the less interesting—relative to the capability of leprosy cases to react to tuberculin and other similar antigens which await answers. This article is a review of the available literature bearing on the subject, not exhaustive but probably adequate, which leads to fewer conclusions than questions.

THERAPEUTIC TUBERCULIN INJECTIONS

When, in 1890, Koch introduced his *Heilmittel* for the treatment of tuberculosis by subcutaneous injection it was immediately tried out in its sister disease (Josef, Kaposi, Arning, Babes, Danielssen), whereupon there arose the question of the specificity of the febrile reactions which it induced. Babes (3) found that they differed in several respects from those produced in tuberculosis, being of the nature of lepra reaction and ascribable to the leprosy infection itself. Others (e.g., Nicolle (27)) were of like mind, and although a few (Slatinéanu and Daniélopolu (35) and Meier (32)) believed that the reactions were due to complicating tuberculosis, the reports of the therapeutic use of tuberculin in leprosy leave no doubt that it frequently gave rise to lepra reaction. Considering the fact that lepromatous cases do not respond in that way to such injections of the leprosy bacillus and its products (8, 13) whereas tuberculoid cases respond with a triple (local, focal and general) reaction (13), it would be of interest to know if the tuberculin-reactive cases were of tuberculoid nature, or if tuberculin—at least of the old variety—produces nonspecifically an effect in lepromatous cases which the specific antigen does not.

DIAGNOSTIC TUBERCULIN TESTS

The diagnostic tuberculin tests were also tried out in leprosy as soon as they were introduced (1907 and 1908). Nicolle (27)

obtained negative results with the ophthalmic and the von Pirquet tests in the same three patients who had reacted to subcutaneous injections, and others had similar experiences. Contrarily—and apparently alone—Brinkerhoff (7) in Hawaii saw positive reactions to the "transcutaneous" (Moro) test in nontuberculous leprosy patients and ascribed them to a chemical relationship between the two kinds of microorganisms which made the test of no differential value.

RESULTS WITH THE VON PIRQUET TEST

For a time most of the tuberculin testing of leprosy patients was by this method, with of course Old Tuberculin. No serious doubt seems to have arisen about the specificity of the results of this test, although as will be seen it was ultimately questioned by certain Italian writers, with no affirmation.

In Crete, Photinos and Michaélides (29) tested 204 cases and reported the results by type of case: nodular (only 24 cases), 67 per cent positive; mixed (80 cases), 57 per cent; neural (100 cases), 56 per cent; nothing was said of controls. Manteufel (21), finding only 7 per cent of 57 cases of various forms to be positive, concluded that uncomplicated leprosy does not sensitize to tuberculin. Hall (17), in Fiji, found 65 per cent of 121 patients positive, similar to a record of 62 per cent for 224 Fijians of the general population.

Later results are: Igarashi (19), testing 826 cases in Toyko, got the same percentage of positives, 67 per cent, in the macular and nodular groups. There was a relationship to the length of hospitalization since two recently-admitted groups gave just over 50 per cent. From these figures and from autopsy findings he concluded that tuberculin allergy in leprosy is not a group reaction. Adant (1), and later Dubois (10), in the Belgian Congo, saw no difference between leprosy patients and healthy controls; the latter found 22 per cent positive in 551 patients and 23 per cent in 3,041 controls and concluded that a positive reaction signifies tuberculous infection.

One record has been found, made without comment by de Souza-Araujo (36), of a type-difference similar to those to be seen later. His 90 cutaneous and mixed cases gave only 24 per cent positive, against 42 per cent among 33 neurals.

RESULTS WITH THE MANTOUX TEST

Although Perrin (28) of Marseille applied the intradermal test as early as 1910, finding 3 cases to be all negative, no other reports earlier than 1930 have been found. In this connection reference is made only to this test done with Old Tuberculin.

Leigh Evans (11), in Jamaica, tested 90 patients and 100 healthy adult controls and concluded that leprosy infection did not influence the results. Cummins and le Roux (9), in South Africa, found 23 of 25 leprosy patients positive (92%), 11 of 12 tuberculosis patients (92%, but stronger reac-

tions), and 11 of 14 healthy persons (78%), and they discarded the idea that widespread latent leprosy might be responsible for the high positivity rates in the native population. Sakurai (32), in Japan, tested 510 cases and obtained 77 per cent positive in nodular and 81 per cent in neural, with a relationship to time in the hospital; and, like Igarashi, he ascribed the reactions to tuberculous infection.

Austin (2), in Fiji, has recently told of a tuberculin survey of Makogai patients (cf Hall, above), among whom 44 per cent of 86 school-children and 55 per cent of 309 adults were positive to 1:1,000 OT. A subsequent test of 224 new cases in which the maximum concentration was 1:100 revealed 80 per cent positive—90 per cent of 88 tuberculoid cases and 74 per cent of 136 lepromatous ones, although his total figures show 76 per cent for 337 of the former type and 77 per cent for 532 of the latter.

Some time earlier Rotberg (30) made an especially detailed analysis of the results of 377 tests with a bovine OT in 219 leprosy patients of various kinds and 135 controls comprising 63 preventorium children and 72 adults, mostly skin clinic patients. The leprosy patients gave somewhat more reactions than the controls, both in total (48% *vs* 38%) and at the different age levels. The bacteriologically positive cases gave, altogether, a higher positive rate than the negatives (53% *vs* 41%), but that result was due to inclusion of the children; the bacteriologically positive adults (76 cases) gave 63 per cent positive against 73 per cent among the bacteriologically negatives (26 cases). For the type groups, considering only the 102 adults, the lepromatous group (37 cases) gave 76 per cent positive against 67 per cent for the tuberculoids (9 cases) and 59 per cent for the maculoneurals (56 cases).

These results led Rotberg to disagree with the Italian writers who had held that leprosy affects reactivity to tuberculin, and to conclude that no particular form of the disease presents any peculiarity in this matter. He ascribed the higher percentage of positives among his nodular cases to the habitually higher frequency of tuberculosis among them.

DATA FROM TUBERCULIN-LEPROMIN STUDIES

In recent years interest has been taken in the relationship of the tuberculin and lepromin reactions, but few of the records contribute to the question of the relation of leprosy infection and tuberculin sensitivity.

Fernandez (14) worked first in São Paulo where he used the von Pirquet and Mantoux tests in parallel, but for the latter only the low 1:10,000 dilution; the results of the two tests were not recorded separately. Among 176 adult leprosy patients, mostly lepromatous, he got the extraordinarily low figure of 41 per cent positive, hardly more than in the younger groups; of 227 young patients 32 per cent reacted, and of 251 child contacts 35 per cent. In Rosario, where factory workers are said to vary from 87 per cent to 100 per cent positive in different age groups (33), he used a 3-dose Mantoux test, the third dose the massive one of 1:10 (i.e., 10 mgm.), and got 93 positives in 100 leprosy patients, but only 28 per cent in 193 orphan-asylum children and 46 per cent in 50 leprosy-contact

children. He concluded that there is no relation to the type of the disease, for 95 per cent of the lepromatous cases were positive and 91 per cent of the tuberculoids. There was a difference, probably due to sampling, between the 32 contacts of lepromatous cases and the 18 contacts of neural cases, 59 per cent of the former being positive and only 22 per cent of the latter. No explanation of this difference was offered.

In French Guiana, Floch and Lajudie (15), with the von Pirquet test, found no evidence of a tuberculosis sensitizing effect in leprosy or of any difference between the types in this respect. Children with leprosy at the Marchoux School under 15 years of age (79 cases) were 32 per cent positive, and those over 15 (22 cases) 54 per cent, as compared with 25 per cent (1,116 persons) and 37 per cent (257 persons) in the same age groups of the normal creole population. Of 11 lepromatous cases 36 per cent were positive, and of 39 others 41 per cent.

On the other hand Schujman (33), testing adult patients with the same high maximum dose as Fernandez had used, observed 96 per cent positive in 88 tuberculoid cases and 81 per cent in 122 lepromatous ones. The difference was greater with the first dose (1:10,000), the percentages being 89 and 63, respectively. Nevertheless he does not accept the idea of anergy to tuberculin in leprosy (33a).

EVIDENCE OF TUBERCULIN ANERGY IN LEPROSY

It appears that, back in 1924, Bernucci (5) asserted that leprosy infection causes reduction of reactivity ("anergizes") to tuberculin or any other antigen, specific or nonspecific; with tuberculin, he had found only 32 per cent of 34 cases positive and only 1 case strongly so. Two other Italian authors are cited in this connection by Rotberg, but their views regarding "anergy" and "hyperergy" in leprosy were based on still fewer tests. Apart from the data given without comment by Souza-Araujo (von Pirquet test), and those of Schujman just related (Mantoux test), the significant information in this field comes from Hawaii and the Philippines, and is based on the Mantoux test done mostly with "purified protein" tuberculins, together with simultaneous tests with antigens of other acid-fast bacilli which materially broaden—and complicate—the matter.

REPORTS FROM HAWAII

The first specific observations in this field are those of Wayson (38), who in 1934 reported results of intradermal tests of 150 noninfirm cases at Kalihi, presumably mostly lepromatous. Besides OT he used—apparently for the first time in leprosy work—a "purified protein" tuberculin, and also for the first time he made parallel tests with other comparable antigens.

The new tuberculin was of the MA-100 kind, the proteins of the culture fluid precipitated by half-saturation with ammonium sulfate (first dose, 0.0005 mgm.; second dose, 0.001 mgm.). The other antigens varied.

The OT tuberculin gave only about 36 per cent positive reactions, in both the 10 to 19-year group and older patients. This figure he compared with recorded findings of from 54 per cent to 76 per cent in local school populations by the same technique. And yet the inmate children were 45 per cent positive or suspicious for pulmonary tuberculosis against only 2 per cent of the school children, and the findings in the adult inmates were comparable.

In view of the work of Mariette and Fenger (22), who in large-scale testing in Minnesota with MA-100 tuberculins had gotten higher positive rates with an avian tubercle antigen than with human (29% *vs* 16%), and much higher (47%) with timothy (*M. phlei*), Wayson tested 56 of his patients with the several antigens as shown in Table 1 hereof. The OT caused more reactions than did the precipitated tuberculo-protein, but the cases were few and he did not regard the difference as significant because in previous testing of 129 patients the two antigens had given practically equal results.

TABLE 1.—*Results of tests by Wayson, in Hawaii, with two tuberculins and other antigens.*

Antigen	Dosage	(Per cent positive)
Old Tuberculin	0.01 and 0.1 mgm.	48
Human MA-100	0.0005 and 0.001 mgm.	32
Avian "proteid"	0.001 mgm.	21
Timothy "proteid"	0.01 mgm.	23
"A3" culture, OT	0.1 and 1.0 mgm.	20

These findings Wayson regarded as all in agreement: the patients were but one-half to one-third as frequently positive to the tuberculins as were nonleprous people in the same community, and only one-half to one-third as frequently positive to the antigens of other acid-fast bacilli as had been reported from elsewhere. The relatively fewer reactions to the other antigens is the reverse of what Mariette and Fenger had found in their work. Wayson suggested that the low tuberculin reactivity observed might be due in part to interference with the circulation in the skin, but that "other unknown causes must be operating."

Several years later Badger *et al.* (4) reported some comparative skin tests made in the same institution during a serological study of certain cultures obtained from leprosy patients there and that of Lleras-Acosta.

The tuberculin used in this work was Seibert's PPD. (Doses: first, the usual 0.00002 mgm.; second, 0.0002 mgm., 1/25th of the usual amount.)

The other antigens were OT preparations of a Kalihi strain, the Lleras-Acosta strain, and *M. phlei.* (Doses: 0.1 cc. of 1:10 dilutions.) The results are summarized in Table 2.

TABLE 2.—*Results (per cent positive) of tests by Badger et al., in Hawaii, with PPD tuberculin and other antigens.*

Case group	No. of cases	Antigen			
		PPD	Lleras	Kalihi	Phlei
Leprosy:					
Maculoanesthetic	50	84	80	84	96
Nodular & infiltrative	60	55	55	58	88
Tuberculosis:					
Disease stationary	31	*a*	100	90	-----
Disease progressing	18	*a*	78	44	-----

a Not tested; presumably mostly tuberculin sensitive.

The first point of interest is the markedly lower frequency of response to PPD of the lepromatous cases than of the "maculoanesthetic" ones. Second, the results with the Lleras and Kalihi antigens, as used, were quite the same as those with the tuberculins. Third, the *phlei* antigen gave very high, and only slightly different, rates in both leprosy groups, contrary to Wayson's results with an antigen of that microorganism. Fourth, the Lleras and Kalihi antigens gave extremely high percentages in the stationary tuberculosis cases, but not in the progressive tuberculosis group. In short, high proportions of the maculoneural cases were reactive to all four antigens, whereas the lepromatous cases were highly reactive only to the antigen of *M. phlei,* the only frank saprophyte involved. The high rates with that antigen are like those obtained with it by Fenger *et al.* (12) in all adult groups tested in Minnesota, in tuberculosis cases and others alike.

The authors spoke of the reactions to the Lleras and Kalihi antigens as "nonspecific," and noted—without discussing the point—that in both the leprosy and the tuberculosis groups there was an "indirect" (i.e., inverse) relationship between activity of the disease and reactivity to all of the antigens. Nor did they mention Wayson's conclusion that leprosy lessens reactivity to tuberculin; on the contrary, they concluded that "leprosy will cause positive tuberculin reactions when a purified protein derivative is employed..." The basis for that conclu-

sion is not evident, but if it is correct it could apply only to their maculoneural group and does not negative the suggestion of an anergizing influence in the lepromatous group.

Other pertinent reports.—Mention should be made of the findings of Tovar Daza (37), in Columbia, with an OT-type preparation of the Lleras bacillus.

Whereas he found 91 per cent of 23 healthy persons to give positive reactions, all but one of them 3+, and 73 per cent of 15 cases of pulmonary tuberculosis, the results in the leprosy groups were: arrested (12 cases), 58 per cent; bacteriologically negative (29 cases), 32 per cent; bacteriologically positive (48 cases), 19 per cent.

There is interest in the 3:1 ratio of the arrested and bacteriologically positive leprosy cases—the negative group intermediate, and none as high as either of the control groups—and also in the fact that the cases of pulmonary tuberculosis had a lower reaction rate than the healthy controls. This recalls the experience of Rotberg and de Oliveira (31) with the lepromin reaction in tuberculosis cases. Thirty-five per cent of those in bad condition were negative, against only 7.5 per cent of negatives among those in good condition.

REPORTS FROM THE PHILIPPINES

The most extensive and diversified investigation in this field was carried out in the Philippines in 1937 by a committee whose work has been largely ignored because it failed in its objective of arriving at a specific skin test for leprosy (24, 25). Furthermore, the report is embarrassing because of the abundance of the data, which pertain to 5,174 tests made with many antigens and numerous groups of people. There was to be a separate paper on the tuberculin tests with reference to tuberculosis in the various groups studied, but it was not and cannot be written. To facilitate their examination the principal data have been reduced to Table 3, which shows only rounded-off percentages of positive reactions in the principal tests.

The ten antigens shown in the table were of Seibert's TPT (tuberculin-protein-trichloroacetic-acid-precipitated) type, which preceded the now standard PPD variety. The *hominis* lot proved in preliminary trials to be of low antigenicity, so a one-dose test was used with the recommended second dose (0.005 mgm.)—the proper one for human MA-100 (26). With it only 8.4 per cent of the positive reactions were 1+, but on the other hand only 4.2 per cent were 4+; nor does it seem to have been excessive as regards false positives. The *avium* antigen was used in the same dose, while the others were used in double that amount.

Regarding the groups tested, it should be recalled that the "Welfareville noncontacts" were inmates of a training school for both orphans and

TABLE 3.—*Results, in percentages found positive, obtained by the McKinley Committee (1937) with 10 TPT "tuberculins" of various mycobacteria.* a

Group and number of individuals b	Cases	Hominis (0.005 mgm.)	Avium (0.005 mgm.)	Marinum (0.01 mgm.)	Smegmatis (0.01 mgm.)	Phlei (0.01 mgm.)	Karlinski (0.01 mgm.)	Daines (0.01 mgm.)	Phipps L-1 (0.01 mgm.)	Duval (0.01 mgm.)	Rat leprosy (0.01 mgm.)
Manila groups											
Welfareville noncontacts	110	90	87	(89)	57	-----	61	69	64	(100)	-----
Culion-born children	112	86	68	-----	36	-----	55	51	57	-----	-----
San Lazaro inmates	100	85	54	(30)	26	-----	20	29	32	(60)	-----
Culion groups											
Staff members	84	54	-----	-----	-----	85	82	90	77	-----	88
Active cases	95	69	-----	-----	-----	57	57	76	73	-----	72
Preparole cases	92	93	-----	-----	-----	75	75	79	78	-----	81
Cebu groups											
Family contacts	109	64c	-----	-----	-----	-----	49	-----	-----	-----	-----
New inmates	77	51	-----	-----	-----	-----	(24)	-----	-----	(43)	-----
Preparole cases	100	78	-----	-----	-----	-----	29	-----	-----	53	-----

a The last five antigens were of supposed "leprosy" cultures.

b Figures in parentheses refer to other and smaller groups. The two such figures underlined were of 30 cases; the others were of around 10 cases.

c This group was 50.4 per cent positive to bovis tuberculin.

young delinquents and therefore not all young children; that the Culion-born "contacts," younger children in another department of the same institution, had been for years mostly away from their parents; that the Culion staff members represent "contacts" but not of intimate degree; that the "family contacts" in Cebu were relatives mainly of bacteriologically negative cases in children, and like the recently-admitted Cebu inmates were mostly country people; that in the Philippines only bacteriologically positive cases are segregated, wherefore the "active" cases were mostly lepromatous; and that the "preparole" patients had previously been of that category.

The results do not indicate a definite conclusion that the reactivity to the human tuberculin in the dose used is affected adversely in lepromatous leprosy, but some degree of that effect may be suspected. Considering how overcrowded was the leprosy department of the San Lazaro hospital it is unexpected that the inmates did not give more, instead of fewer, positives than the much younger Welfareville noncontacts. At Culion the living conditions are decidedly more healthy, but considering the fact

that for many years there tuberculosis was the principal cause of death the positivity rate of the inmates seems decidedly low, as does that of the new inmates at Cebu compared with the family contacts. While the higher rate of the preparole cases at Cebu might be ascribed to longer hospitalization, it may be asked if the very high rate of the comparable group at Culion is ascribable solely to that factor. The possibility suggests itself that subsidence of a repressive factor with recovery from leprosy may also be involved in the relatively high rates of these groups.

As for the other antigens, the fact that the San Lazaro patients should have been so much less reactive to them than were the two other Manila groups affords a definite analogy to the findings with such antigens seen in the Honolulu reports. This condition appears again, though far less strikingly, in the Culion data; the staff members, although only 54 per cent reactive to human tuberculin, gave percentages of between 80 and 90 with all of the other antigens used, whereas the active inmate group gave lower rates with all, and materially lower with *phlei* and one other (contrary to the experience of Badger *et al.*, who found high rates with *phlei*, only, in all leprosy groups, but more in accord with Wayson's results) ; and the preparole cases again showed more reactivity than the active ones.

Finally, a later report from the same source (26) presents limited data on the tuberculin reactions. Early in 1939 the committee was reconvened in Manila to try out there certain spleen-derived materials to test which McKinley himself, in the previous summer, had started for the Philippines in a trans-Pacific airplane which disappeared without trace between Guam and Manila.

The tuberculin in this instance was commercial PPD, and it was used only in the standard first dose. The cases tested were from the same Manila sources as before, 100 Welfareville training-school inmates, 100 Culion-born children, and 100 San Lazaro patients.

Again the two control groups gave practically identical rates, 39 and 38 per cent—naturally much lower than before because of the small dose used—whereas in this instance only one-half as many leprosy patients, 21 per cent, were negative. Whatever may have happened had the nonreactors been tested with a second dose, it can at least be said that the test as applied showed a strikingly low positivity rate in a group of patients which would be expected to have a relatively high index of tuberculosis infection. Here, then, is a more distinct parallel with the condition

to which Bernucci and Wayson called attention, and with that seen in Schujman's first-dose results.

DEGREE OF POSITIVE REACTIONS

If reactivity to tuberculin is interfered with in lepromatous leprosy, it might be expected that not only would fewer such cases give positive reactions but that in those who do so the reactions would be weaker. Only the reports of the McKinley Committees permit examination of this point, and in them no such tendency is found.

From the data in the first of those reports it turns out that the intensities of the reactions in the San Lazaro inmates and the contact children averaged 2.6+ and those of the noncontacts 2.4+. The corresponding groups of the second investigation gave reactions which work out 2.1+, 2.2+ and 1.9+, respectively. The averages for the three Culion groups are identical, all 2.1+. Those of the Cebu family contacts and preparole cases are 2.1+ and 2.0+, while that of the active cases is 1.6+; but this difference can hardly be regarded as significant in view of the findings at the other places.

DISCUSSION

Concerning the early experience with tuberculin in the treatment of leprosy, the fact that it is capable of inducing lepra reaction which products of the leprosy bacillus itself cannot do—at least in lepromatous cases—raises the question whether the cases which so reacted were lepromatous or tuberculoid, or whether tuberculin can, by a group effect, do in the former type of case what specific products cannot do. If the answer to this question is to be found in any later work, it has not been seen.

Subsequent experience with the diagnostic tuberculin tests with the original type of antigen applied by the von Pirquet method gave no reason to question the usual conclusion that the reaction is specific for concomitant tuberculosis in leprosy cases, or to suspect that the leprosy infection in any form may interfere with tuberculin reactivity. Only one report (36) has been seen which has a suggestion of the latter effect, but it does not suffice to engender a doubt.

Results of the original Mantoux test, with Old Tuberculin, have for the most part been of like tenor, certainly giving no support to the idea that leprosy sensitizes to tuberculin. On the other hand one worker, Wayson (38), recorded discordant results which suggest that in leprosy—type not stated—there is a depression of reactivity which he ascribed in part to interference with circulation but in part to other, unknown causes. An indi-

cation of this effect, confined to lepromatous cases only, is found in the results recorded by Schujman (33) with a low first dose of OT, and perhaps also in some of the recent findings of Austin (2), although both have disavowed the idea of a type difference (personal communications).

This indication has been decidedly stronger in the results of intradermal tests with purified protein tuberculins carried out in Hawaii and the Philippines. Wayson got even fewer reactions in his cases with the MA-100 type than with OT; and Badger *et al.* (4), with PPD, got much fewer positives in their lepromatous cases than in their maculoanesthetics. The results reported by the first McKinley Committee (29) with the TPT variety of tuberculin are in some respects suggestive, but those of the second committee (26) with the small first dose of PPD are more so. In consequence, the possibility must be entertained that the peculiar immunological characteristic of lepromatous leprosy, the virtually complete anergy to leprosy-bacillus antigens, may by group effect tend to diminish the cutaneous sensitivity to such tuberculins—which would be the other factor that Wayson believed must exist.

That this may be the case is also suggested by the less debatable fact that also the "tuberculins" of other acid-fast bacilli of various kinds, from the "paratuberculosis" strains isolated from leprosy to the frankly saprophytic *M. phlei*, have been found in the Hawaii and Philippine investigations to induce fewer positive reactions in lepromatous cases than in others. The indication of recovery of reactivity to the various antigens after the disease has been cleared up (seen especially in the Culion groups of the first McKinley committee) is also suggestive. On the other hand, if there is a tendency toward lessening of *frequency* of positive tuberculin reactions in lepromatous leprosy, the few records which permit the analysis give no indication of a lessening of *degree* of positivity in the cases which do react.

The evidence that the type of tuberculin and the method of administering it may be of significance in the present connection is not without some degree of support from other directions. Seibert (34) finds that of three types of protein found in tuberculin, one ("C") has a broader effect than the others—i.e., is especially responsible for nonspecific reactions to large doses—and that OT has more of it than PPD has. And Heimbeck (18) has recently asserted that, at least as a guide to BCG vaccination, the von Pirquet test is superior to the Mantoux because it is

more "stable," although it cannot be said whether that factor is of present significance. Be that as it may, the factor of dose in the Mantoux test is apparently important, whatever type of tuberculin is used. It is with the lower doses that evidence of a type difference of sensitivity is most likely to be seen. Very high doses are liable to give nonspecific effects, for which reason Bjørnstad (6) has recently said that as large a dose as 0.1 cc. of a 1:10 dilution of OT should not be used even in anergic sarcoid cases.

Except for Wayson's limited tests, no record has been found of parallel tests in leprosy with different varieties of human-type tuberculins. Nor has any record been found comparing the results obtained with different methods of testing. Such an investigation could readily be made today only with OT and PPD, it appearing that the older of Seibert's products are not available (34a); and any such study would of course involve variable dosage as well as different methods of application, and could be extended by parallel application of antigens of other mycobacteria.

The whole matter is to some extent complicated by the fact that active tuberculosis cases may give fewer positive reactions to tuberculin and other antigens than quiescent cases. This has been seen in the data of Badger *et al.* (and also of de Tovar to his Lleras OT), so that the former spoke of diminution of reactivity in both "active" leprosy and tuberculosis; and others have spoken of differences in the degree of sensitivity to tuberculin showing an inverse relation to the severity of the tuberculous infection (16). But, quite apart from the fact that actively tuberculous people are sick, while most people with lepromatous leprosy who would be tested are not sick in the same sense, the immunological conditions in leprosy and tuberculosis are very different. Only in Boeck's sarcoid is there an anergy to tuberculin—not at all understood—in any way comparable to that of lepromatous leprosy to lepromin; and the similarity between the two is incomplete because tuberculin-negative sarcoid cases will give a late reaction to injected tubercle bacilli (20), whereas in typical lepromatous cases lepromin does not induce any such reaction.

It is in the problem of the nature of the anergy to lepromin, more than in the question of whether tuberculin testing will reveal tuberculous infection in leprosy patients as well as it does in the general population, that the interest of the present inquiry lies. In tuberculosis a clear distinction is made between the

"native" or "original" anergy of the uninfected state, the "negative" anergy of certain febrile and depleted states, and the "positive" anergy exemplified by the nonreactivity (or loss of reactivity) of sarcoid (20). It has not ben established to what class the lepromin anergy of lepromatous leprosy belongs. Nonleprous children found unresponsive to both tuberculin and lepromin have been made responsive to both by BCG vaccination by the cutaneous and subcutaneous routes (there being here a definite indication of a cross effect between the two antigens, seen also in the high degree of lepromin positivity in cutaneous or glandular—but not pulmonary—tuberculosis); but although lepromatous cases will respond to intracutaneous injections of tubercle-bacillus suspensions, there is no evidence that that response induces lepromin reactivity in those cases. The possibility that light may be thrown on the nature of this state of leprosy thereby would seem to justify an intensive investigation of the kind here suggested.

SUMMARY AND CONCLUSIONS

When Koch's Old Tuberculin was given by subcutaneous injection in treatment, it often induced lepra reaction. It is not known whether they were tuberculoid cases which reacted in that way, or whether tuberculin can by nonspecific effect induce reactions in lepromatous cases which lepromin cannot provoke.

Diagnostic skin tests employing Old Tuberculin by the von Pirquet method have given results which afford no evidence that leprosy infection may give rise to false positive reactions. In all instances where control data on normal-population groups are given, the results are closely comparable. Furthermore, except perhaps for a single report found there is no evidence of a case-type difference in reactivity with this test.

The results of diagnostic tests by the Mantoux method with Old Tuberculin are mostly of like tenor. One author, however, reported fewer reactions in leprosy cases than in normals and suggested that there may be operative some unknown factor which affects reactivity. An indication of such an effect in lepromatous cases is to be seen in certain data of low-dose tests recorded by one or two other workers.

When purified protein derivatives have been used in the Mantoux test there is evidence of a tendency to lowered frequency of reaction in lepromatous leprosy than in other forms. These products are less prone to cause nonspecific reactions than is OT, at least when large doses are used.

Lowered reactivity of lepromatous cases has been more conspicuous in the results of tests made with tuberculin-like products of other mycobacteria. The differences have, on the whole, been marked with certain strains of uncertain status ("paratuberculosis" cultures) more than with the frankly saprophytic timothy bacillus, presumably because its antigenic structure is more different from those of the pathogens.

In lepromatous cases which have recovered there is a suggestion of a tendency to recovery of reactivity to various antigens. The indication seen in one report that children living in contact with lepromatous cases may be more reactive to tuberculin than contacts of tuberculoid cases is also of interest.

Further investigation in this field, with various antigens applied in varying doses and perhaps in different ways, might be profitable especially with respect to the elucidation of the unexplained lepromin anergy characteristic of the lepromatous type of leprosy.

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