

alone, it is clearly undesirable to use a drug which is poisonous in doses only a little above those which are effective. In obstinate cases its use may be countenanced, but only when strictly controlled by the doctor, who must be guided by knowledge of the basal metabolic rate. If these capsules be given to patients in bulk it will not be long before one of them doubles or trebles the dose in the same light-hearted way with which thyroid is treated, and then we shall have further scares from the coroner's courts.

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CUTANEOUS SENSITIVITY TO ACID-FAST BACILLI IN SUSPENSION

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Muir in India and Mitsuda and Hyashi in Japan have shown that, while advanced cases of nodular leprosy are negative to intradermal injections of "leprolin," a suspension of leprosy nodule in a state of fine division, the mode of preparation of which has been described in their articles on the subject, the more resistant types of anaesthetic lepers react positively to these injections. They report also that, while infants and young children are negative, healthy non-leprosy adults are usually positive to such injections, just as are the more favourable anaesthetic cases. Muir, being anxious to ascertain for certain whether healthy adults in countries where leprosy is no longer endemic reacted as do non-leprosy adults in India, suggested to one of us that he would be prepared to supply "leprolin" if these tests could be performed. We received from Calcutta a supply of Muir's "leprolin" early in October. This preparation, examined microscopically, was found to contain very large numbers of acid-fast bacilli irregularly distributed as single rods, small clumps, and large bundles. Tested for sterility, it gave no growth either aerobically or anaerobically, and a guinea-pig, into which 1 c.cm. was inoculated subcutaneously, has remained free from signs of infection to date.

RESULTS OF TESTS

Through the kindness of Dr. P. K. McCowan and his staff it was possible to carry out these tests on a group of twenty-five non-tuberculous male adults at the Cardiff City Mental Hospital, where successive series of tuberculin tests, designed to throw light on the degree of sensitivity of the population of a mental hospital, have been in progress for some years. As the tests proceeded it became clear that we ought to discover, as far as possible, how far the positive reactions noted were comparable, not only with tuberculin sensitivity, but with sensitivity to a suspension of killed tubercle bacilli, and our tests were accordingly supplemented to allow of this comparison.

On October 30th, 1933, each of the twenty-five men received in the skin of the right upper arm an intradermal injection of 0.1 c.cm. of "leprolin," diluted to 1 in 5 in sterile carbol

saline, and, at the same time, 0.1 c.cm. of a 1 in 2,000 dilution of old tuberculin in the skin of the left arm. The results were observed, and, where positive, measured in extent of raised palpable reaction area, on the third day and afterwards at weekly intervals up to the end of the sixth week.

All those tested gave the usual positive response to tuberculin, which reached its maximum in most cases on the third day, was still well marked, though fading, after one week, and, except in five cases, ceased to be measurable by the end of the second week.

With the "leprolin," thirteen cases were recorded as negative on the third day, and twelve gave more or less marked positive reactions, but the majority had become positive by the end of the first week, five only being recorded as negative or doubtful on the eighth day. All, with the exception of one patient, a Dane, who attained to a "doubtful" only on the eighth day, and was negative at all other dates, were "positive" sooner or later during the time of observation. Their reactions will be considered in greater detail later. The rapid disappearance of the well-marked reactions to old tuberculin, a filtrate containing the soluble elements of acid-fast organisms, as compared with the persistent though less extensive reactions following the inoculation of a suspension of whole leprosy bacilli, led us naturally to attempt a comparison between these latter and a suspension of unbroken tubercle bacilli, killed by heating, as had been the leprosy bacilli. To this end an egg culture of "human" tubercle bacilli, eleven days old, was suspended evenly in distilled water, counted, killed by heating, and diluted with carbol saline so as to contain 100 million bacilli in 1 c.cm. The sterilization was effected at a temperature of between 90° and 95° C. for one hour.

On October 20th, the remains of the tuberculin tests having by now practically disappeared, each of the twenty-five already tested were given an intracutaneous inoculation of 0.1 c.cm. of tubercle bacillary suspension, equivalent to 10 million dead bacilli, into the skin of the left upper arm, thus permitting a comparison with the leprolin reactions, many of which still persisted. As before, the results were read on the third day and at weekly intervals up to the end of the third week.

In examining cutaneous sensitivity to suspensions of acid-fast bacilli, the reactions, both to leprolin and to tubercle suspensions, were found to fall into three types, the distribution of these types, however, being very different in the tested group. These types are as follows:

- Type A.—"First high." Maximum reaction on third day.
 Type B.—"First low." Maximum reaction on eighth day.
 Type C.—"First negative." Negative on third day developing later.

The distribution of these types to leprolin and to tubercle bacilli respectively was as follows:

Reaction Type	Leprolin		Tubercle Bacilli	
	No.	%	No.	%
Type A	6	24	21	84
Type B	6	24	2	8
Type C	13	52	2	8

It will be noted that the great majority gave their maximum reaction to tubercle bacilli on the third day, just as they had done to old tuberculin; whereas the majority of the group were negative to leprolin on the third day.

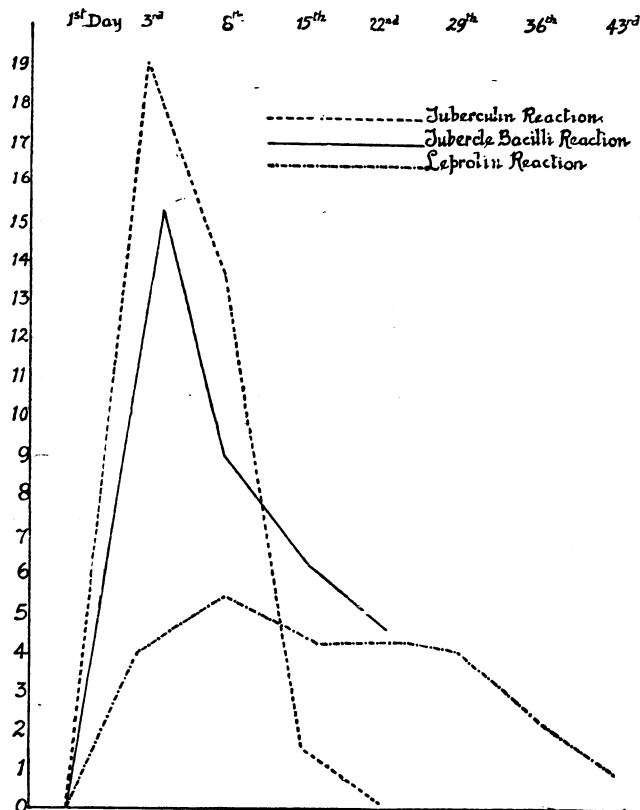
The reaction size in millimetres—maximum transverse measurement—is given, as the average for those included in each type, on each day of observation up to the end of the third week, by which date all the reaction areas were rapidly diminishing in intensity.

Average Reaction Size in Millimetres

Reaction Type	Antigen	3rd Day	8th Day	15th Day	22nd Day	No.
Type A	Leprolin	9.7	7.5	4.3	4.3	6
	T. B.	17.6	9.6	7.7	4.2	21
Type B	Leprolin	6.8	9.5	6.4	6.0	6
	T. B.	9.0	13.0	12.0	8.5	2
Type C	Leprolin	0	3.2	3.5	3.8	13
	T. B.	0	5.2	6.0	5.2	2

It will be noticed that, in addition to the fact that a much larger proportion reacted, in the "Type A" manner, to tubercle bacilli than to leprolin, the reactions to tubercle bacilli were more extensive than those to leprolin in all the types, and on every day of observation. It is interesting to see that the "Type B" reactions persisted longer as a fairly extensive area of inflammatory thickening than the other types, both for leprolin and for tubercle bacilli. "Type C" was characterized by consisting, on the whole, of weak reactors. It is worth noting that the two persons giving a "Type C" reaction to tubercle bacilli were both "C" types to leprolin also, and were the two who reacted least to leprolin, both being so poor in response that it was a matter of some doubt as to whether they should be recorded as positive.

It seems from the results recorded that, in the "healthy" persons tested, the typical reaction to tubercle



bacilli is, like the reaction to tuberculin, one of early development with a maximum on the third day, while the typical reaction to leprolin is characterized by a slow development, being at first negative or doubtful, and only generally reaching its maximum at the end of the third week.

The relative extent and duration of the reactions to tuberculin, tubercle bacilli, and leprolin respectively is illustrated in the chart; but it is to be added that the reactions to tubercle bacilli had all the appearance of persisting quite as long as, or longer than, those to leprolin when the observations were brought to an end at the twenty-second day.

To see how tuberculous patients reacted to a tubercle bacillary suspension it was decided to test the same suspension, diluted so that 0.1 c.cm. contained 1 million bacilli only, in a series of clinically definite cases.

Five adult males with relatively chronic pulmonary tuberculosis, and three children with non-pulmonary lesions, were inoculated intradermally on November 27th, 1933, two children with "doubtful" non-pulmonary lesions being included as controls. All the definitely tuberculous cases

reacted according to the "A" type, while the two "doubtful" children proved negative. Tested with a dilution of 1 in 5,000 of old tuberculin on December 6th, the two "doubtfuls" were again negative, all the definite cases being markedly positive on the third day.

It is to be noted that, where bacillary suspensions were used for intradermal injection, there was a decided tendency to a central necrosis, a small loss of substance at the centre of the reaction area in certain cases, not necessarily those who had reacted most extensively at first. In the leprolin series five showed this central lesion on the twenty-second day, two more on the twenty-ninth, and still another on the thirty-sixth. In the tubercle bacillary series this central necrosis was earlier in appearance and more common, six cases showing it on the eighth day, while a further eleven persons had central loss of substance by the fifteenth day, the remaining eight having unbroken reaction areas up to the twenty-second day, after which observations ceased. By that date the majority of the reaction ulcers resulting from the necrotic process and noted on the eighth day had already dried up or healed, and the leprolin reactions, too, had scabbed over or disappeared by the forty-third day of observation.

SUMMARY OF OBSERVATIONS

The factors determining the responses noted to the intradermal inoculation of heat-killed acid-fast bacillary suspensions in persons free from the signs of clinically active tuberculosis call for further study, and can only be discussed as a part of the larger subject of bacterial hypersensitivity. Here it will suffice to summarize the points brought to light in the series of observations described.

1. The typical reaction to tubercle bacillary suspension resembles the typical intradermal tuberculin reaction in reaching its maximum on or about the third day. It differs from the tuberculin reaction in persisting longer and showing a tendency to late central necrosis. The writers have noted central necrosis as a rare occurrence after intracutaneous tuberculin tests, but these have been marked at the third day at the height of the reaction, whereas the central necrosis caused by bacillary suspension comes on as the initial inflammatory reaction is fading.

2. The typical reaction to leprolin (suspension of heat-killed leprosy bacilli and leprosy tissue), when applied to healthy persons in an area free from endemic leprosy, differs from the intracutaneous tuberculin reaction in remaining for some days negative or doubtful, gradually developing to a maximum between the eighth and the fifteenth day, and lasting on for from four to six weeks as a diminishing zone of inflammatory oedema, often showing late central necrosis.

3. Six out of twenty-five persons tested with leprolin reacted to the injection in a manner similar to the usual response to intracutaneous tuberculin or to tubercle bacillary suspension, showing that they were hypersensitive to a bacillary antigen to which, presumably, their tissues were "virgin soil." This result suggests that "group" sensitivity must play a definite part in reactions to acid-fast bacillary constituents.

4. It is of interest that, in two probably non-tuberculous children tested with intracutaneous tubercle bacillary suspension, no reaction was observed either late or early, the bacilli being disposed of without inflammatory response.

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