

HYPERSENSITIVENESS TO TUBERCULIN AS DETERMINED BY INTRACUTANEOUS INJECTION OF DIFFERENT DOSAGES*

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Hypersensitiveness to tuberculin was studied in 28 patients, 13 males and 15 females. Fifteen were 10 years old or younger, 4 were between 11 and 20 years of age, 5 between 21 and 30, and 4 were between 30 and 60 years of age. Nineteen were in the first stage of the disease, 6 in the second stage, and 3 in the third. Eighteen were in the first class of Turban, 7 in the second class, and 3 in the third. Twenty-two were improving, and 6 were stationary. The patients were on my service in the Eagleville Sanatorium for Consumptives, the Home for Consumptives, Chestnut Hill, the pediatric ward of the Jewish Hospital, and in my private practice.

The tuberculin was injected into the skin, as a rule three injections of different strengths being made at one time in the forearm in a diagonal line, so that no injection was directly below another. With a few exceptions that will be referred to later, the smallest injection was given distally, and the largest proximally. Care was of course taken to insure accuracy of dosage.

T. R. (Tuberculin Rückstand) was injected in the case of all but 2 of the patients; the latter were injected with old tuberculin. As a rule the first injections were one ten-millionth, one millionth, and one hundred-thousandth of a milligram. If no reaction was observed, the patient was next injected with one ten-thousandth, one thousandth, and one hundredth of a milligram. If these injections provoked no reaction, the patient was injected with one tenth of a milligram, one milligram, and ten milligrams. The injected areas were examined at the end of 24 hours in every case, and again at the end of 48 hours in most of the cases, and in a number of cases at other intervals up to 36 days. In a few cases the patient tested was examined at intervals of several hours.

The character of the response varied. An areola alone was noted in 12 patients and 17 tests; induration alone in 4 patients and 5 tests; a papule alone in 4 patients and 5 tests; areola and induration together in 14 patients and 34 tests; areola and papule in 19 patients and 37 tests; induration and papule in 2 patients and 3 tests; and areola, induration, and papule in 17 patients and 48 tests. Only when induration or a papule was present was the response regarded as a true reaction.

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VARIATION IN HYPERSENSITIVENESS

The patients varied greatly in their degree of hypersensitiveness, one patient reacting to one ten-millionth of a milligram, and another only to ten milligrams, a dose one hundred million times as great (Table 1). Six patients reacted to one ten-millionth of a milligram, 2 patients to one millionth of a milligram, 7 to one one-hundred-thousandth of a milligram, 2 to one ten-thousandth of a milligram, 1 to one thousandth of a milligram, 1 to one hundredth of a milligram, 3 to one

TABLE 1
THE REACTION IN EACH PATIENT TO THE DIFFERENT DOSES OF TUBERCULIN

Patient	Duration	Milligrams Injected								
		.0000001	.000001	.00001	.0001	.001	.01	.1	1	10
S. G.	2 wk.	+	—	++	?	++	+++			
J. G.	2 wk.	—	—	++	—	+++	+			
C. C.	2 wk.	+	+	+	+	+++	++			
Y. D.	2 wk.	+	+	+	+	+++	++			
M. C.	2¼ mo.	—	—	+	+++	++	+++			
J. P.	2¼ mo.	—	—	+	+	+++	+++			
J. Y.	2¼ mo.	—	—	++	++	—	—			
R. P.	2 mo.	—	—	++	++	+	+++			
J. B.	2 wk.	—	—	—	++	+	+++			
D. A.	2¼ mo.	—	—	++	++	++	+++			
Y. S.	6 wk.	—	—	—	+	—	—	++	++	
R. G.	2¼ mo.	—	+	—	++	++	+			
E. P.	6 wk.	+	+	—	—	+	+	+++	++	
R. B.	2 wk.	+	?	—	+	+	++			
I. A.	2 wk.	?	?	++	++	++	++			
S. K.	1 day	—	+	—	—	—	—			
O. W.	2 wk.	+	+	+	?	?	?			
E. J. M.	1 wk.	—	—	—	?	+	+		
I. P.	1 day	—	—	?	—	—	?	?	+++
E. J.	1 wk.	—	—	—	—	—	?	?	+++
G. R.	10 days	+	—	—	+++	+
H. G.	1 day	—	—	—
G. F.	1 day	—	—	—
H. J.	1 day	+	+	—
W. S.	1 day	+	+	—
F. M.	1 day	—	+	—

The letters are the initials of the patients' names, "Duration" refers to the time from the first to the last injection, — = no reaction, + = slight reaction, ++ = moderate reaction, and +++ = marked reaction.

tenth of a milligram, 2 to one milligram, and 1 to ten milligrams. Great irregularity was shown in the reactions. Only 12 of the 28 reacted to all the doses of tuberculin above the one that caused the minimal reaction. The rest failed to react in one or more instances to a dose larger than that which caused a distinct reaction. In 10 of these the injection of both doses was made at the same time. In 5 of the 16, including one of the group just mentioned, the larger dose to which they failed to react was the first of a subsequent series of 3 injections given after a short interval — in some cases 2 weeks, and in one 2 months, after the previous series. Failure to react, therefore, may have been due to

a lessening of the hypersensitiveness during the interval. In 1 patient the first reaction was slight and may have been a false reaction. One patient failed to react at all to a dose of one-hundredth milligram.

In only 1 patient was there any systemic reaction. A woman, 26 years of age, in the third stage and in the third class of Turban, showed no reaction of any sort to doses of one ten-millionth, one millionth, one one-hundred-thousandth, one ten-thousandth, one thousandth, and one hundredth of a milligram. Following a subsequent injection of one-tenth milligram there appeared an areola one-fourth inch in diameter, and following the simultaneous injection of 1 milligram an areola one-half inch in diameter. Following the injection at the same time, however, of 10 milligrams, an abscess developed, which after 3 weeks still contained fluid. The patient developed a fever which persisted and she became progressively worse. Three other patients developed abscesses at the site of inoculation, not due to infection, and resembling the abscesses I have seen occasionally develop after the therapeutic injection of tuberculin and of Sherman's "non-virulent tubercle bacilli vaccine." A boy aged 7 years, an

TABLE 2

REACTIONS IN THE SAME PATIENTS TO THE SAME DOSES, THE LARGEST DOSE ON ONE OCCASION HAVING BEEN INJECTED DISTALLY AND ON ANOTHER PROXIMALLY

Patient	8/23/15			10/16/15		
	Proximal .0000001 mg.	Middle .000001 mg.	Distal .00001 mg.	Distal .0000001 mg.	Middle .000001 mg.	Proximal .00001 mg.
S. G.	—	—	—	+	—	++
J. R.	—	+	+	—	—	++
C. C.	—	?	?	+	+	+
Y. D.	+	+	?	+	+	—

incipient case in Turban's Class 1, had shown very slight induration and no areola to an injection of one hundred-thousandth of a milligram. Ten weeks later he showed a slight papule one-fourth inch in diameter, covered with a slight areola, at the site of the injection of one ten-thousandth of a milligram, and a marked and indurated papule with redness in the center and a slight areola seven-eighths inch in diameter at the point where one-hundredth milligram had been injected simultaneously. This papule was still hard at the end of a month, and most of the abscesses began thus altho no abscess developed here. Between these two papules, however, where one-thousandth milligram had been injected at the same time, a very marked and indurated papule appeared, seven-sixteenths inch in diameter, with marked redness and with a moderate areola seven-eighths inch in diameter. This papule remained hard and indurated for 2 weeks, then became fluctuating, and shortly afterward disappeared, leaving an area of induration that persisted for several weeks. Another boy 9 years old, in the first stage and the first class of Turban, who had not reacted to one ten-thousandth of a milligram, developed small abscesses the size of peas 1 week after the injection at the same time of one thousandth and one hundredth of a milligram, the site of the former having shown a marked and indurated papule and a slight areola, five-eighths inch in diameter, and the latter a slight papule without much induration and a slight areola, three-fourths inch in diameter. A girl aged 12 years, in the first stage and the first class

TABLE 3
THE CHARACTER OF THE REACTION AFTER DIFFERENT INTERVALS

Patient	Milligrams Injected	24 Hours			
		Papule	Induration	Areola	Tender
R. G.001	—	+	++	—
	.01	++	++	++	+
	.1	++	++	++	+++
E. P.000001	—	+	+	+
	.01	—	+	+	+
	.1	—	+++	++	++
S. G.01	+	+	+	—
	.1	++	+	+	—
	1	++	+++	+	—
C. C.00001	+	—	+	—
J. Y.01	—	+	+	—
	.1	+	++	+	—
	1	++	+++	++	—
R. P.001	—	++	+	+
	.01	—	+	+	+
	.1	++	+++	++	+++
J. B.001	—	++	+	+
	.01	—	++	+	++
	.1	+	++	++	+++
D. A.00001	—	+	+	++
	.0001	—	+	+	—
	.001	+	++	+	—
M. C.0001	—	++	++	—
	.001	+	+++	++	++
	.01	—	+	+	++
J. P.001	—	+	+	++
	.01	—	+	+	++
	.1	—	+	+++	+
L. A.00001	++	++	+	—
C. W.0000001	—	—	++	—
	.000001	—	—	++	—
	.00001	—	—	++	—
R. V.000001	++	+	++	—
	.000001	++	+	++	—
	.00001	++	+	++	—
E. G.001	—	—	+	+
	.01	+	+	+++	+
	.1	+	+	+++	+
G. P.000001	—	—	+	—
	.0001	—	—	+	—

TABLE 3—Continued

THE CHARACTER OF THE REACTION AFTER DIFFERENT INTERVALS

48 Hours				15 Days			
Papule	Induration	Areola	Tender	Papule	Induration	Areola	Tender
— ++ +++	++ + +++	++ ++ ++	— + +	++ ++ ++++	++ ++ +++	— — —	— — ++
— — —	— — ++	— — ++	— — —	— — ++	+ ++ +++	— — —	— — —
— — —	— + +	— — —	— — —	— — —	— — —	— — —	— — —
— + +	— — +	— — —	— — —	— ++	— ++	— —	— —
— ++	+++ ++	++ ++ ++	++ ++ ++	— —	+ ++	— +	— —
— +	— +	— —	— —	— —	— ++	— —	— —
— — —	— + —	— — —	— — +	— + —	— + —	— — +	— — —
++ ++	— +	++ —	— —	— —	+ +	— +	— —
— — —	— + —	— — ++	— — ++	++ ++	++ ++ +++	++ ++ ++	— — —
— + +	++ + +	++ ++ ++	— — —				
+++ +++ +++	+ + +	++ ++ ++	— — —				
— + —	— + —	— + —	— + —				

of Turban, on the day following the injection of one-tenth milligram developed a distinct papule, induration, and areola, the latter measuring 1 inch by $1\frac{3}{8}$ inch, with marked tenderness but no pain. The next day the area was marked, indurated, and tender and surmounted by an acutely inflamed papule, one-eighth inch in diameter. The areola remained 3 days, but the papule became a pustule or abscess, at the end of 2 weeks still showing induration, softening, and tenderness.

THE LYMPHATIC CIRCULATION AS A FACTOR

In order to avoid the possibility of the lymphatics carrying part of a larger dose of tuberculin to the place where a smaller dose was injected, the largest dose was injected proximally and the smallest distally. For the same reason the injections were made in a diagonal line so that no two would lie in the same direct line of lymphatic circulation.

By mistake, however, in the first tests that were made, the smallest dose was injected proximally and the largest dose distally (Table 2). As these patients were 7 weeks later given the same dosages in the reverse order, they should furnish an interesting example of the difference in reaction of 3 doses dependent on their position. The reactions showed such variance, however, in the 4 cases records of which were available, that no conclusion can be drawn.

CHANGES OCCURRING IN THE CHARACTER OF THE INDIVIDUAL REACTION

Another interesting study is furnished by observations of the result of the test at various intervals (Table 3).

One patient who received injections of one ten-millionth, one millionth and one one-hundred-thousandth of a milligram on the one arm showed the same reactions to all. An hour and a half after the injection there was marked erythema; 5 hours after there was an area of erythema 7 or 9 mm. in diameter; $14\frac{1}{2}$ hours after there was a pink areola 5 mm. in diameter; 45 hours after there was a slight elevation and the pink areola was 7 mm. in diameter; and 65 hours after the injection there was a slight areola 1 cm. in diameter with a slight elevation.

Forty reactions in 15 patients were examined both on the day following and on the second day following the injection. The reaction was greater after 48 hours than after 24 hours in 7 cases and 10 tests, less in 12 cases and 25 tests, and the same in 4 cases and 5 tests. I have no notes for the third and fourth days. One patient, who showed

no reaction after 24 hours, showed elevation and a slightly red areola after 5 days. In another case the papule was still hard and raised on the sixth day. I have no notes for the seventh day. A marked reaction was noted on the eighth day in a test which showed nothing after 24 hours and a diminishing reaction on the fifth day. I have then no

TABLE 4
THE DECREASE IN HYPERSENSITIVENESS IN PATIENTS AFTER AN INTERVAL OF SEVERAL MONTHS

Patient	Interval	Milligrams Injected								
		.0000001	.000001	.00001	.0001	.001	.01	.1	1	10
S. G.	5½ mo.	+	—	++	?	++	+++ +	+	+++	
J. R.	5 mo.	—	—	++ ++	—	+++ ++	+			
C. C.	5 mo.	+	+ ++	+ ?	++	++	++			
Y. D.	5 mo.	+	+	—	+	++	++ +	++	++	
M. C.	2¼ mo.	—	—	+	+++ ++	++ ++	+++ +			
J. P.	2¼ mo.	—	—	+	+	+++ ?	+++ +	+		
J. Y.	2¼ mo.	—	—	++	++	+	— ?	++	+++	
R. P.	2¾ mo.	—	—	++	—	++ ++	+++ +	+++		
J. B.	2¼ mo.	—	—	—	++	+	+++ ++	++		
D. A.	2¼ mo.	—	—	++ +	++ +	++ ++	+++			
Y. S.	4 mo.	—	—	—	—	—	— ?	++ +	++ +++	
R. G.	2¼ mo.	—	+	—	++	++ +	++ +++	++		
E. P.	3½ mo.	+	+	—	—	+	+	+++ ++	++	
R. B.	5 mo.	+	?	—	+	+	++ ++			
I. A.	5 mo.	?	?	++	++ ++	++ ++	++ ++			

records until the fifteenth day, when the reaction was observed in 9 patients and 27 tests. The reaction was greater 15 days after the test than it was on the day after in 3 cases and 7 tests, and greater than on the second day after the test in 7 cases and 13 tests. It was less than on the day after the test in 8 cases and 16 tests, and less also than on

the second day after the injection in 7 cases and 8 tests. It was the same as on the day following the injection in 5 cases and 5 tests, and it was the same as on the second day after injection in 4 cases and 5 tests. A tender lump was noted on the sixteenth day in one patient, and an abscess on the eighteenth day in another. Five patients were observed on the twenty-second day after injection. In one a scar and induration marked the places where on the day following the injections there had been only a slight papule and a slight induration respectively. A slight papule and marked induration were seen in another patient where on the first day there had been slight induration at one spot and a negative reaction at another. Two showed nothing where there had been very slight induration. One showed no induration where there

TABLE 5
THE ALTERATION IN TUBERCULIN HYPERSENSITIVENESS FOLLOWING A COURSE OF TUBERCULIN TREATMENT*

Patient	Date	Intradermal Test in Milligrams	Date	Dose of Tuberculin in Milligrams
S. G.	10/16/15	.00001	11/ 1/15	.00001
J. R.	10/16/15	.00001†	11/ 1/15	.00001
C. C.	10/16/15	.0000001†	11/ 1/15	.00000001
Y. D.	10/16/15	.0000001	11/ 1/15	.00001
M. C.	11/27/15	.00001	12/ 5/15	.00001
J. P.	11/27/15	.00001	1/ 2/16	.00001
J. Y.	11/27/15	.00001	12/ 5/15	.00001
R. P.	11/27/15	.00001	12/ 5/15	.00001
J. B.	2/ 5/16	.0001	2/20/16	.0001
D. A.	11/27/15	.00001	12/ 5/15	.00001
R. G.	11/27/15	.000001	12/ 5/15	.00001
R. B.	10/16/15	.0000001	11/ 1/15	.00001
I. A.	10/16/15	.00001	10/30/15	.00001
Y. S.	11/27/15	.1	12/ 5/15	.01
E. P.	10/30/15	.001	12/ 5/15	.01

* A comparison of the dose of tuberculin administered therapeutically by mouth with that producing a reaction both before its administration and again several months later during the course of tuberculin treatment; and the effect of the tuberculin given therapeutically in reducing the temperature and producing general benefit.

† Smallest amount tested.

had been very slight induration at one place and fairly marked induration at another. One showed slight induration where the induration had been marked. One exhibited a papule and marked induration where there had been a very slight papule and marked induration, and also where there had been no papule but marked induration. A papule was still palpable in one case on the twenty-third day. Induration following an abscess was present on the twenty-eighth day in one patient. On the thirty-sixth day in another patient discoloration, papule, and induration were observed where only slight induration had been noted on the day following the injection.

DECREASE IN HYPERSENSITIVENESS

Fifteen patients were again tested from $2\frac{1}{4}$ to $5\frac{1}{2}$ months after the degree of hypersensitiveness had been first determined. Five reacted in about the same manner as before. Four reacted to 10 times the previous minimal reaction dose, 3 to 100 times it, 1 to more than 100 times it, and 1 to 1,000 times it, while 1 reacted to one hundredth of it.

RELATION BETWEEN TUBERCULIN HYPERSENSITIVENESS AND
TUBERCULIN TOLERANCE

In these 15 cases it was also possible to study the relation between tuberculin hypersensitiveness and tuberculin tolerance. Nine patients

TABLE 5—*Continued*
THE ALTERATION IN TUBERCULIN HYPERSENSITIVENESS FOLLOWING A COURSE OF TUBERCULIN TREATMENT*

Benefit	Reduction of Temperature	Date	Dose of Tuberculin in Milligrams	Benefit	Reduction of Temperature	Date	Intradermal Test in Milligrams
+	—	4/15/16	.05	+	+	4/15/16	.01†
—	—	3/25/16	.01	+	—	3/25/16	.00001†
+	—	3/25/16	.00000001	+	+	3/25/16	.000001†
+	?	3/25/16	.2	+	?	3/25/16	.01†
+	?	4/15/16	.0005	+	?	4/15/16	.0001†
+	—	4/15/16	.1	+	?	4/15/16	.01
+	—	4/15/16	.02	+	—	4/15/16	.1
—	—	4/15/16	.08	+	+	4/15/16	.001†
?	—	4/15/16	.01	—	+	4/15/16	.001†
+	—	4/15/16	.0002	+	—	4/15/16	.00001†
+	—	4/15/16	.01	+	+	4/15/16	.001†
?	—	3/25/16	.0008	?	?	3/25/16	.0001†
—	+	3/25/16	.01	+	—	3/25/16	.0001†
+	—	3/25/16	.3	+	+	3/25/16	.1†
	—	4/15/16	.1	+	+	4/15/16	.001

were given by mouth as an initial therapeutic dose the exact amount that produced the minimal intracutaneous reaction, 2 were given one tenth of this amount, 2 ten times it, and 2 one hundred times the amount. The initial dose was one one-hundred-millionth of a milligram in 1 case, one one-hundred-thousandth of a milligram in 11 cases, one ten-thousandth of a milligram in 1 case, and one hundredth of a milligram in 2 cases. In no case was the initial dose followed by either a favorable or an unfavorable reaction. My method of giving tuberculin is to hold the dose when it is followed by a favorable reaction, to diminish it when it is followed by an unfavorable reaction, and to increase it when it fails to produce any reaction at all. The early course of tuberculin treatment was apparently of benefit in 9 cases, of possible benefit in 2 cases, and of no benefit in 4. It apparently

reduced the temperature in 1 case, reduced it for a time in 2 cases, but had no lasting or definite effect in the others. There were no untoward effects in any case. After a period varying from 2 to 5½ months the therapeutic dose of tuberculin had been increased until it was 10 times the initial dose in 1 case, 20 times it in 1 case, 30 times it in 2 cases, 50 times it in 1 case, 100 times it in 1 case, 1000 times it in 5 cases, 3000 times it in 1 case, 5000 times it in 1 case, and 20,000 times it in 1 case. In 1 case the dose remained the same.

The actual doses were one one-hundred-millionth of a milligram in 1 case, one five-thousandth of a milligram in 1 case, three ten-thousandths of a milligram in 1 case, one two-thousandth of a milligram in

TABLE 6
DEGREE OF TUBERCULIN HYPERSENSITIVENESS ACCORDING TO AGE, SEX, STAGE, AND PROGRESS OF THE DISEASE

	Total	Milligrams Injected								
		.0000001	.000001	.00001	.0001	.001	.01	.1	1	10
1st stage.....	19	5 1*	2	6	1 1* 1†	1	0	0	1	
2nd stage.....	6	0	0	1	1	1†	0	1 1†	1	
3rd stage.....	3	0	0	0	1	0	1	0	0	1
Male.....	13	1	1	3	3	1	1	1†	2	
Female.....	15	4 1*	1	4	1* 1†	0 1†	0	1	0	1
10 yr. and under.	15	5 1*	0	5	1 1* 1†	0	0	1		
11 to 20 yr.	4	0	2	2						
21 to 30 yr.	5	0	0	0	0	1 1†	1	0	1	1
31 to 40 yr.	1								1	
41 to 50 yr.	1							1†		
51 to 60 yr.	1									
61 to 70 yr.	1									
Improving.....	22	5 1*	2	7	1 1* 1†	1 1†	0	1	1	0
Stationary.....	6	0	0	0	2	0	1	1†	1	1

* Did not react to a smaller dose.

† Tested with O.T. (all others tested with T.R.).

1 case, one hundredth of a milligram in 5 cases, three hundredths of a milligram in 2 cases, a twentieth milligram in 1 case, a tenth milligram in 1 case, a fifth milligram in 1 case, and three-tenths milligram in 1 case. These doses caused favorable reactions in 3 patients and unfavorable reactions in none; they apparently produced beneficial results in 13, possibly in 1, and were of no benefit in 1; they apparently depressed the temperature in 7 patients and possibly in 4 (and not at all in 4 others); they caused harmful effects in none. The intracutaneous test made at this time showed a striking correspondence between the dose clinically determined as the appropriate one and that giving a

minimal reaction. The latter was the same in 1 case, less than a tenth of the therapeutic dose in 5 cases, one tenth in 2, between a tenth and a hundredth in 3, a hundredth in 2, a thousandth in 1 and a hundred times it in another.

A study of the minimal reactions in the patients grouped according to age, sex, stage of disease, and progress reveals certain tendencies: a greater degree of hypersensitiveness seemed to be present in the young, in females, in the first stage, and in improving cases.

SUMMARY

Intracutaneous tests can be made with tuberculin T. R. just as well as with O. T., the preparation usually employed.

The character of the reaction to an intracutaneous injection varies. Reactions most commonly met with, in the order of their frequency, are: areola, induration, and papule; areola and papule; areola and induration; and last areola alone.

Reaction can follow so small a dose as 0.000,000,1 mg., or may not occur until the dose reaches 10 mg., the degree of hypersensitiveness therefore varying 100,000,000 times.

Despite the size of the doses, systemic reaction occurred in only 1 patient, and abscess at the site of inoculation in only 4, the latter probably not being due to infection.

The reaction was greater after 48 hours than after 24 hours in one fourth of the tests; still present after 2 weeks in three fourths of the tests studied, in a number of instances being more marked than after 24 or 48 hours; still present after 3 weeks in 4 of 6 cases studied, in some instances being more marked than after 24 hours; and still present after 5 weeks in 1 case.

Tuberculin hypersensitiveness seems to correspond with tuberculin tolerance. The appropriate therapeutic dose of tuberculin is the dose that gives the minimal reaction when injected intracutaneously. This applies equally well to the initial dose and to any subsequent dose.

The appropriate therapeutic dose as determined by intracutaneous injection is approximated clinically by increasing the dose until a favorable systemic reaction is produced, then maintaining the dose producing this until it no longer produces such reaction, and then again increasing it.

The therapeutic value of tuberculin, properly administered, can be seen in the accompanying decrease in hypersensitiveness.