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Studies of Pulmonary Findings and Antigen Sensitivity Among Student Nurses

V. Doubtful Reactions to Tuberculin and to Histoplasmin

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One of the most difficult problems in many fields of science arises in connection with observations which are often called doubtful or questionable. This problem frequently arises in the medical sciences and is nowhere more strikingly evident than in the interpretation of various diagnostic cutaneous tests.

In observing and interpreting the results of cutaneous tests, reactions are observed which, because of their perceptual characteristics, seem to lie somewhere in-between those which appear to be definitely positive or definitely negative. The existence of such in-between reactions is sometimes denied by establishing rules of classification, often quite arbitrarily, which demand that each reaction be designated as either positive or negative. As those who have had much practical experience know, sharp lines of demarcation are difficult to follow. Many workers, recognizing the difficulty, attempt to solve it by setting up in-between or doubtful categories to which are allocated those observations which seem to be equivocal because of their perceptual characteristics. Such a procedure, while obviously failing to solve the basic problem, does focus attention on the fact that criteria for interpreting cutaneous reactions are not as yet wholly satisfactory.

It is apparent that both the quantitative and qualitative characteristics of reactions to most tests form a continuous scale—from large typical reactions to no perceptible reactions. The problem is further complicated since reactions are not always consistent or stable because of physiological factors associated with local cutaneous or general

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systemic variables within the individual being tested. In addition, mechanical factors in making tests and observing reactions probably produce considerable variation. The existence of false or nonspecific reactions from other causes may well represent another very significant and disturbing element in the interpretation of reactions. The presence of all these factors—the gradual shading of discernible characteristics from one end of the scale to the other, some degree of physiological variation, a sizable experimental error, and nonspecific reactions—provides ample explanation of the difficulty of dividing cutaneous reactions into positive and negative groups.

The efficiency of a diagnostic test cannot be judged primarily in terms of the physical characteristics of reactions or the ease with which they are perceived or read, even though these are practical matters of considerable importance. The only way to distinguish positive from negative reactions is in terms of the relationship of the reactions to pertinent facts or factors quite independent of any characteristics of the reactions themselves. Measurement of the efficiency of a cutaneous test rests, therefore, upon the correlation which may be shown to exist between various classes of reactions and the specific diagnostic fact that the test is presumed to indicate. For example, the efficiency of the tuberculin test is often expressed in terms of the correlation between tuberculin reactions and an index or indices of infection.

Studies on criteria for interpreting cutaneous tests actually become, then, a matter of studying the whole range of reactions to determine where, along a continuous scale, the most significant separation can be made between positive and negative reactions. Theoretically, the objective is to find a point on the scale, above which all or nearly all reactions can be regarded as positive and below which nearly all can be regarded as negative. In practical work, the point tends to become an interval on the scale, a category of reactions where a major transition in interpretation takes place. That whole category of reactions may be considered as doubtful entirely on the basis of the fact that they are doubtful or equivocal, with respect to their interpretation. In other words, such a class of reactions must be considered equivocal purely because of the doubt regarding their meaning not because of uncertainties regarding their physical characteristics.

It is apparent therefore that there are two quite separate and distinct ways of defining doubtful reactions—one on the basis of equivocal appearances, the other on the basis of equivocal interpretations. For any specific test, these two classes of reactions may or may not coincide.

An opportunity to study doubtful reactions and to examine present criteria of interpreting tuberculin and histoplasmin reactions is afforded in material from an extensive study of tuberculosis in student nurses. Several reports bearing on criteria of interpreting reactions have been published from that investigation. In part IV of the series, a preliminary consideration is given specifically to questions of doubtful reactions. The present study is a continuation of that analysis, based on the same data. In the main, however, this report must also be considered as preliminary, essentially only an illustration of a method of analysis.

Methods and Hypotheses

Although the above is a general statement of our perspective on judging cutaneous reactions, definitive analysis requires a much more rigorous formulation of basic conditions and assumptions. To express these matters in explicit terms involves the risk of oversimplification of many aspects of a very complex problem. Nevertheless, we have attempted to define terms, to formulate certain simple hypotheses, and then to illustrate some of the more pertinent consequences. Other hypotheses might be proposed and the rather simple formulation presented here aims only at an explanation of certain major issues and reserves for later consideration such elaborations as would be required to explain many of the complex problems of interpreting cutaneous reactions.

It is assumed, first of all, that the fundamental objective of a diagnostic test is to furnish a technique for separating a population into two groups: for the tuberculin test, for example, into those infected and those not infected with the tubercle bacillus. By definition, the former are designated as *true positive reactors*, the latter as *true negative reactors*.

In actual practice the tests do not divide a population only into two groups. In some respects the tests do more, and no special question is raised by the fact that they permit the further subdivision of positive reactions into different degrees or classes of positivity. For negative reactions, the fact is not so commonly considered but there can be no question that the test reveals similar classes or degrees of negativity.

The idea that one point divides the scale into positive and negative reactions implies that the former are distributed continuously over a part of the scale ending abruptly at a certain point; that the latter are distributed continuously over another part of the scale ending abruptly at a certain point; and that these two points coincide. On both theoretical and practical grounds, this theory appears untenable; it does, however, lead to a simple hypothesis of erroneous classification which is proposed as the central thesis of the present paper: Positive and negative reactions are distributed continuously over a quantitative reaction scale but in such a way that the two distributions overlap to a smaller or larger extent. It is explicitly assumed in this connection that positive and negative reactions cannot be distinguished by the perceptual characteristics of the reactions themselves. As a consequence, any observed distribution of reactions represents a composite one, made up of the addition of the two hypothetical distributions.

If the variations in reactions were mainly caused by experimental errors, the two distributions could, with a uniform testing and reading technique, be assumed to be stable.

The variations in reactions are presumably due, not only to experimental errors, but also to physiological variability of sensitivity. However, if the conditions underlying such physiological variations could be assumed constant, we would still expect the two separate distributions to be very much the same in different populations, for example, in different geographic areas.

Since we assume that the distributions of true positive and true negative reactions overlap, the number of persons showing reactions represented by a certain interval of the scale will consequently consist of a constant proportion of the true positives and another constant proportion of the true negatives. If the overlapping can be regarded, at least from a practical point of view, as taking place only on part of the scale, the scale can be divided into three intervals corresponding to a classification frequently used in current practice. Thus the scale would separate into three classes: (1) Definite reactions, representing

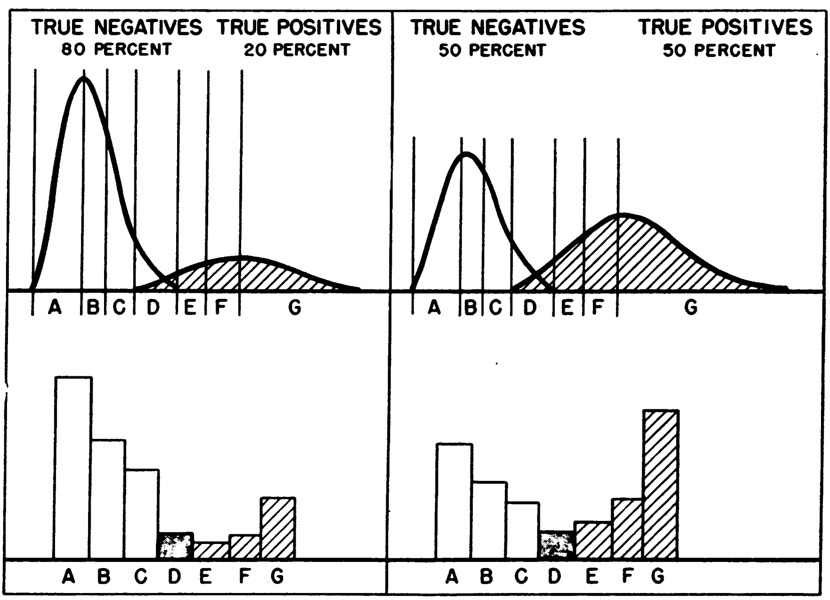

Figure 1. Hypothetical distributions of true negative and true positive reactions and corresponding histograms for different levels of prevalence of true positive reactions, when $\alpha=\beta$.

only true positives; (2) doubtful reactions, representing a constant proportion of the true positives and a constant proportion of the true negatives; (3) no reactions, representing only true negatives.

To express the relations in symbols, let a population consist of true positives in the proportion p, and true negatives in the proportion q, $(p+q=1)$. Then we would expect to find:

a relative frequency of definite reactions

$$x=(1-\alpha)p$$

a relative frequency of doubtful reactions

$$z=\alpha p+\beta q$$

and a relative frequency of no reactions

$$y=(1-\beta)q$$

α and β being the proportions of true positives and true negatives, respectively, classified as doubtful.

According to this formulation of the problem, the doubtful will be a proportion of the total number tested, that proportion being constant if $\alpha=\beta$, increasing if $\alpha>\beta$, and decreasing if $\alpha<\beta$, with increasing prevalence of true positives (p). The proportion of doubtfuls that are true positives which will increase with increase of p, can be expressed as:

$$\frac{\alpha p}{\alpha p+\beta q}=\frac{\alpha p}{\beta+(\alpha-\beta)p}$$

To demonstrate the implications of the hypothesis, two schematic examples are shown in figure 1. The two hypothetical distributions of reactions for true negatives and true positives, respectively, are drawn as smooth curves to a scale representing the degrees of reaction. This scale has been divided by arbitrary vertical lines into sections labelled A, B, C, etc., corresponding to degrees of reaction sometimes used in practical work. Throughout this example the same two distributions are used, but they have been drawn to illustrate different levels of prevalence of true positives. In the lefthand section, the hypothetical distributions were drawn in accordance with a prevalence of positive reactors equal to 20 percent of the total population, that is, the area under the smooth curve representing negatives is four times as large as the area occupied by the positives. In the righthand section of the figure, a prevalence of 50 percent was assumed and the areas under the two hypothetical curves are equal. The histograms placed below the smooth curves are constructed by combining the two hypothetical distributions of true positives and true negatives. They correspond with composite distributions such as are found when actual obser-

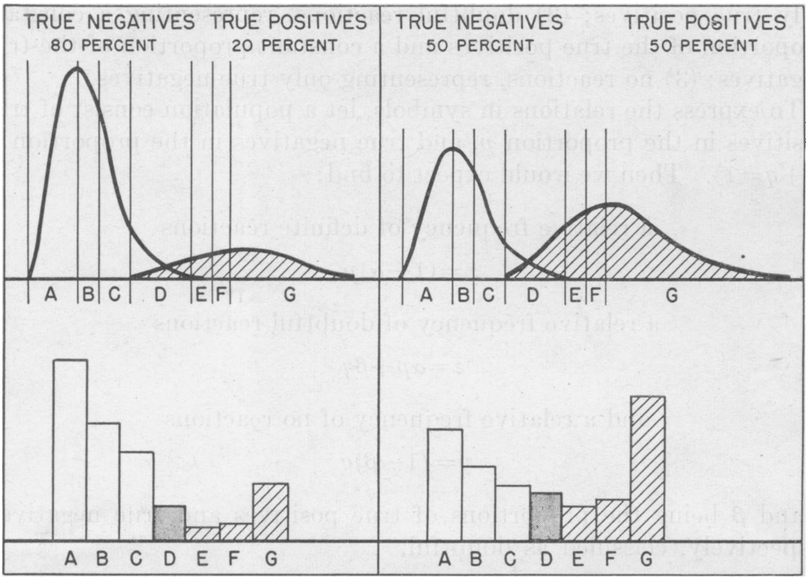

Figure 2. Hypothetical distributions of true negative and true positive reactions and corresponding histograms, for different levels of prevalence of true positive reactions, when $\alpha > \beta$.

vations are classified. An interval on the scale representing doubtful reactions was chosen in such a way as to cut off equal proportions of both distributions, that is, under the special condition as formulated above when $\alpha = \beta$. Comparison of the two histograms illustrates that under this special condition, the number of doubtful reactions remain in the same proportion to the total population, even though the form of the observed distribution changes with varying prevalence of positive reactions.

Figure 2 has been prepared in exactly the same way, except that the range defined as doubtful was shifted to include a higher percentage of the positive reactions than of the negative, that is, under the condition in which $\alpha > \beta$. This is an example of how the frequency of doubtful reactions will increase with the prevalence of positive reactions.

In the simple form the hypothesis of erroneous classification applies only to populations with a constant distribution of degrees of reactions among true positives and with another constant distribution among true negatives. That such populations do exist seems to be confirmed by observations from a number of city areas (see the following section). On the other hand, the possibility should not be excluded that the distributions, in level and pattern of degrees of reaction, could vary from one area to another, for the true positives as well as for the true negatives.

In this connection, the possible existence of nonspecific reactions

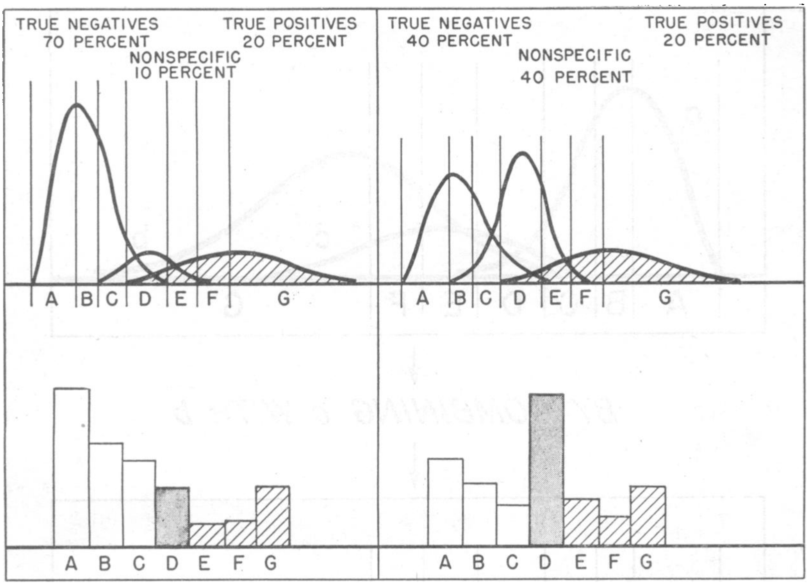

Figure 3. Hypothetical distributions of true negative, nonspecific, and true positive reactions, and corresponding histograms, for different levels of prevalence of non-specific reactions.

deserves special attention. In a population in which a certain number of persons had developed a nonspecific sensitivity to the antigen in question, the simple approach might fail or rather be insufficient. The basic idea of overlapping distributions, however, could still be a useful tool, for the general principle is easily expanded to a case where a distinction is made among three different overlapping distributions: true negatives, true positives, and nonspecific reactions. Figure 3 schematically illustrates two situations, one in which 10 percent of the total population exhibits nonspecific reactions, the other, 40 percent.

In drawing the graphs it was assumed that the distribution of non-specific reactions, according to degree of reaction, is distinctly different from those of true negatives and those of true positives, so that they would fall in the middle part of the scale somewhere between typical negatives and positives. In this case, the shape of the observed distribution may be markedly distorted from a U-shape to a trimodal curve as illustrated by the right-hand section of figure 3.

This situation would be readily recognized in actual observations, but the effect of an added group of nonspecific reactions would be much less obvious if the group were small, as illustrated in the left-hand section of figure 3, or if its distribution according to degree of reaction were more similar to either that of the true negatives or that of the true positives. In case, for example, the nonspecific reactions had exactly the same distribution as the specific (true) reactions, the

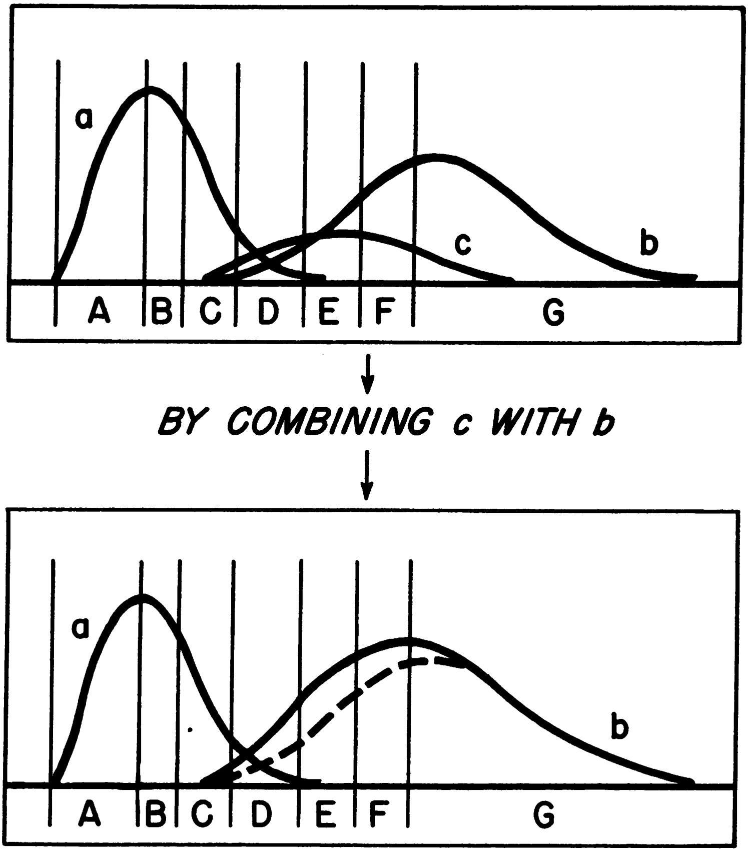

Figure 4. Hypothetical distributions of true negative, nonspecific, and true positive reactions.

skin test could contribute nothing to a division. However, if the nonspecific reactions were, for example, somewhat less marked on an average than the true reactions, a situation would arise where statistical investigation might still disclose the existence of nonspecific reactions. In such a circumstance, the simplest approach may be to conceive of two overlapping distributions, one of which would be composed of both specific and nonspecific reactors as illustrated in figure 4, which shows how the two distributions, positive and nonspecific, are combined into one.

Compared with a population otherwise similar but with no nonspecific reactors, this situation would be characterized by a shift or displacement of the distribution of positives (since these would now include the nonspecific). One consequence of this would be that a higher percentage of the positives would be registered as doubtful. An analogous situation would arise if, for example, a nonspecific factor created a very low degree of sensitivity. In this case the distribution curve of the negative reactors would appear to shift to the right and a higher proportion of the negatives would be classified as doubtful. Both situations are conceivable, and both could be recognized in practical research through statistical comparisons between different groups of persons, geographically or otherwise.

It would not be possible, of course, by this approach alone to establish the existence of nonspecific infection, but shifts in distributions would call for some explanation. Changes in the form of the observed distributions of the types shown in figures 3 and 4 could be explained by the existence of nonspecific allergy; but they might also be explained by other theories, for example, by different degrees or types of infections with the same organism.

The basic principle discussed in this section, however, is not necessarily combined with any definite theory of the nature of different degrees of reactions. Starting from the simple notion of overlapping distributions, its justification as a promising foundation for analysis of observations must be the assumption that each of the distributions remains constant under certain circumstances. This would permit the setting up of a normal pattern, which might in many cases be sufficient to explain the main characteristics of observed material. At the same time, this normal pattern could serve as a standard of comparison and thus be useful in locating exceptional distributions.

The general hypothesis was formulated as a tool for interpreting certain problems which arose in the nurses study, and the following sections will illustrate its application in a preliminary way.

Material

The fourth report in the series from the nurses study deals primarily with the relationship between pulmonary calcification and sensitivity to tuberculin and histoplasmin. It contains a detailed description of the plan, scope, and procedures of the study. In addition, it furnishes extensive tabulations of the results of tuberculin and histoplasmin tests and X-ray examinations of over 16,000 nurses from 11 widely separated metropolitan centers in the United States. The only descriptive material and tabulations given here will be those especially needed for this presentation. For a better understanding of the present discussion, the reader is referred to the previous report.

Basic numerical tabulations which are used for this analysis are given in the appendix. The left-hand section of the table shows the number of student nurses cross-tabulated according to their reactions to both tuberculin and histoplasmin. The right-hand section gives a similar cross-tabulation for those nurses whose chest X-ray film showed the presence of pulmonary calcification. Both tuberculin and histoplasmin reactions are classified into 7 groups. The data are given separately for each of the 11 metropolitan areas as well as for the total group of 16,320 student nurses.

Certain details regarding the cutaneous tests are essential for this discussion. Only one dose of histoplasmin of a 1/1000 dilution of stock antigen was given. With respect to tuberculin, two doses of PPD-S were used: the first usually being 0.0001 mg.; the second, 0.005 mg. The second dose was given when less than 10 mm. of firm induration was observed as the reaction to the preliminary dose. Tests with both antigens were intradermal—made on the volar surface of the forearm, using 1/10 cc. of solution. Reactions were usually read at 48 hours; the widest transverse diameter of erythema and of induration and a qualitative description of the character of induration were recorded. Although the nurses were routinely tested at 6-month intervals, the only observations tabulated here are those for the first tuberculin and first histoplasmin test. In a high proportion of cases, these first tests were made at the time the nurses entered training. With respect to several variables, the population under study was very homogeneous: all were student nurses, all were female, 80 percent were between 20 and 22 years of age, and an estimated 99 percent or more were white.

Because of the uses made of the records in this study, it is of the utmost importance to state that over 95 percent of all of the reactions were read by only two persons and more than two-thirds of them by only one person. The uniformity thus obtained is highly important to the present analysis in which the experimental error has been assumed to be constant.

The measurements of the diameter of erythema and induration are similar to those ordinarily made of tuberculin and histoplasmin reactions. The qualitative description of the induration, however, was developed especially for the study of the student nurses. Four categories are used to classify all indurations measuring 5 or more mm. in diameter. The numeral I is used to describe a typical textbook reaction with an area of induration which is firm, elevated, clearly defined, and well circumscribed. At the other end of the scale, IV is used to describe a questionable induration which is soft, ill-defined, and not well circumscribed. Numerals II and III are used to describe reactions which do not entirely fulfill the conditions for either I or IV, but fall somewhere between the two; II denotes the reaction showing greater similarity to that described as I, and III, showing greater similarity to IV.

Through the use of these descriptive designations and the measurements of erythema and induration, each histoplasmin and tuberculin reaction was classified into one of seven categories. Since histoplasmin tests were done with one dose and tuberculin tests with two doses, two different schemes of classifications were used. For purposes of tabulation the various categories are labeled arbitrarily by letters of the alphabet arranged to obtain a graduated scale of the level or degree of reaction to histoplasmin and to tuberculin, expressed in terms of size and intensity of the reactions.

The categories for histoplasmin are:

A—Reactors with induration of 10 or more mm., described as I.
B—Reactors with induration of 10 or more mm., described as II.
C—Reactors with induration of 5–9 mm., described as I or II, or of 5 or more mm., described as III.
D—Reactors with induration of 5 or more mm., described as IV.
E—Reactors with small undescribed induration.
F—Reactors with erythema only of 5 or more mm.
O—Nonreactors or those with only erythema of less than 5 mm.

The categories for tuberculin are:

G—Reactors with induration of 10 or more mm. to 0.0001 mg., described as I.
H—Reactors with induration of 10 or more mm. to 0.0001 mg., described as II.
I—Reactors with induration of 5–9 mm. to 0.0001 mg., described as I or II, or of 5 or more mm., described as III.
J—Reactors with induration of 10 or more mm. to 0.005 mg., described as I or II.

K—Essentially nonreactors with induration of less than 10 mm. to 0.005 mg., described as I or II, or induration, described as III or IV.

L—Essentially nonreactors with erythema only of 10 or more mm. to 0.005 mg.

O—Nonreactors or those with erythema only of less than 10 mm. to 0.005 mg.

Both scales can be taken as rough indices of the degree of reaction. In neither case is the scale strictly quantitative, since it is based on the character of the reaction as well as on measurement. Further, the two scales are fundamentally different in that the intermediate grades on the histoplasmin scale represent minor reactions to a given dose, but on the tuberculin scale include very substantial reactions to a large dose of antigen. In spite of this difference it seems permissible to interpret the two scales in very much the same way, letting the extreme ranges of the scales stand for definite reactions or no reactions, respectively, and a certain central part of the scale correspond to the equivocal reactions.

This implies that different levels of sensitivity could be established either by measuring the size of reaction to a given dose, or by determining the minimum dose necessary to produce a given reaction. We have not hesitated, therefore, in applying the same interpretation to both scales on the assumption that both represent an approximately correct distribution of reactions on a continuous quantitative reaction scale from unequivocally positive through equivocally positive or negative, to unequivocally negative.

On the other hand, it is evident that the classification of reactions into the groups defined above is largely arbitrary, and that a further element of arbitrariness is introduced if the distributions are simplified by designating a certain range to cover the doubtful reactions.

In the previous study it was found expedient to designate as doubtful those reactions to histoplasmin of the types described as D, E, and F, while A, B, and C were considered definite, and O was used as the definition of no reaction. For tuberculin reactions a similar broad distribution was applied, including four categories: definite reactors, G, H, and I; questionable reactors, J; essentially nonreactors, K and L; and nonreactors, O. These broader groupings, as well as the more detailed classifications described above and given in the appendix, are used in this study.

In this connection it may be pointed out that the terms used to designate the broad groups, especially those for tuberculin reactions, do not closely follow current practices. The category J of questionable tuberculin reactions would ordinarily be considered from physical characteristics as strong positive second-dose reactions; and many of those in the essentially nonreactors groups K, and L would be considered as positive reactors by most workers. The doubtful group of histoplasmin reactors as defined here would have been considered as negative by most workers. However, doubtful or questionable, as used here and in the earlier paper, indicates that the interpretation of the reactions is equivocal, as determined through the use of pulmonary calcification as an index of infection.

Doubtful Reactions to Histoplasmin

In paper IV of the series, it was shown that the frequency of definite reactors to histoplasmin in the student nurses varies greatly in the 11 cities, from a high of nearly 60 percent in Kansas City to a low of less than 5 percent in Minneapolis. In addition, it was found that the frequency of reactions classified as doubtful also varies. A preliminary analysis of this latter variation included in the previous report was carried only to the point of indicating that, in general, relatively more doubtful reactors were found in cities of high than in cities of low prevalence of sensitivity to histoplasmin. Further study, however, resulted in the formulation of the rather simple hypothesis of erroneous classification given above.

A test of the hypothesis on observed data may be made by attempting to determine whether the frequency of doubtful reactors among nurses in the different cities is approximately what it would be if a certain percentage of true positives and a certain percentage of true negatives had been misclassfied as doubtful. The initial step is to estimate what these two percentages might be, and to do this a simple graphic analysis was applied.

As above, let the proportion of true positive reactors in a population be p, and the proportion of true negatives be $q=1-p$ and assume that the fraction α of the positives and the fraction β of the negatives are classified as doubtful. The relation between the expected proportion of definite reactions, x, and of no reactions, y, found in any population can then be expressed as the linear equation:

$$y=(1-\beta)-\frac{1-\beta}{1-\alpha}x$$

the graph of which is a straight line intercepting the x-axis at the point $1-\alpha$ and the y-axis at $1-\beta$. From the findings of the 11 cities shown in table 1, the percentages of nonreactors were plotted against percentages of definite reactors and a straight line was visually fitted to the points, as shown in figure 5. The values of α and β were then immediately determined to be .09 and .02, respectively. More refined methods of graduation could be considered, of course, but it was decided that very great precision could not be expected and that

Table. 1. *Number of student nurses tested with histoplasmin in specified cities and percentage classified as definite, doubtful, and nonreactors*

City	Number of nurses tested	Percentage			
		Definite reactors (A, B, C)[1]	Doubtful reactors (D, E, F)[1]	Non-reactors (O)[1]	Total
Kansas City, Mo	1,131	57.7	7.1	35.2	100.0
Columbus, Ohio	1,330	55.6	4.9	39.5	100.0
Kansas City, Kans	532	45.3	5.8	48.9	100.0
New Orleans	1,290	21.2	7.2	71.6	100.0
Baltimore	1,971	22.0	3.3	74.7	100.0
Detroit	1,250	12.6	1.7	85.7	100.0
Los Angeles	1,778	10.6	3.7	85.7	100.0
Philadelphia	2,179	10.5	3.2	86.3	100.0
San Francisco	1,111	7.0	2.7	90.3	100.0
Denver	1,329	6.6	1.8	91.6	100.0
Minneapolis	2,419	4.2	2.7	93.1	100.0
All cities	16,320	19.5	3.7	76.8	100.0

[1] See text for description of classifications.

the simple visual method of fitting the line would be sufficient for present purposes.

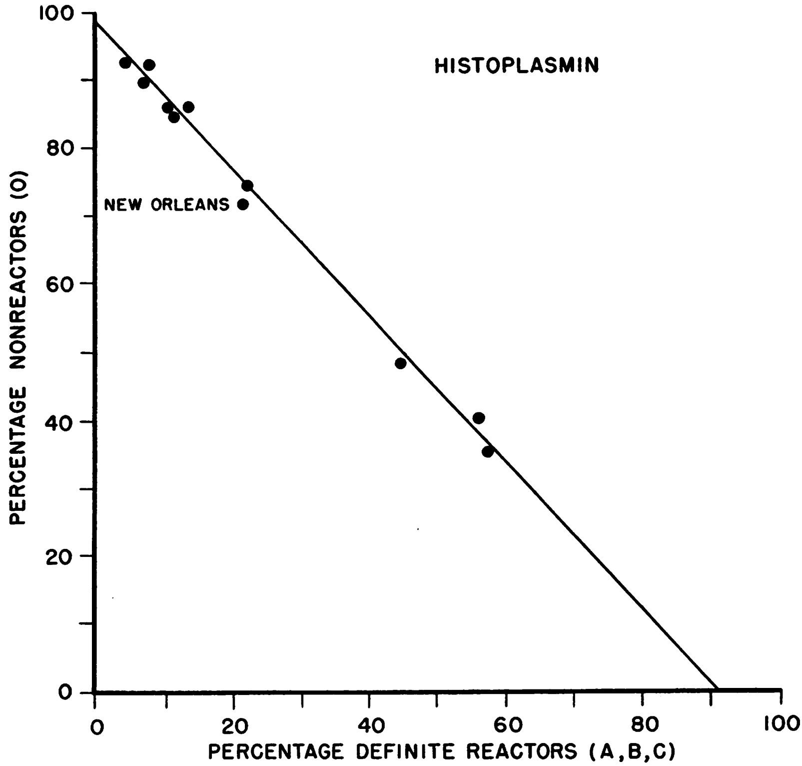

Figure 5. Graphical fitting of the straight line $y=(1-\beta)-\frac{1-\beta}{1-\alpha}x$, where x and y are the proportions of definite and nonreactors to histoplasmin, respectively, among student nurses tested in 11 cities. Each point represents a city.

Thus it is estimated that approximately 9 percent of the true positive reactors and approximately 2 percent of the true negative reactors are erroneously classified as doubtful. Thus, in a population with a prevalence of true positives of p, the expected distribution of readings would be:

definite reactions $x=.91\ p$
no reactions $y=.98\ (1-p)$
doubtful reactions $z=.09\ p+.02\ (1-p)=.02+.07p$

where obviously $x+y+z=1$.

From these results, table 2 was prepared to show, for various values of p, the estimated or hypothetical distributions of histoplasmin reactions. In an area with a prevalence of $p=.10$, for example, we find that 2.7 percent of the population would be classified as doubtful but if the prevalence were .60 we should expect 6.2 percent. Table 2 also shows the change in percentage of true positives expected

Table 2. *Hypothetical distributions*[1] *of histoplasmin reactors and the frequencies of true positives among doubtful reactors at different levels of prevalence of true positive reactors in the population*

Prevalence of true positive reactors	Percentage					
	Definite reactors	Doubtful reactors			Non-reactors	True positives among doubtful reactors
		Positives	Negatives	Total		
0	0.0	0.0	2.0	2.0	98.0	0.0
5	4.6	.4	1.9	2.3	93.1	19.1
10	9.1	.9	1.8	2.7	88.2	33.3
15	13.6	1.4	1.7	3.1	83.3	44.3
20	18.2	1.8	1.6	3.4	78.4	52.9
25	22.8	2.2	1.5	3.7	73.5	60.0
30	27.3	2.7	1.4	4.1	68.6	65.9
35	31.8	3.2	1.3	4.5	63.7	70.8
40	36.4	3.6	1.2	4.8	58.8	75.0
45	41.0	4.0	1.1	5.1	53.9	78.6
50	45.5	4.5	1.0	5.5	49.0	81.8
55	50.0	5.0	.9	5.9	44.1	84.6
60	54.6	5.4	.8	6.2	39.2	87.1
65	59.2	5.8	.7	6.5	34.3	89.3
70	63.7	6.3	.6	6.9	29.4	91.3
75	68.2	6.8	.5	7.3	24.5	93.1
80	72.8	7.2	.4	7.6	19.6	94.7
85	77.4	7.6	.3	7.9	14.7	96.2
90	81.9	8.1	.2	8.3	9.8	97.6
95	86.4	8.6	.1	8.7	4.9	98.8
100	91.0	9.0	.0	9.0	.0	100.0

[1] Assuming that 9 percent of true positives and 2 percent of true negatives are classified as doubtfuls.

among the doubtfuls, with change in the prevalence of true positives. When $p=.10$ only one third of the 2.7 percent classified as doubtful would be true positives, while when $p=.60$, nearly 90 percent of the 6.2 percent classified as doubtful would be true positives.

Figure 6 illustrates the hypothetical distribution graphically, the shaded area showing the proportion of true positives, the unshaded area the proportion of true negatives, and the area between the two lines showing the true positives and true negatives erroneously classified by observation as doubtful.

The prevalence of true positives cannot be found by direct observation, of course, but it can be estimated in accordance with the hypothesis, and such estimates were made for the nurses in the different cities, as shown in table 3. The estimates were obtained by a somewhat crude method which was considered sufficiently accurate. They are simple unweighted averages of two different estimates, one found by dividing the observed percentage of definite reactors in the city by $1-\alpha=0.91$, the other as 100 minus the percentage of nonreactors divided by $1-\beta=0.98$.

The data given in tables 1 and 3 now permit a comparison of observed frequencies of doubtful reactors and those which would be expected under our hypothesis. This is done in two ways: Table 4 shows the absolute observed and expected numbers, and figure 7

Table 3. ***Estimated prevalence of true positive reactors among student nurses tested with histoplasmin in specified cities, expected distributions of reactors, and estimated frequencies of true positives among doubtful reactors***

City	Percentage				
	Estimated prevalence of true positive reactors	Definite reactors	Doubtful reactors	Nonreactors	Estimated true positives among doubtful reactors
Kansas City, Mo.	63.8	58.1	6.4	35.5	89.1
Columbus, Ohio	60.4	55.0	6.2	38.8	87.1
Kansas City, Kans	50.0	45.5	5.5	49.0	81.8
New Orleans	25.1	22.8	3.8	73.4	60.5
Baltimore	24.0	21.8	3.7	74.5	59.5
Detroit	13.2	12.0	2.9	85.1	41.4
Los Angeles	12.1	11.0	2.9	86.1	37.9
Philadelphia	11.7	10.6	2.9	86.5	37.9
San Francisco	7.8	7.1	2.5	90.4	28.0
Denver	6.9	6.3	2.5	91.2	24.0
Minneapolis	4.8	4.4	2.3	93.3	17.4
All cities	21.5	19.6	3.5	76.9	54.3

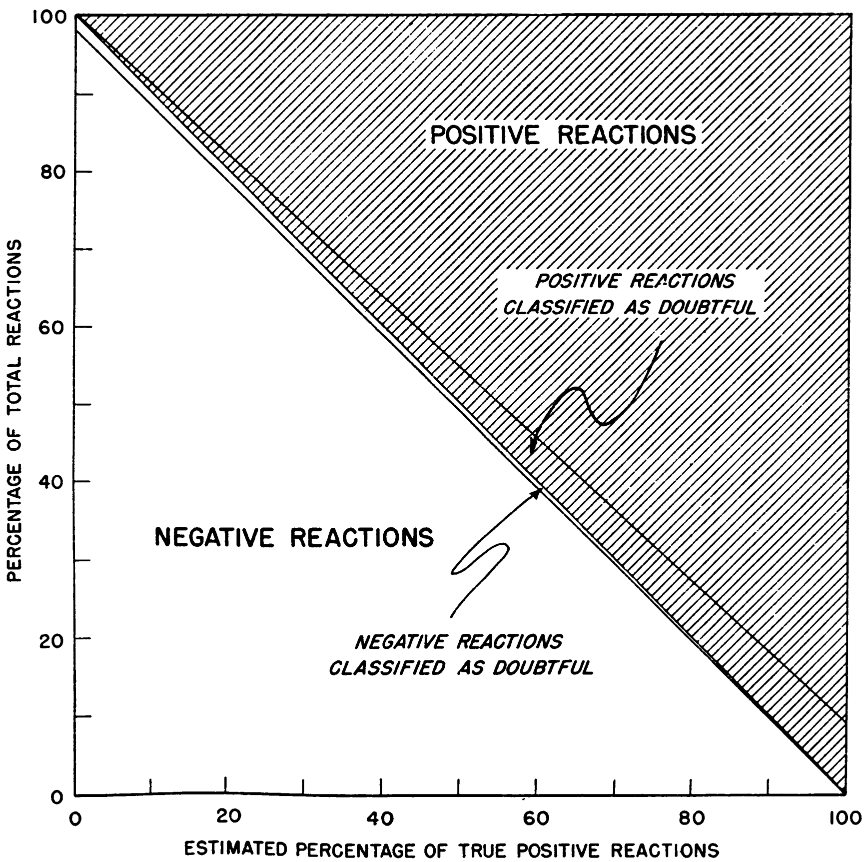

Figure 6. Hypothetical distribution of histoplasmin reactions. The center diagonal line represents the separation of true positive reactions and true negative reactions. The two outer diagonal lines enclose the hypothetical distribution for doubtfuls.

Table 4. *Number of student nurses tested and observed and expected number of definite, doubtful, and nonreactors to histoplasmin in specified cities*

City	Nurses tested	Definite reactors		Doubtful reactors		Nonreactors	
		Observed	Expected	Observed	Expected	Observed	Expected
Kansas City, Mo	1,131	653	657	80	72	398	402
Columbus, Ohio	1,330	740	732	65	82	525	516
Kansas City, Kans	532	241	242	31	29	260	261
New Orleans	1,290	273	294	93	49	924	947
Baltimore	1,971	434	430	65	73	1,472	1,468
Detroit	1,250	158	150	21	36	1,071	1,064
Los Angeles	1,778	189	196	65	51	1,524	1,531
Philadelphia	2,179	228	231	71	63	1,880	1,885
San Francisco	1,111	78	79	30	28	1,003	1,004
Denver	1,329	88	84	24	33	1,217	1,212
Minneapolis	2,419	101	106	65	56	2,253	2,257
All cities	16,320	3,183	3,201	610	572	12,527	12,547
All cities, except New Orleans	15,030	2,910	2,907	517	523	11,603	11,600

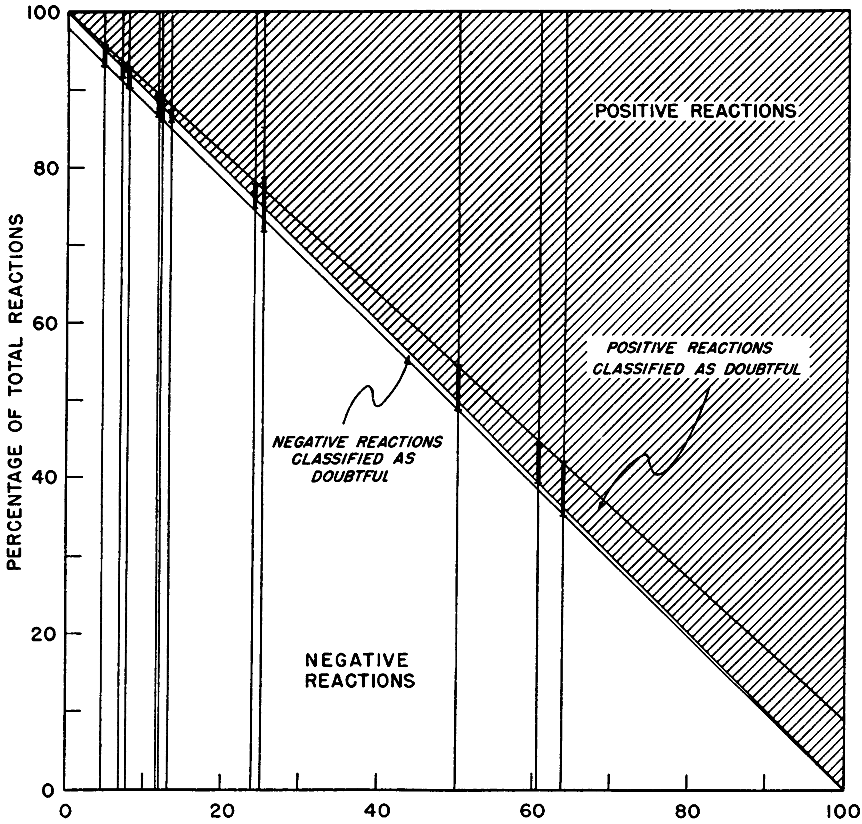

Figure 7. Observed histoplasmin reactions for 11 cities superimposed on hypothetical distribution of reactions. Vertical lines are placed on horizontal axis at estimated percentage of true positive reactions for each city; heavy segment of each vertical line indicates percent of observed doubtful reactions.

gives a graphic comparison of the distributions. From the table it appears that with the exception of New Orleans there is fairly close agreement between observed and expected numbers of doubtful reactors.

In figure 7 the observed frequencies for the 11 cities are superimposed on the hypothetical distribution as illustrated in figure 6. Each vertical line represents the subdivision of histoplasmin reactors into the definite, doubtful, and nonreactor categories, the position of the line on the horizontal axis being determined by the estimated prevalence of true positives for the city.

The reasonably close agreement between theory and findings is again brought out in figure 7. Here and in table 4, it appears that the distribution of reactions in New Orleans nurses follows a pattern somewhat different from that observed in nurses in the other cities. Because the deviation is so great, it would seem appropriate to give this city separate consideration. In the following section it will be shown that, with respect to tuberculin sensitivity also, the observations from New Orleans deviate very strikingly from the findings in the other cities.

Special attention should be given to one of the important implications of the theoretical interpretation of doubtful histoplasmin reactions. If, in the nurses study, 9 percent of the true positives and 2 percent of the true negatives are classified as doubtful reactors, this group will be composed very differently in areas with high and low prevalence of histoplasmin sensitivity. The right-hand column of table 3 shows the proportions of the doubtful groups in each city estimated to be true positive reactors. In Kansas City, Missouri, for example, where there is the highest prevalence of sensitivity to histoplasmin, nearly 90 percent of the nurses classified as doubtful reactors would be expected, according to the theory, to be true positives. In Minneapolis, where the prevalence of sensitivity is the lowest observed (about 5 percent), less than 20 percent of the doubtfuls are presumed to be true positives. The consequence of this difference in the meaning to be attached to doubtful reactions could be expected to manifest itself in a variety of ways. And it is of considerable interest that the frequency of pulmonary calcification in the chest X-ray films of the nurses varies as would be expected if the hypothesis were correct. The data which bear on this matter are given in the previous report and will not be repeated here. However, the finding is quite unmistakable: In those cities which have the highest prevalance of histoplasmin reactors (Kansas City, Missouri, and Columbus), and where a very high proportion of the doubtful groups may be regarded, according to the theory, to be true positives, one finds very little difference in the frequency of pulmonary calcification for the definite and doubtful reactors to histoplasmin. In the cities with a low

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prevalence of histoplasmin reactors (San Francisco, Denver, and Minneapolis) the frequency of calcification is very much lower among the doubtfuls, tending to approach the low rate found among the nonreactors.

Questionable Reactions to Tuberculin

The interpretation of different classes of tuberculin reactions presents a problem similar to that of histoplasmin reactions. In the data from the nurses study, the intermediate classes of tuberculin reactions represent substantial reactions to a large dose of antigen (.005 mg. PPD) but are taken as evidence of a low degree of sensitivity comparable to slight reactions to a lower dose. In the previous study, the reactions classified as J were described as questionable while the higher grades were considered as definite and the lower grades as nonreactors or essentially nonreactors. The two latter groups are combined into one and the observations from the 11 cities shown in table 5 are analyzed by the method described above.

Table 5. *Number of student nurses tested with tuberculin in specified cities and percentage classified as definite, questionable, and nonreactors* [1]

City	Number of nurses tested	Percentage			
		Definite reactors (G, H, I) [2]	Questionable reactors (J) [2]	Nonreactors[1] (K, L, O) [2]	Total
Kansas City, Mo.	1,131	10.9	5.4	83.7	100.0
Columbus, Ohio	1,330	11.4	3.3	85.3	100.0
Kansas City, Kans.	532	13.7	7.7	78.6	100.0
New Orleans	1,290	13.3	14.3	72.4	100.0
Baltimore	1,971	17.9	5.7	76.4	100.0
Detroit	1,250	13.9	4.2	81.9	100.0
Los Angeles	1,778	18.7	5.0	76.3	100.0
Philadelphia	2,179	22.8	4.5	72.7	100.0
San Francisco	1,111	18.6	4.0	77.4	100.0
Denver	1,329	18.8	5.1	76.1	100.0
Minneapolis	2,419	7.9	3.1	89.0	100.0
All cities	16,320	15.5	5.3	79.2	100.0
All cities, except New Orleans	15,030	15.7	4.5	79.8	100.0

[1]Including essentially nonreactors. [2] See text for description of classifications.

In contrast to the findings for histoplasmin, the frequency of questionable reactors to tuberculin does not appear to be correlated with the prevalence of reactors. On the contrary, the frequency seems to fluctuate around 5 percent, ranging without any obvious systematic tendency from 3.1 percent in Minneapolis to 7.7 percent in Kansas City, Kansas. There is one outstanding exception, New Orleans, where nearly 15 percent of all nurses tested were classified as questionable reactors. Leaving out this city, however, the hypothesis of erroneous classification would suggest that a little less than 5 percent of the true positive and about the same percentage of the true negative reactors had been classified as doubtful.

Since the range of tuberculin sensitivity in the different cities is much smaller than that of histoplasmin, the visual fitting of a line by the same method as applied in figure 5 to histoplasmin reactions is

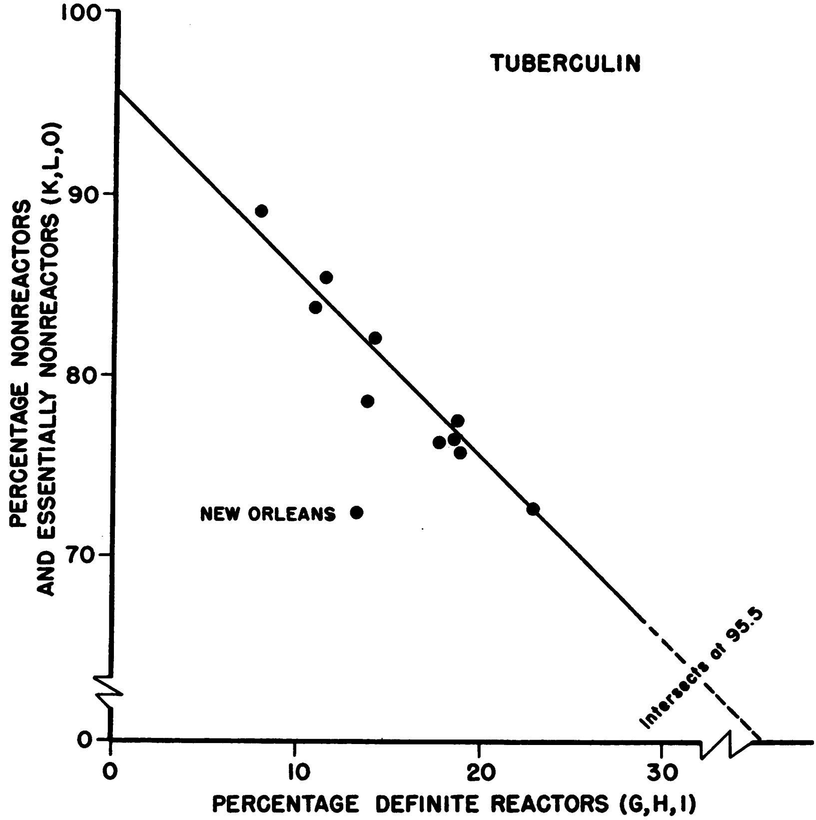

Figure 8. Fitting of the straight line $y=(1-\beta)-x$ where x is the proportion of definite reactors and y the proportion of nonreactors and essentially nonreactors to tuberculin among student nurses tested in 11 cities. Each point represents a city.

somewhat less reliable for tuberculin reactions. This would appear from figure 8 which is analogous to figure 5, but drawn to a larger scale. The straight line in figure 8, however, was drawn in accordance with the hypothesis that 4.5 percent of both positive and negative reactors were registered as questionable, 4.5 percent being the over-all frequency of questionable reactors in all cities except New Orleans. It appears that the line determined in this way gives a fair fit, except that it leaves the point representing New Orleans far out compared with the others. Although this variance is evidence of some distinctly different phenomenon in New Orleans, we shall at the moment omit a discussion of these factors and assume that in the 10 other cities the questionable reactors to tuberculin can be considered as a composite group comprising about 4.5 percent of the true positives and the true negatives in each city. The comparison between observed and hypothetical numbers shown in table 6, further demonstrates a fair

Table 6. *Number of student nurses tested and observed and expected number of definite, questionable, and nonreactors*[1] *to tuberculin in specified cities*

City	Number						
	Nurses tested	Definite reactors		Questionable reactors		Nonreactors[1]	
		Observed	Expected	Observed	Expected	Observed	Expected
Kansas City, Mo	1,131	123	129	61	51	947	951
Columbus, Ohio	1,330	151	144	44	60	1,135	1,126
Kansas City, Kans	532	73	81	41	24	418	427
New Orleans	1,290	171	234	185	58	934	998
Baltimore	1,971	353	365	112	89	1,506	1,517
Detroit	1,250	174	173	52	56	1,024	1,021
Los Angeles	1,778	333	336	88	80	1,357	1,362
Philadelphia	2,179	497	497	98	98	1,584	1,584
San Francisco	1,111	207	203	44	50	860	858
Denver	1,329	250	254	68	60	1,011	1,015
Minneapolis	2,419	192	177	74	109	2,153	2,133
All cities	16,320	2,524	2,593	867	735	12,929	12,992
All cities, except New Orleans	15,030	2,353	2,359	682	677	11,995	11,994

[1] Including essentially nonreactors.

correspondence, though the deviations appear to be larger than could be expected from random errors. However, there is no obvious evidence of systematic deviations.

As in the case of histoplasmin, the hypothesis implies that the proportion of true positives included among the questionable reactors will vary with the level of sensitivity, but since it is assumed that the same probability of misclassification applies to both negative and positive reactors, the same proportion of true positive reactors in the questionable group as in the total population would be expected. The proportion for each city was estimated from the observations by the same method as applied to histoplasmin. Table 7 shows the observed

Table 7. *Estimated prevalence of true positive reactors among student nurses tested with tuberculin in specified cities, expected distributions of reactors and estimated frequencies of true positives among questionable reactors*

City	Percentage				
	Estimated prevalence of true positive reactors	Definite reactors	Questionable reactors	Nonreactors[1]	Estimated true positives among questionable reactors
Kansas City, Mo	11.9	11.4	4.5	84.1	11.9
Columbus, Ohio	11.3	10.8	4.5	84.7	11.3
Kansas City, Kans	16.0	15.3	4.5	80.2	16.0
New Orleans	19.0	18.1	4.5	77.4	19.0
Baltimore	19.4	18.5	4.5	77.0	19.4
Detroit	14.4	13.8	4.5	81.7	14.4
Los Angeles	19.8	18.9	4.5	76.6	19.8
Philadelphia	23.9	22.8	4.5	72.7	23.9
San Francisco	19.2	18.3	4.5	77.2	19.2
Denver	20.0	19.1	4.5	76.4	20.0
Minneapolis	7.6	7.3	4.5	88.2	7.6
All cities	16.6	15.9	4.5	79.6	16.6
All cities, except New Orleans	16.4	15.7	4.5	79.8	16.4

[1] Including essentially nonreactors.

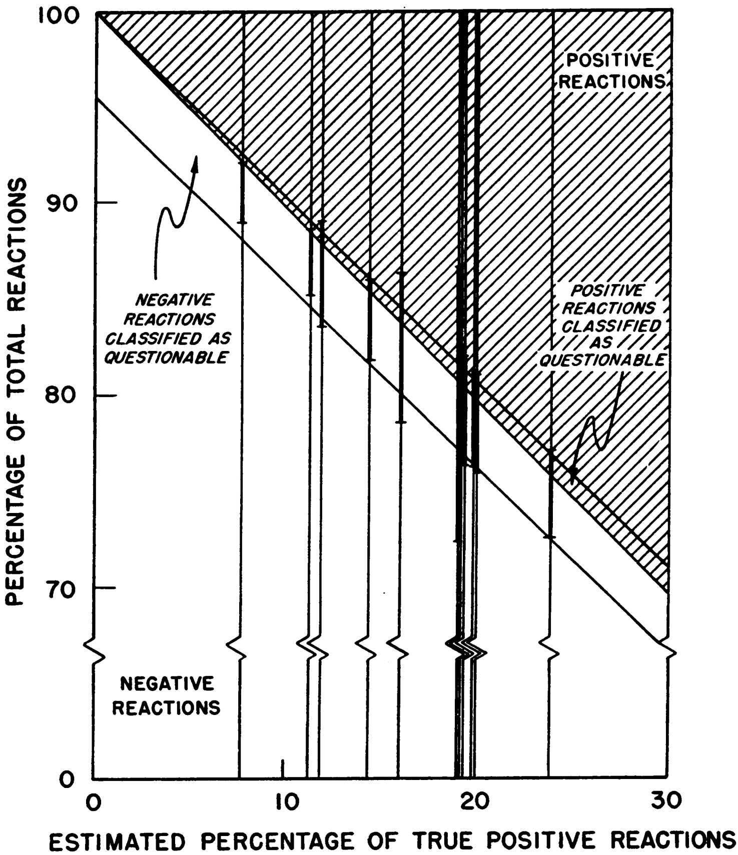

Figure 9. Observed tuberculin reactions for 11 cities superimposed on hypothetical distribution of reactions. Vertical lines are placed on horizontal axis at estimated percentage of true positive reactions for each city; heavy segment of each vertical line indicates percent of observed questionable reactions.

and expected numbers, and figure 9 gives a graphic comparison of the distributions analagous to that shown for histoplasmin in figure 7.

The validity of our hypothesis cannot easily be verified in terms of the frequency of pulmonary calcification in questionable tuberculin reactors because of the low rate of calcifications associated with tuberculin sensitivity and because of the small variations in prevalence of definite tuberculin reactions in the different cities. The available material can only be used to indicate the relationship for the total group of all nurses in all cities. Thus, among nurses with no reaction to histoplasmin, the results presented in the previous report (IV) show that 11.0 percent of those reacting definitely to tuberculin had pulmonary calcifications, as against only 1.8 percent for those classified as questionable tuberculin reactors and 0.7 percent for the nonreactors.[1] In accordance with the hypothesis, calcification would be

[1] These figures do not agree entirely with those given in the earlier report because these quoted here are for all cities except New Orleans.

expected at the rate of 0.7 percent in the 84 percent of the questionable reactors which are true negatives and at the rate of 11 percent of the

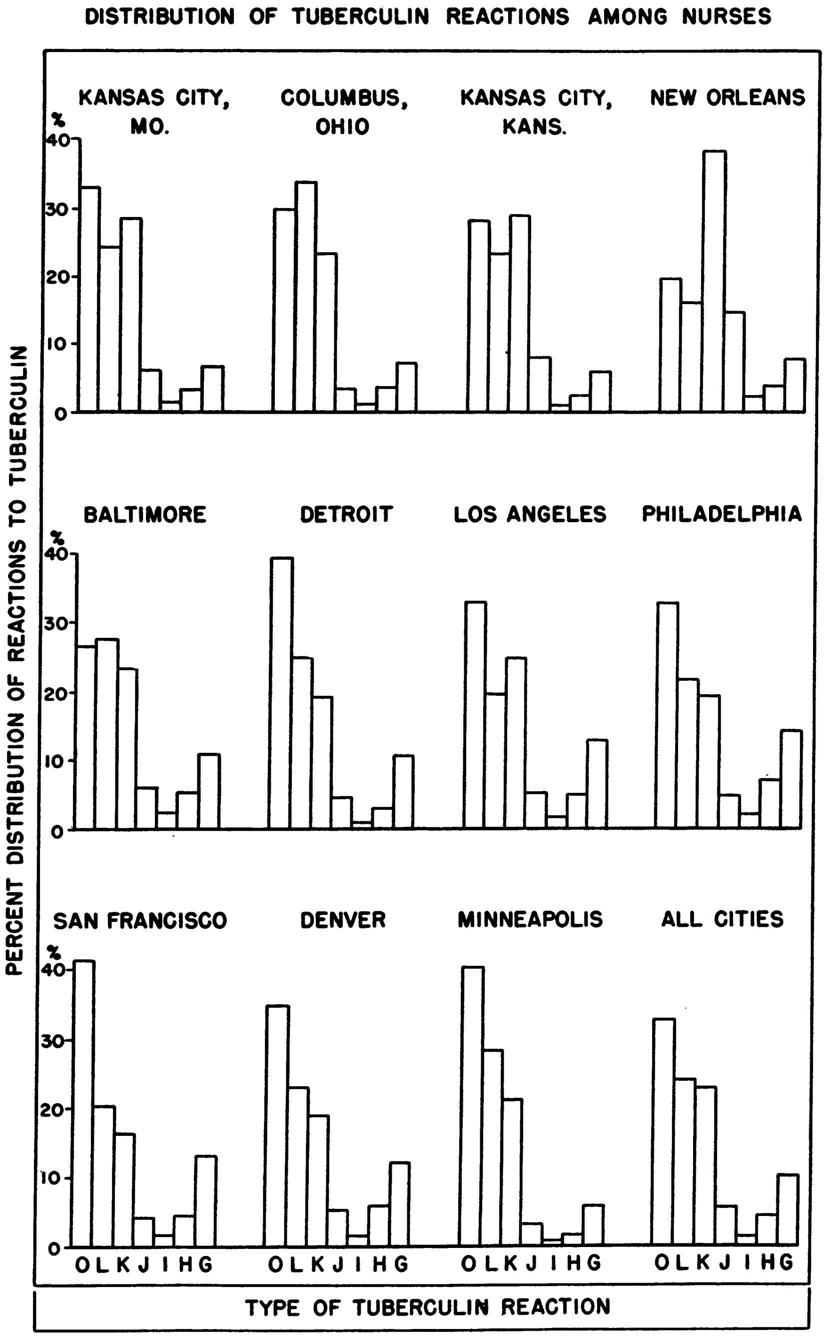

Figure 10. Distributions of student nurses tested in specified cities, according to tuberculin reaction.

remaining 16 percent which are true positives. This would equal 2.3 percent of the total group of questionable reactors, in reasonably close agreement with the actually observed frequency of 1.8 percent.

Although the hypothesis of erroneous classification seems to explain some of the less obvious results from the nurses study, it is clear that it does not explain everything. The fact that one of the 11 cities, New Orleans, differs so much from the others calls for supplementary consideration. In this connection, another step can be taken by examining the detailed classification of tuberculin reactions for each of the 11 cities, as shown in figure 10.

Careful inspection of figure 10 shows that five cities, Philadelphia, Denver, San Francisco, Detroit, and Minneapolis, have graphs of closely similar pattern, a fairly regular U-shaped curve with the modal frequency being the nonreactor in the O class. This form of curve is common to the five cities in spite of the varying frequency of definite tuberculin reactors, ranging from the lowest to the highest among the cities covered by the study. Compared with these, the graphs for Columbus and Baltimore show a conspicuous shift toward the right, the modal class being reactions classified as L. A further shift in the same direction is found in the graphs for Kansas City (both areas) and Los Angeles, where K reactions are more frequent. Finally, the distribution from New Orleans is evidently quite different. What appeared to be a gradual change in other cities is so pronounced in New Orleans that the distribution of tuberculin sensitivity exhibits a pattern with little resemblance to the usual U-shape. In New Orleans, an extraordinarily high percentage of the nurses reacted to the second dose of tuberculin and were classified as J or K, questionable reactors or essentially nonreactors. Certainly, for this city, the questionable reactors cannot be explained by random errors or considered merely a group of erroneously classified positive and negative reactors. The observations definitely indicate the existence of some unusual sensitivity to tuberculin. Corresponding with the hypothetical case illustrated in figure 3, the widespread existence in New Orleans of a nonspecific factor could produce sensitivity to high doses of tuberculin in such a way that the distribution of nonspecific reactions would be between those for true negative and true positive reactions, falling in that interval of the scale of reactions designated as questionable.

The same factor—or similar factors—may exist in the other cities but if so it is apparently of much less importance than in New Orleans. It is possible that the five cities with U-shaped distributions of tuberculin reactions of the same regular pattern, were practically free of the nonspecific sensitivity while some of the other cities had enough questionable reactions due to nonspecific sensitivity to influence the shape of the distribution.

The presumptive evidence presented here on the existence of nonspecific tuberculin reactions may be of great practical importance. The data clearly indicate that enormous variation in the percentage of so-called positive tuberculin reactions can be obtained by varying the criteria for interpreting reactions to the higher tuberculin test doses. Further, the extent of this variation is probably chiefly dependent upon geographic factors. For example, among New Orleans nurses at least as many as 40 percent, rather than 14 percent, could be designated as positive reactors by the use of criteria that are widely used in the United States today. Findings presented here suggest that this nearly threefold difference is due to the inclusion of nonspecific reactors in the higher estimate.

To speculate as to the cause of the nonspecific tuberculin sensitivity, it seems most likely that it is an infection with one or several organisms (perhaps of the alcohol-acid-fast variety) which, in effecting its (or their) own specific allergy, produces a cross sensitivity which may be brought out by the higher doses of tuberculin used in human testing.

Correlation Between Tuberculin and Histoplasmin Reactions

The analysis in the preceding sections, relatively crude as it has been, shows that the hypothesis of erroneous classification, even in its simplest form, offers a plausible and extremely simple explanation of certain findings which would not be easy to interpret in other terms.

Of the several factors which complicate the general application of the hypothesis, however, only one will be considered briefly: the evidence of a lack of independence of the reactions to tuberculin and histoplasmin. There is no substantial correlation or cross reaction, but unmistakable indication of some association. This appears from the two-dimensional distribution of the total 16,320 nurses according to the detailed classification of degrees of reaction to both antigens.

Table 8. *Expected distribution of student nurses tested and differences between observed and expected number according to histoplasmin and to tuberculin reaction—for all cities*

Tuberculin reaction [1]	Expected distribution of nurses tested: Histoplasmin reaction [1]								Difference between observed and expected number of nurses: Histoplasmin reaction [1]							
	A	B	C	D	E	F	O	Total	A	B	C	D	E	F	O	Total
G	140	79	68	20	20	20	1,287	1,634	20	0	13	2	10	10	−55	0
H	58	36	29	7	8	7	521	666	−11	7	6	4	9	0	−15	0
I	21	12	12	4	0	3	172	224	−5	3	1	2	9	2	−12	0
J	79	52	42	14	10	13	657	867	−4	−1	−2	−3	−3	−5	18	0
K	366	229	194	58	48	49	2,777	3,721	12	−32	9	−14	−1	7	19	0
L	393	228	186	54	46	44	2,943	3,894	−7	5	−12	1	−4	−3	20	0
O	464	264	231	63	62	60	4,170	5,314	−5	18	−15	8	−20	−11	25	0
Total	1,521	900	762	220	194	196	12,527	16,320	0	0	0	0	0	0	0	0

[1] See text for description of classifications.

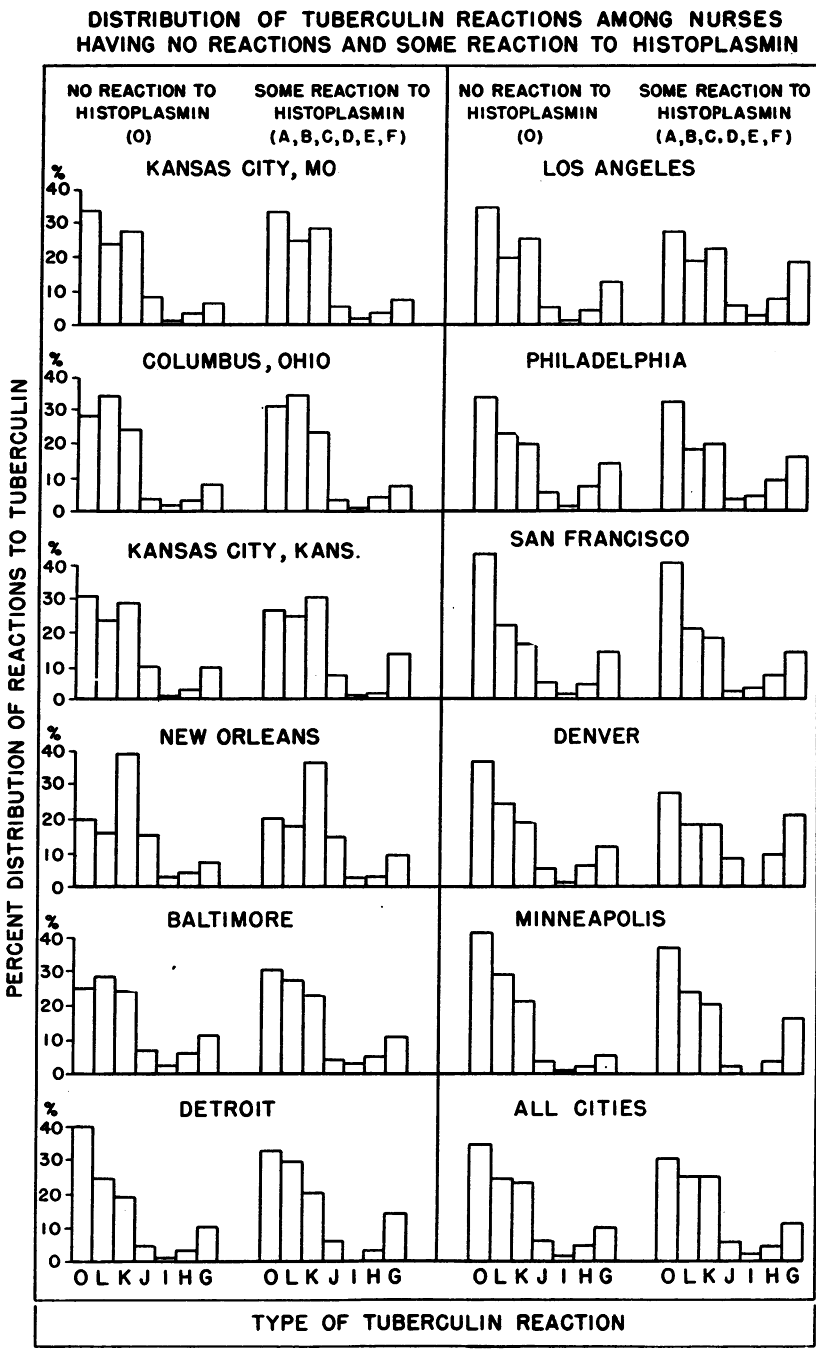

Figure 11. Distributions of student nurses tested in specified cities, according to tuberculin reaction, for nurses having some reaction and no reaction to histoplasmin, respectively.

The observed distribution is shown in the appendix; it should be compared with a hypothetical distribution computed under the assumption of independence of the two tests. Such distributions were computed for each city and added to give the expected distribution for all cities as shown in table 8. To facilitate the comparison, the differences between observed and expected frequencies are shown in another section of the same table.

In general, the deviation between observed and expected frequencies is not great, except for one section of the table—the upper middle part where the observed frequencies exceed the expected ones. Relatively more doubtful reactions to histoplasmin are found among the nurses with a strong reaction to tuberculin than among those with no reaction to tuberculin, or, conversely, there are more definite reactions to tuberculin among those who displayed some reaction to histoplasmin than among those who did not.

It would be desirable to divide the observations for each city according to the degree of reaction and to study the distribution of reactions to each test for each class of reactions to the other test. In spite of the large number of nurses examined, there is only enough material to make profitable a comparison between two groups for each test.

The distributions of tuberculin reactions were made separately for one group of nurses with definite and doubtful reactions to histoplasmin and another with no reaction. These two distributions are shown for each city in figure 11, from which it appears that tuberculin

Table 9. ***Number of student nurses tested in specified cities and percentage classified as definite, questionable, and nonreactors [1] to tuberculin, for nonreactors and reactors [2] to histoplasmin, respectively***

City	Nonreactors to histoplasmin					Reactors [2] to histoplasmin				
	Number of nurses tested	Percentage				Number of nurses tested	Percentage			
		Definite reactors (G, H, I) [3]	Questionable reactors (J) [3]	Nonreactors [1] (K, L, O) [3]	Total		Definite reactors (G, H, I) [3]	Questionable reactors (J) [3]	Nonreactors [1] (K, L, O) [3]	Total
Kansas City, Mo	398	10.0	7.5	82.5	100.0	733	11.3	4.2	84.5	100.0
Columbus, Ohio	525	11.7	3.6	84.7	100.0	805	11.1	3.1	85.8	100.0
Kansas City, Kans	260	11.9	8.9	79.2	100.0	272	15.4	6.6	78.0	100.0
New Orleans	924	13.1	14.5	72.4	100.0	366	13.7	13.9	72.4	100.0
Baltimore	1,472	17.9	6.4	75.7	100.0	499	18.0	3.6	78.4	100.0
Detroit	1,071	13.7	4.0	82.3	100.0	179	15.0	5.0	80.0	100.0
Los Angeles	1,524	17.2	4.8	78.0	100.0	254	28.0	5.9	66.1	100.0
Philadelphia	1,880	21.9	4.6	73.5	100.0	299	28.4	3.8	67.8	100.0
San Francisco	1,003	18.3	4.2	77.5	100.0	108	22.3	1.8	75.9	100.0
Denver	1,217	17.8	4.9	77.3	100.0	112	29.4	8.0	62.6	100.0
Minneapolis	2,253	7.2	3.1	89.7	100.0	166	18.7	1.8	79.5	100.0
All cities	12,527	15.1	5.4	79.5	100.0	3,793	16.5	5.1	78.4	100.0

[1] Including essentially nonreactors.
[2] Including doubtful reactors.
[3] See text for description of classifications.

sensitivity is uniformly higher among histoplasmin reactors. The difference between the two groups is small in the cities with high histoplasmin sensitivity but quite substantial in those where histoplasmin reactors are rare.

The device used earlier, in which straight lines were fitted to points made by plotting percentages of nonreactors against percentages of definite reactors, was also applied to tuberculin reactions separately for reactors and nonreactors to histoplasmin, and it was found that the same line fitted both groups. Thus, as also seen directly in table 9, the percentage of questionable reactions is about the same in both groups, and not appreciably correlated with the prevalence of tuberculin sensitivity.

The corresponding examination in table 10 of degrees of histoplasmin reactions among reactors and nonreactors to tuberculin, however, reveals another picture, as would be expected from the character of the two-dimensional distribution in table 8. Because so many areas have very few histoplasmin reactors, graphic presentation of the detailed distribution for each city would not be informative. The straight-line technique, however, indicates that a higher percentage of doubtful histoplasmin reactors is found among reactors than among nonreactors to tuberculin.

According to the basic hypothesis of this paper the situation found by considering both tuberculin and histoplasmin reactions can be described thus:

The prevalence of definite reactions to tuberculin among reactors to histoplasmin seems to be higher than among nonreactors to histo-

Table 10. *Number of student nurses tested in specified cities and percentage classified as definite, doubtful, and nonreactors to histoplasmin, for not definite and definite reactors to tuberculin, respectively*

City	Not definite reactors to tuberculin					Definite reactors to tuberculin				
	Number of nurses tested	Percentage				Number of nurses tested	Percentage			
		Definite reactors (A, B, C)[1]	Doubtful reactors (D, E, F)[1]	Nonreactors (O)[1]	Total		Definite reactors (A, B, C)[1]	Doubtful reactors (D, E, F)[1]	Nonreactors (O)[1]	Total
Kansas City, Mo	1,008	57.8	6.7	35.5	100.0	123	56.9	10.5	32.6	100.0
Columbus, Ohio	1,179	56.0	4.6	39.4	100.0	151	52.3	7.3	40.4	100.0
Kansas City, Kans	459	44.7	5.4	49.9	100.0	73	49.3	8.2	42.5	100.0
New Orleans	1,119	21.2	7.1	71.7	100.0	171	21.1	8.2	70.7	100.0
Baltimore	1,618	22.0	3.3	74.7	100.0	353	22.4	3.1	74.5	100.0
Detroit	1,076	12.7	1.4	85.9	100.0	174	12.1	3.4	84.5	100.0
Los Angeles	1,445	9.7	3.0	87.3	100.0	333	14.7	6.5	78.8	100.0
Philadelphia	1,682	9.8	2.9	87.3	100.0	497	12.6	4.4	83.0	100.0
San Francisco	904	6.6	2.7	90.7	100.0	207	8.7	2.9	88.4	100.0
Denver	1,079	6.0	1.3	92.7	100.0	250	9.2	4.0	86.8	100.0
Minneapolis	2,227	3.9	2.2	93.9	100.0	192	7.8	8.4	83.8	100.0
All cities	13,796	19.5	3.4	77.1	100.0	2,524	19.4	5.4	75.2	100.0

[1] See text for description of classifications.

plasmin, but there is nothing to indicate that the distributions of true positives and true negatives, respectively, are different in the two groups. On the contrary, there is evidence of a shift in the pattern of the distributions according to degrees of reaction to histoplasmin when nonreactors to tuberculin are compared with reactors. For tuberculin the situation is similar to the hypothetical case shown in figure 1, and for histoplasmin there is a resemblance to the theoretical possibility illustrated in figure 4.

Certainly, different hypotheses could be formulated to explain this, and one simple possibility should be considered. Tuberculous infection occasionally might produce some allergy to histoplasmin in addition to tuberculin sensitivity. If so, we should expect to find a certain number of nonspecific histoplasmin reactions among persons reacting to tuberculin, but none, or at least not many, among nonreactors to tuberculin. At the same time a sample of histoplasmin reactors would include a higher percentage of persons with a tuberculin reaction than a sample of nonreactors to histoplasmin, simply because the former would include the cases where a cross reaction had taken place.

This highly speculative hypothesis was suggested by the findings from the nurses study, but the available material was not considered sufficient to carry the analysis further.

Summary

A statistical method has been developed as an approach to the interpretation of cutaneous tuberculin and histoplasmin reactions.

Certain characteristics of reactions are pointed out: (a) from their perceptual appearances, reactions form a continuous scale, from large apparently typical reactions to no observable reactions; (b) reactions are influenced to a considerable extent by experimental and physiological errors; and (c) nonspecific reactions may exist and create special problems in interpretation.

In view of these characteristics the simple notion that on the continuous scale of reactions there is a point which separates positives and negatives, becomes insufficient on both practical and theoretical grounds. In its stead, there is proposed the hypothesis that positive and negative reactions are distributed over the scale, the positives tending to be at one end and the negatives at the other, but with some overlapping in an interval or zone on the reaction scale. Reactions in this in-between zone may be designated as doubtful or questionable, and the hypothesis provides that, though it is not possible to distinguish them individually, the group consists of a mixture of erroneously classified true positive and true negative reactions.

A simple mathematical formulation of the hypothesis is applied to

actual data gathered from an extensive study of tuberculosis in student nurses. The theory satisfactorily explains a number of findings which appear very difficult to explain in other ways.

In order to take account of the postulated existence of nonspecific reactions, the simple hypothesis was extended to include a third distribution, superimposed upon the distributions of positive and negative reactions. Schematic illustrations show how an observed distribution of combined positive and negative reactions might be distorted by the presence of a distribution of nonspecific reactions. Examination of the data showed that distortions or perturbations of observed distributions of tuberculin reactions actually do occur and that they suggest that in the prevalence of nonspecific reactions there is a geographic pattern quite different from the pattern of specific reactions.

It is suggested that certain tuberculin reactions, particularly reactions to the high doses in common use today, are actually nonspecific and that they most probably arise as cross reactions resulting from tuberculin hypersensitivity produced by infection with other alcohol-acid-fast organisms.

ACKNOWLEDGMENT

Grateful acknowledgment is made to various members of the staff of the Field Studies Branch, particularly to Dr. Charlotte Silverman, Assistant Nurse Officer (R) Virginia S. Trevett, Dr. Henry Zwerling, Surgeon Eugene Gillespie, and Senior Surgeon Ira Lewis for their untiring work in the collection and interpretation of the original field data which are the basis for this report. We are indebted also to Mrs. Anna Gelting of the WHO Tuberculosis Research Office for statistical advice and assistance.

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PREVIOUS STUDIES IN SERIES

Palmer, Carroll E.: Nontuberculous pulmonary calcification and sensitivity to histoplasmin. Pub. Health Rep. **60**: 513–520 (1945).

Palmer, Carroll E.: Geographic differences in sensitivity to histoplasmin among student nurses. Pub. Health Rep. **61**: 475–487 (1946).

Edwards, Lydia B., Lewis, Ira, and Palmer, Carroll E.: III. Pulmonary infiltrates and mediastinal adenopathy observed among student nurses at the beginning of training. Pub. Health Rep. **63**: 1569–1600 (1948).

Goddard, Jennie C., Edwards, Lydia B., and Palmer, Carroll E.: IV. Relationship of pulmonary calcifications with sensitivity to tuberculin and histoplasmin. Pub. Health Rep. **64**: 820–846 (1949).

APPENDIX

Number of student nurses tested, and number with pulmonary calcifications, according to histoplasmin and to tuberculin reaction, in specified cities throughout the United States

Tuberculin reaction [1]	Number of nurses tested								Number of nurses with pulmonary calcifications							
	Histoplasmin reaction [1]								Histoplasmin reaction [1]							
	A	B	C	D	E	F	O	Total	A	B	C	D	E	F	O	Total
KANSAS CITY, MO.																
G	14	13	16	1	1	5	24	74	7	8	5	0	0	1	3	24
H	6	7	7	1	0	1	12	34	3	3	1	1	0	1	2	11
I	2	3	2	1	2	1	4	15	2	1	2	0	1	1	0	7
J	16	4	8	2	0	1	30	61	6	0	4	0	0	0	1	11
K	66	54	63	8	6	8	107	312	28	14	19	3	3	4	3	74
L	63	51	44	12	5	2	91	268	27	23	16	3	3	0	6	78
O	76	76	62	12	2	9	130	367	30	32	30	4	1	4	3	104
Total	243	208	202	37	16	27	398	1,131	103	81	77	11	8	11	18	309
COLUMBUS, OHIO																
G	26	15	7	3	3	1	38	93	16	3	3	1	1	0	9	33
H	14	6	6	1	2	0	16	45	3	2	1	1	1	0	2	10
I	3	2	0	1	0	0	7	13	2	1	0	1	0	0	0	4
J	12	8	2	3	0	0	19	44	5	2	0	1	0	0	1	9
K	96	46	25	6	6	2	123	304	39	13	13	3	0	0	2	70
L	122	80	46	13	3	4	176	444	47	29	14	7	2	1	0	100
O	123	67	34	8	2	7	146	387	48	29	16	2	0	2	5	102
Total	396	224	120	35	16	14	525	1,330	160	79	47	16	4	3	19	328
KANSAS CITY, KANS.																
G	16	5	9	2	2	0	23	57	7	3	3	0	2	0	5	20
H	2	1	2	0	0	0	7	12	1	1	1	0	0	0	2	5
I	0	0	1	1	0	1	1	4	0	0	0	0	0	0	0	0
J	6	7	4	1	0	0	23	41	3	2	3	0	0	0	2	10
K	41	8	19	2	8	1	71	150	12	4	5	0	2	0	0	23
L	32	10	14	4	2	1	59	122	16	2	0	0	1	1	0	20
O	28	23	13	2	3	1	76	146	8	5	4	0	1	0	1	19
Total	125	54	62	12	15	4	260	532	47	17	16	0	6	1	10	97
NEW ORLEANS																
G	13	4	7	3	2	2	64	95	9	0	3	1	1	0	4	18
H	1	4	1	2	2	0	36	46	0	2	0	0	0	0	2	4
I	2	2	2	0	3	0	21	30	0	0	0	0	0	0	1	1
J	12	19	12	1	5	2	134	185	4	6	2	0	2	0	1	15
K	31	37	34	11	4	14	354	485	14	16	10	2	1	2	1	46
L	17	13	10	10	4	9	138	201	9	5	3	2	0	0	0	19
O	16	22	14	12	3	4	177	248	6	5	3	0	1	0	2	17
Total	92	101	80	39	23	31	924	1,290	42	34	21	5	5	2	11	120
BALTIMORE																
G	21	15	11	2	3	1	156	209	10	6	6	0	1	0	26	49
H	10	5	5	1	2	0	79	102	2	0	2	1	1	0	9	15
I	7	2	3	0	2	0	28	42	2	0	3	0	0	0	0	5
J	9	3	3	2	0	1	94	112	3	0	2	0	0	0	1	6
K	41	35	21	6	3	4	346	456	13	12	8	0	0	0	0	33
L	47	41	29	7	2	5	406	537	13	14	10	2	0	2	6	47
O	63	39	24	17	3	4	363	513	32	15	10	5	0	1	4	67
Total	198	140	96	35	15	15	1,472	1,971	75	47	41	8	2	3	46	222

Number of student nurses tested, and number with pulmonary calcifications, according to histoplasmin and to tuberculin reaction, in specified cities throughout the United States—**Continued**

Tuberculin reaction [1]	Number of nurses tested								Number of nurses with pulmonary calcifications							
	Histoplasmin reaction [1]								Histoplasmin reaction [1]							
	A	B	C	D	E	F	O	Total	A	B	C	D	E	F	O	Total
DETROIT																
G	9	6	4	0	3	1	107	130	3	2	2	0	1	0	15	23
H	1	1	0	0	1	1	31	35	1	0	0	0	0	0	3	4
I	0	0	0	0	0	0	9	9	0	0	0	0	0	0	1	1
J	6	0	2	0	1	0	43	52	1	0	1	0	0	0	0	2
K	24	3	4	0	1	3	199	234	12	2	2	0	0	0	0	16
L	28	10	8	2	2	1	254	305	12	2	3	0	0	0	0	17
O	35	6	11	2	0	3	428	485	15	2	6	0	0	1	1	25
Total	103	26	29	4	8	9	1,071	1,250	44	8	14	0	1	1	20	88
LOS ANGELES																
G	23	4	6	1	7	6	176	223	9	1	0	0	0	2	16	28
H	3	7	2	4	0	2	66	84	2	1	0	0	0	0	4	7
I	0	2	2	1	0	1	20	26	0	0	1	0	0	0	0	1
J	2	3	7	1	0	2	73	88	0	1	1	0	0	1	2	5
K	26	7	11	6	3	2	381	436	8	1	2	0	0	0	2	13
L	24	9	3	1	4	5	299	345	8	2	2	0	0	0	3	15
O	24	10	14	5	7	7	509	576	11	5	2	1	0	0	1	20
Total	102	42	45	19	21	25	1,524	1,778	38	11	8	1	0	3	28	89
PHILADELPHIA																
G	22	6	7	4	1	6	261	307	6	1	2	2	0	1	23	35
H	6	9	5	0	6	1	22	149	1	3	1	0	0	0	9	14
I	2	4	2	1	1	2	29	41	1	2	1	0	0	0	1	5
J	2	3	2	1	1	2	87	98	1	0	0	0	0	0	0	1
K	25	6	13	1	1	11	360	417	6	1	4	0	0	0	3	14
L	18	9	8	1	9	7	413	465	7	3	1	0	0	0	1	12
O	41	23	15	4	7	4	608	702	17	8	5	1	0	0	3	34
Total	116	60	52	12	26	33	1,880	2,179	39	18	14	3	0	1	40	115
SAN FRANCISCO																
G	6	2	3	2	0	1	131	145	2	0	2	1	0	0	16	21
H	1	2	3	1	0	0	41	48	0	2	1	0	0	0	1	4
I	0	0	1	1	1	0	11	14	0	0	0	0	0	0	1	1
J	1	1	0	0	0	0	42	44	0	0	0	0	0	0	3	3
K	10	0	3	0	1	5	156	175	1	0	0	0	0	0	1	2
L	6	2	6	4	1	2	205	226	2	1	0	1	0	0	0	4
O	10	3	18	5	5	1	417	459	5	1	3	1	0	0	1	11
Total	34	10	34	13	8	9	1,003	1,111	10	4	6	3	0	0	23	46
DENVER																
G	6	5	5	1	1	5	137	160	1	5	1	0	0	1	22	30
H	3	0	4	0	3	0	65	75	1	0	1	0	1	0	6	9
I	0	0	0	0	0	0	15	15	0	0	0	0	0	0	2	2
J	6	3	0	0	0	0	59	68	2	1	0	0	0	0	0	3
K	5	0	8	2	2	3	228	248	2	0	4	0	0	1	0	7
L	12	3	1	1	2	1	282	302	6	2	0	0	0	0	2	10
O	16	7	4	1	2	0	431	461	5	4	0	0	0	0	3	12
Total	48	18	22	5	10	9	1,217	1,329	17	12	6	0	1	2	35	73

APPENDIX—Continued

***Number of student nurses tested, and number with pulmonary calcifications, according to histoplasmin and to tuberculin reaction, in specified cities throughout the United States—*Continued**

Tuberculin reaction [1]	Number of nurses tested								Number of nurses with pulmonary calcifications							
	Histoplasmin reaction [1]								Histoplasmin reaction [1]							
	A	B	C	D	E	F	O	Total	A	B	C	D	E	F	O	Total
MINNEAPOLIS																
G	4	4	6	3	7	2	115	141	3	3	3	1	2	0	14	26
H	0	1	0	1	1	2	31	36	0	0	0	0	0	1	3	4
I	0	0	0	0	0	0	15	15	0	0	0	0	0	0	1	1
J	3	0	0	0	0	0	71	74	0	0	0	0	0	0	0	0
K	13	1	2	2	12	3	471	504	4	0	0	0	1	0	3	8
L	17	5	5	0	8	4	640	679	4	2	1	0	0	0	3	10
O	27	6	7	3	8	9	910	970	7	1	0	0	1	0	5	14
Total	64	17	20	9	36	20	2,253	2,419	18	6	4	1	4	1	29	63
ALL CITIES																
G	160	79	81	22	30	30	1,232	1,634	73	32	30	6	8	5	153	307
H	47	43	35	11	17	7	506	666	14	14	8	3	3	2	43	87
I	16	15	13	6	9	5	160	224	7	4	7	1	1	1	7	28
J	75	51	40	11	7	8	675	867	25	12	13	1	2	1	11	65
K	378	197	203	44	47	56	2,796	3,721	139	63	67	8	7	7	15	306
L	386	233	174	55	42	41	2,963	3,894	151	85	50	15	6	4	21	332
O	459	282	216	71	42	49	4,195	5,314	184	107	79	14	4	8	29	425
Total	1,521	900	762	220	194	196	12,527	16,320	593	317	254	48	31	28	279	1,550

[1] See text for description of classifications.

INCIDENCE OF DISEASE

No health department, State or local, can effectively prevent or control disease without knowledge of when, where, and under what conditions cases are occurring

UNITED STATES

REPORTS FROM STATES FOR WEEK ENDED DECEMBER 17, 1949

For the seventeenth consecutive week the total reported incidence of poliomyelitis in the Nation decreased from the preceding week. The total number of cases reported for the week is 243 as compared with 322 last week and 115 for the 5-year (1944–48) median. Twenty-six States reported an aggregate decrease from the preceding week of 122 cases, ranging from 1 in 9 States to 22 (from 56 to 34) in California. Fifteen States reported an aggregate increase of 43 cases, ranging from 1 in 6 States to 9 (from 0 to 9) in Vermont.

Compared with last week, decreases occurred in diphtheria, influenza, measles, scarlet fever, and whooping cough. The incidence of each disease was also below the 5-year median. Increases may be noted in meningococcal meningitis (from 56 cases last week to 76 currently) and tularemia (from 22 to 34). One case of leprosy was reported in California.

A sharp increase in influenza occurred in Hawaii with 530 cases reported for the week as compared with 229 last week. For the months of February and March of this year there were 936 and 952 cases, respectively, reported in Hawaii. No unusual influx of influenza has occurred in the Pacific States. California, Oregon, and Washington reported 9, 8, and 1 cases, respectively, for the current week.

Of 40 States and the District of Columbia reporting on rabies in animals, 21 and the District of Columbia reported no cases, while the remaining 19 reported a total of 105 cases. The States reporting the largest numbers were Texas (20), New York (14), and Ohio (12). The total number of rabies in animals reported to date is 5,459, which includes 8 delayed cases in Arkansas.

A total of 9,366 deaths was recorded during the week in 93 large cities in the United States as compared with 9,491 last week; 9,664 and 9,430, respectively, for the corresponding weeks of 1947 and 1948; and 9,430 for the 3-year (1946–48) median. For the year to date the total is 456,537 as compared with 456,826 for the same period last year. Infant deaths for the current week totaled 593; for last week, 696; for the corresponding week last year, 744; and the 3-year median, 744. The cumulative figure is 32,566 as compared with 33,324 for the corresponding period last year.

Telegraphic case reports from State health officers for week ended December 17, 1949

[Leaders indicate that no cases were reported]

Division and State	Diphtheria	Encephalitis, infectious	Influenza	Measles	Meningitis, meningococcal	Pneumonia	Poliomyelitis	Rocky Mt. spotted fever	Scarlet fever	Smallpox	Tularemia	Typhoid and paratyphoid fever [1]	Whooping cough	Rabies in animals
NEW ENGLAND														
Maine	------	------	------	8	------	6	2	------	4	------	------	------	2	------
New Hampshire	------	------	1	------	------	------	------	------	------	------	------	------	------	------
Vermont	------	------	------	1	------	1	9	------	6	------	------	------	6	------
Massachusetts	3	1	------	25	2	------	2	------	62	------	------	------	87	------
Rhode Island	------	------	------	1	------	2	1	------	9	------	------	------	4	------
Connecticut	------	------	------	31	4	48	4	------	16	------	------	------	89	------
MIDDLE ATLANTIC														
New York	3	------	([2])	112	4	245	28	1	[3] 45	------	1	2	193	14
New Jersey	------	------	8	117	------	41	4	------	20	------	------	------	125	1
Pennsylvania	3	------	------	46	7	70	3	------	65	------	------	------	137	------
EAST NORTH CENTRAL														
Ohio	4	------	1	28	5	69	9	------	185	------	3	------	106	12
Indiana	6	------	4	30	3	4	1	------	36	------	2	------	16	5
Illinois	------	1	------	44	3	56	10	------	45	------	[5] 5	2	85	3
Michigan [4]	4	------	1	347	6	50	18	------	91	------	1	1	182	3
Wisconsin	2	------	13	73	------	22	16	------	51	------	------	1	146	------
WEST NORTH CENTRAL														
Minnesota	2	------	------	74	4	4	4	------	25	------	1	------	12	1
Iowa	1	------	------	31	------	1	10	------	11	------	------	------	3	2
Missouri	8	------	4	5	3	15	2	------	20	------	2	------	25	9
North Dakota	------	------	15	19	------	------	------	------	------	------	------	------	3	------
South Dakota	------	------	------	2	------	------	1	------	7	------	------	------	------	------
Nebraska	------	------	2	24	1	------	7	------	6	------	------	------	------	------
Kansas	1	------	------	4	------	14	6	------	18	------	------	2	8	2
SOUTH ATLANTIC														
Delaware	------	------	------	5	2	------	1	------	2	------	------	------	8	------
Maryland [4]	1	------	------	15	------	24	2	------	16	------	1	------	71	------
District of Columbia	------	------	------	43	------	6	------	------	3	------	------	1	2	------
Virginia	6	------	187	8	3	55	1	------	10	------	5	2	19	1
West Virginia	1	------	145	131	------	14	------	------	10	------	1	1	15	------
North Carolina	9	------	------	42	4	------	7	------	82	------	------	1	19	------
South Carolina	5	------	37	10	------	26	------	------	11	------	------	2	6	3
Georgia	8	------	67	8	2	20	3	------	29	------	1	1	6	8
Florida	3	------	8	7	------	13	3	------	12	------	1	1	2	------

EAST SOUTH CENTRAL														
Kentucky	11	----	17	16	5	39	1	----	60	----	2	6	21	3
Tennessee	14	----	29	7	3	66	2	----	60	----	1	----	18	6
Alabama	5	----	30	6	----	69	2	----	27	----	----	----	2	7
Mississippi [4]	10	----	15	27	----	16	2	----	7	----	----	1	----	----
WEST SOUTH CENTRAL														
Arkansas	5	----	62	1	1	64	5	----	3	----	2	----	36	3
Louisiana	13	----	----	5	----	17	1	----	4	----	----	----	4	----
Oklahoma	3	----	31	12	1	19	5	----	4	----	----	----	9	----
Texas	17	3	1,592	39	8	347	12	----	23	----	----	2	90	20
MOUNTAIN														
Montana	1	----	1	32	----	----	----	----	12	----	3	----	1	----
Idaho	----	----	30	9	----	10	7	----	1	----	----	----	7	----
Wyoming	----	----	----	3	1	7	1	----	----	----	1	----	----	----
Colorado	----	----	14	18	----	1	3	----	18	----	----	2	1	----
New Mexico	----	----	----	17	----	5	1	1	3	----	----	----	----	----
Arizona	1	----	108	28	1	16	1	----	6	----	----	----	20	----
Utah [4]	----	----	1	72	----	2	3	----	5	----	1	1	6	----
Nevada	----	----	----	----	----	----	----	----	----	----	----	----	----	----
PACIFIC														
Washington	----	----	1	106	----	2	2	----	70	----	----	----	44	----
Oregon	----	----	8	22	----	23	7	----	12	----	----	----	11	----
California	3	2	9	63	5	14	34	----	80	----	----	4	71	2
Total	153	7	2,441	1,774	78	1,523	243	2	1,292	----	34	33	1,718	----
Median, 1944–48	396	8	2,924	2,592	70	----	115	1	2,267	3	36	56	2,125	----
Year to date 49 weeks	7,750	738	101,488	602,862	3,303	74,572	[5] 42,025	560	72,561	48	1,074	3,540	65,274	----
Median, 1944–48	13,434	612	309,648	600,719	5,535	----	19,107	522	109,152	330	965	3,925	96,419	----
Seasonal low week ends	(27th) July 9	----	(30th) July 30	(35th) Sept. 3	(37th) Sept. 17	----	(11th) Mar. 19	----	(32d) Aug. 13	(35th) Sept. 3	----	(11th) Mar. 19	(39th) Oct. 1	----
Since seasonal low week	3,982	----	25,621	14,344	787	----	[5] 41,110	----	14,301	7	----	3,080	18,672	----
Median, 1944–45 to 1948–49 [6]	6,946	----	29,177	21,111	869	----	18,844	----	22,857	51	----	3,450	20,544	----

[1] Including paratyphoid fever currently reported separately as follows: New York 1, Kansas 2, Georgia 1, Colorado 1, California 2. Cases reported as salmonella infection not included in the table were as follows: New York 2, Pennsylvania 1.

[2] New York City only.

[3] Including cases reported as streptococcal sore throat.

[4] Period ended earlier than Saturday.

[5] Deduction: Michigan, 1 case week ended December 3.

[6] The median of the 5 preceding corresponding periods (1944–45 to 1948–49).

Leprosy: California 1 case.

Alaska: Influenza 5, measles 6, pneumonia 1, septic sore throat 1.

Hawaii: Influenza 530, measles 1, meningitis 1.

FOREIGN REPORTS

CANADA

Provinces—Notifiable diseases—Week ended November 26, 1949.—During the week ended November 26, 1949, cases of certain notifiable diseases were reported by the Dominion Bureau of Statistics of Canada as follows:

Disease	New-foundland	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia	Total
Chickenpox			2		246	315	89	61	65	134	912
Diphtheria				1	12	1					14
Dysentery, bacillary					1	2					3
German measles					13	18		5	53	8	97
Influenza			3			6	1	1			11
Measles			2	1	234	142	163	135	98	145	920
Meningitis, meningococcal					1	1				1	3
Mumps			42		90	207	2	17	37	172	567
Poliomyelitis					1	2	1	2		1	7
Scarlet fever	5		4	6	64	22	22	4	26	5	158
Tuberculosis (all forms)	22		1	6	80	21	11	4	134	30	309
Typhoid and paratyphoid fever				1	11	1				3	16
Undulant fever					1		2				3
Venereal diseases:											
Gonorrhea	7	5	4	15	101	68	29	15	43	73	360
Syphilis	3	4	10	11	62	32	9	5	1	10	147
Whooping cough	2				201	60	3	1	2	17	286

WORLD DISTRIBUTION OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER

From consular reports, international health organizations, medical officers of the Public Health Service, and other sources. The reports contained in the following tables must not be considered as complete or final as regards either the list of countries included or the figures for the particular countries for which reports are given.

CHOLERA

(Cases)

NOTE.—Since many of the figures in the following tables are from weekly reports, the accumulated totals are for approximate dates.

Place	January—September 1949	October 1949	November 1949—week ended—			
			5	12	19	26
ASIA						
Burma	245			[1] 1		
Bassein	183					
Moulmein	2			[1] 1		
Rangoon	[2] 3					
Ceylon	2					
Trincomalee	2					
China:						
Amoy	[3] 1					

See footnotes at end of table.

Place	January—September 1949	October 1949	November 1949—week ended—			
			5	12	19	26
ASIA—continued						
India	77,732	6.663	1,730	41	24	54
Ahmedabad	1					
Allahabad	13	4				
Bombay	[1] 6					
Calcutta	[4] 4,805	222	57	40	24	54
Cawnpore	188	2				
Cocanada	14					
Cuddalore	2					
Lucknow	[2] 33			1		
Madras	429	4				
Masulipatam	1					
Nagpur	24	18	2			
Negapatam	26					
New Delhi	[2] 19	1				
Tuticorin	14					
India (French):						
Karikal	55					
Pondicherry	100					
Indochina (French):						
Cambodia	45					
Cochinchina	11					
Pakistan	25,024	786	1	1		
Chittagong	75					
Dacca	99		[5] 1	[5] 1		
Lahore	[3] 24					
Siam (Thailand)	9					
Bangkok	8					

[1] Imported. [2] Includes 1 imported case. [3] Suspected, with 2 deaths. [3] Suspected. [4] Includes imported cases. [5] Death.

PLAGUE

(Cases)

Place	January—September 1949	October 1949	November 1949—week ended—			
			5	12	19	26
AFRICA						
Basutoland	42					
Belgian Congo	[1] 15				1	
Costermansville Province	3				1	
Stanleyville Province	[1] 12					
British East Africa:						
Kenya	5					
Tanganyika	15					
Madagascar	91	20		[2] 1	[3] 1	
Tananarive	6					
Rhodesia, Northern	2					
Union of South Africa	77	8	2			2
Cape Province	[4] [5] 42	3	1			2
Orange Free State	[4] 12	[6] [7] 2				
Transvaal	4					
ASIA						
Burma	444	[4] 3				
Mandalay	1					
Moulmein	[8] 6					
Rangoon	[8] 8					
China:						
Chahar Province		[9] 49				
Chekiang Province	7					
Wenchow	7					
Fukien Province	20					
Kiangsi Province	9					
India	[8] 27,435	1,670	360		[10] 1	[11] 1
Indochina (French)	126					
Annam	67				1	
Cambodia	24					
Cochinchina	[12] 32					
Laos	3					
Java	225	235	53	38	57	43
Jogjakarta Residency	192	235	53	38	57	43
Siam (Thailand)	166	11	2			
EUROPE						
Portugal: Azores	5					

See footnotes at end of table.

Place	January–September 1949	October 1949	November 1949—week ended—			
			5	12	19	26
SOUTH AMERICA						
Brazil:						
Bahia State	13					
Ceara State	[13] 9					
Pernambuco State	[14] 19					
Ecuador:						
Loja Province	6	3				
Peru:						
Lambayeque Department	10					
Libertad Department	1					
Lima Department	8					
Piura Department	10					
Tumbes Department						[15] 1
Venezuela:						
Aragua State	2					
OCEANIA						
Hawaii Territory					[16] 1	
Plague infected rats [17]		1				[18] 2

[1] Includes 2 cases of pneumonic plague. [2] Nov. 1–10, 1949. [3] Nov. 11–20, 1949. [4] Includes suspected cases. [5] Includes 11 cases of pneumonic plague. [6] Suspected. [7] Includes 1 case of pneumonic plague. [8] Includes imported cases. [9] Deaths. [10] In Calcutta. [11] In Lucknow. [12] Includes 7 cases of pneumonic plague. [13] May 1–June 30, 1949. [14] Jan. 1–May 31, 1949. [15] Nov. 1–30, 1949. [16] At Haina, Hamakua District, Island of Hawaii, onset October 31, 1949. [17] Plague infection has also been reported in Hawaii Territory as follows: On Mar. 12, 1949, in mass inoculation of 2 pools of tissue from 10 rats (8 and 2), taken on Maui Island; on Mar. 16, 1949, in mass inoculation of 3 pools of 29 fleas (7, 12, and 10), on Aug. 4, 1949, in mass inoculation of 15 fleas, on Aug. 18, 1949, in a pool of 31 fleas, and on Sept. 15, 1949, in 49 fleas, all collected from rats taken on the Island of Hawaii. [18] Includes 1 mouse.

SMALLPOX

(Cases)

(P=present)

Place	January–September 1949	October 1949	Nov. 5	Nov. 12	Nov. 19	Nov. 26
AFRICA						
Algeria	211	31		[1] 16		
Angola	[2] 633					
Basutoland	1					
Bechuanaland	3					
Belgian Congo	[2] 1,669	185	20	64	21	
British East Africa:						
Kenya	25					
Nyasaland	1,047	69	1	13		
Tanganyika	699					
Uganda	38					
Cameroon (British)	21					
Cameroon (French)	69	1				
Dahomey	380	30		[1] 13	[3] 10	[4] 6
Egypt	3	[5] 1				
Eritrea	1					
Ethiopia	10					
French Equatorial Africa	253	126		[1] 31		
French Guinea	1					
French West Africa: Haute Volta	121					
Gambia	58					
Gold Coast	50					
Ivory Coast	296	2			[3] 2	
Liberia	3					
Morocco (French)	9					
Morocco (International Zone)	2					
Mozambique	257	40	22	9		
Nigeria	7,844	[6] 96	[6] 21	[6] 14	[6] 10	[6] 16
Niger Territory	603	103		[1] 9	[3] 19	
Portuguese Guinea	1					
Rhodesia:						
Northern	9				2	
Southern	531	171				
Senegal	16					
Sierra Leone	114					
Sudan (Anglo-Egyptian)	[2,7] 217	7	7	2	6	4
Sudan (French)	159					
Togo (French)	136	12				
Tunisia	1					
Union of South Africa	994	89	P	P	P	

See footnotes at end of table.

Place	January–September 1949	October 1949	November 1949—week ended—			
			5	12	19	26
ASIA						
Afghanistan	211					
Arabia	45		4	12		
Bahrein Islands	58	1		1	3	1
Burma	[7] 1,693	122	25	40	40	
Ceylon	[5] 2					
China	967	2		1		
India	62,893	1,606	264	33	39	74
India (French): **Yanaon**	1					
India (Portuguese)	222					
Indochina (French)	2,462	30	21	6	4	
Iran	297	19	6			
Iraq	475	57	1	24	25	28
Israel	5					
Japan	120			1		
Korea (Southern)	8,908	37				
Lebanon	[7] 140				1	
Malay States (Federated)	43	3				
Manchuria: **Port Arthur**	9					
Netherlands Indies:						
Java	[7] 11,101	1,278	113	105	94	78
Riouw Archipelago	2					
Sumatra	[7] 194	21	2		1	
Pakistan	3,736	75				
Palestine	62	25				
Philippine Islands:						
Mindoro Island	11					
Romblon Island	[5] 4					
Tablas Island	2					
Portuguese Timor	4					
Siam (Thailand)	102				1	
Straits Settlements: **Singapore**	[7] 2					
Syria	506	99	11	4	6	1
Transjordan	195					
Turkey. (See Turkey in Europe.)						
EUROPE						
Belgium	1					
Germany (U. S. Zone)	1				1	
Great Britain: England and Wales	[7] 20		[8] 1	[9] 1		
Italy	[10] 98					
Portugal	7					
Spain	3					
Canary Islands	6					
Turkey	92					
NORTH AMERICA						
Cuba: **Habana**	[7] 6					
Guatemala	4					
Mexico	[2] 106	20			2	
SOUTH AMERICA						
Argentina	[2] 253	44		5	4	12
Bolivia	35					
Brazil	[2] 284	24	8	4	4	16
Chile	[5] 2					
Columbia	[2] 2,319	135	18			
Ecuador	[2] 585	26		[11] 1	[11] 3	
Paraguay	[2] 6	2				
Peru	3,678					
Uruguay					[11] 1	[11] 1
Venezuela	[2] 1,903	[11] 7				
OCEANIA						
Guam	2					

[1] November 1–10, 1949. [2] Includes alastrim. [3] November 11–20, 1949. [4] November 21–30, 1949. [5] Imported. [6] In the port of Lagos. [7] Includes imported cases. [8] Laboratory case. [9] Contact of laboratory case. [10] Includes 95 cases of varioloid reported in Rome Jan. 1–June 10, 1949. [11] Alastrim.

TYPHUS FEVER [*]

(Cases)

(P—present)

Place	January—September 1949	October 1949	November 1949—week ended—			
			5	12	19	26
AFRICA						
Algeria	68	7		[1] 5		
Basutoland	24	1				
Belgian Congo	[2] 42					
British East Africa:						
Kenya	76					
Nyasaland	4					
Tanganyika	1					
Egypt	176	1				
Eritrea	67	4		1		
Ethiopia	532					
Gold Coast	3					
Libya	171	9			2	
Madagascar: **Tananarive**	[3] 10					
Morocco (French)	17			[1] 1		
Morocco (Spanish)	23					
Sierra Leone	[2] 1					
Tunisia	69	1				
Union of South Africa	130	8	P	P	P	
ASIA						
Afghanistan	1, 570					
Arabia: **Aden**	[4] 2					
Burma	5					
Ceylon: **Colombo**	[2] 5		[2] 1			
China	53					
India	234	2				
India (Portuguese)	44	17	6			
Indochina (French)	18	1		1	1	
Iran	161	5	2			
Iraq	[3] 65	6	4	2		
Japan	92	5				
Korea (Southern)	[3] 1, 171	8				
Lebanon	[3] 4					
Pakistan	590	2				1
Palestine	110					
Philippine Islands: **Manilla**	[2] 1					
Straits Settlements: **Singapore**	[2] 2	1				
Syria	23			2	1	
Transjordan	60			1		2
Turkey. (See Turkey in Europe.)						
EUROPE						
Belgium	[3, 4] 5					
Bulgaria	393					
Czechoslovakia	22					
France	5					
Great Britain:						
England and Wales	[2, 5] 4					
Malta and Gozo	[2] 18	5	2		2	
Greece	[3] 58			1	12	
Hungary	20					
Italy	[3] 21	4				
Sicily	28					
Poland	295	20				
Portugal	6					
Rumania	417					
Spain	7					
Turkey	171	15	5	5	6	9
Yugoslavia	184	11				
NORTH AMERICA						
Bahama Islands: **Nassau**	[2] 1					
Costa Rica [2]	36	7			1	
Cuba [2]	3					
Guatemala	42					
Jamaica [2]	18	1				
Mexico [2]	185	27	3	8	7	3
Panama Canal Zone [2]	12					
Panama (Republic)	[2] 5					
Puerto Rico [2]	36	7	1			

See footnotes at end of table.

Place	January—September 1949	October 1949	November 1949—week ended—			
			5	12	19	26
SOUTH AMERICA						
Argentina [2]	2					
Bolivia	53					
Brazil	[3] 6					
Chile [3]	258	16		1		
Colombia [3]	2,230	171	8			
Curacao [2]	5					
Ecuador [3]	292	17				
Peru	1,103					
Venezuela [3]	95	3	2			
OCEANIA						
Australia [2]	105	10	3	2		1
Hawaii Territory [2]	13	3				

*Reports from some areas are probably murine type, while others include both murine and louse-borne types.
[1] Nov. 1-10, 1949. [2] Murine type. [3] Includes murine type. [4] Includes imported cases. [5] Imported.

YELLOW FEVER

(C=cases; D=deaths)

AFRICA							
Belgian Congo:							
Stanleyville Province	D	5					
French Equatorial Africa:							
Bangui	D	1					
Gold Coast	C	24	2				
Accra	D		1				
Birim District	C	[1] 3					
Komenda Village [2]	D	1					
Nkwanta Dunkwa Area	D	1					
Oda Area:							
Akwatia	C	[3] 5					
Atiankama	C	[4] 1					
Bawdua	C	[4] 2	[4] 1				
Esuboni	C	[4] 3					
Oseikrome Village	D	1					
Winneba Area:							
Apam	D	1					
Akukuom	D	1					
Nyakrom	C	[5] 5					
Nigeria:							
Kaduna	D	1					
Lagos	D	[6] 2					
Sudan (French):							
Bamako	D	[4] 1					
NORTH AMERICA							
Panama:							
Colon Province	D	3					
Pacora	C	[7] 8					
SOUTH AMERICA							
Brazil:							
Acre Territory	D	1					
Amazonas State	D	1					
Para State	D	3					
Ecuador:							
Napo Pastaza Province	D	1					
Peru:							
Cuzco Department	D	3					
San Martin Department	D	1					

[1] Includes 2 suspected cases. [2] Near seaport of Sekondi. [3] Includes 1 suspected case. [4] Suspected. [5] Includes 2 suspected cases (1 fatal), and 3 fatal confirmed cases. [6] Imported. [7] Reported Jan. 15, 1949. Date of occurrence Nov. 11-Dec. 30, 1948. 5 cases (all fatal) confirmed, 3 suspected cases.

DEATHS DURING WEEK ENDED DECEMBER 17, 1949

	Week ended Dec. 17, 1949	Corresponding week, 1948
Data for 93 large cities of the United States:		
Total deaths	9,366	9,430
Median for 3 prior years	9,430	
Total deaths, first 50 weeks of year	456,537	456,826
Deaths under 1 year of age	593	744
Median for 3 prior years	744	
Deaths under 1 year of age, first 50 weeks of year	32,566	33,324
Data from industrial insurance companies:		
Policies in force	69,962,439	70,759,752
Number of death claims	12,845	12,140
Death claims per 1,000 policies in force, annual rate	9.6	9.0
Death claims per 1,000 policies, first 50 weeks of year, annual rate	9.1	9.2