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Research Contributions of BCG Vaccination Programs

I. Tuberculin Allergy as a Family Trait

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Throughout its long history, tuberculosis has been known as a family disease. In earlier times a predisposition or inherited tendency to consumption was believed to be the chief reason that it appeared to "run in families." In fact, belief in a family weakness was so generally accepted that no one thought it unusual or that the situation could be otherwise, when one after another in a family became ill and died of the disease.

With the development of more scientific knowledge, it became apparent that close association with a tuberculous person was the principal reason for the spread of the disease and its tendency to appear within family groups. The great importance of infection by human contact and the use of this knowledge as the keystone for developing effective tuberculosis control programs have more or less led to a disregard for the possible significance of hereditary or familial factors. When the disease has appeared to be particularly destructive in some families and benign in others, subtle influences of familial susceptibility have been regarded as more or less inconsequential compared with those involving intimacy and repetition of contact, virulence of infecting organism, or gross economic factors of housing and nutrition. The great lack of scientific knowledge of the role of heredity in human tuberculosis is partly a result of the great practical difficulties in separating the certainly powerful effects of exposure to human disease from the possible influences of familial constitution. In fact, considering critically the problems of scientific methodology and analysis, it may even be impossible in naturally occurring tuberculosis in human populations to determine if familial constitution has any influence at all on the development and course of the disease.

A most remarkable possibility (*1*) to investigate many problems in tuberculosis, including familial predisposition, now exists as a conse-

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quence of the extensive BCG vaccination programs which are under way in many places in the world. In place of observations on a relatively few tuberculous families where knowledge of the infecting organism, time and intensity of exposure, mode of infection, etc., are, in the best of circumstances, largely a matter of guesswork, observations can now be obtained on thousands of different family groups, *all of whom are given, at a known time, a relatively uniform, constant, artificial tuberculous infection.* Although vaccination with BCG may constitute a benign nonprogressive infection, many of the responses to vaccination must resemble to some extent those that occur with natural virulent tuberculous infections. Both infections have in common at least two extremely important characteristics: both produce sensitivity to tuberculin and, according to widely held views, some degree of immunity to subsequent infection.

The present paper and others planned to follow are attempts to probe the possibilities of obtaining, through BCG vaccination programs, more knowledge of the nature of human tuberculosis, particularly with respect to fundamental questions of familial resistance and susceptibility. The purpose of this first paper is simply to show that children from different families respond differently in acquiring sensitivity to tuberculin after vaccination with BCG. This new knowledge opens an entirely new approach to the study of the controversial and highly significant question: the relationship between allergy and immunity in human tuberculosis. If the capacity to become allergic to tuberculin is to a considerable extent a familial trait, and if, in turn, it is related to susceptibility and resistance to disease, it should be possible through this approach to evaluate in a way not otherwise possible the significance of familial factors in human tuberculosis.

Material

Records suitable for the present study were obtained as part of a very extensive series of investigations on BCG vaccine undertaken cooperatively by the Danish State Serum Institute, the International Tuberculosis Campaign, the Tuberculosis Research Office of the World Health Organization, and the local health authorities in Denmark responsible for mass BCG vaccination of school children. Previous papers (*2*, *3*, *4*) give information on the scope and plan of the investigations. The second reference is particularly pertinent since it is based on the same series of observations used here and contains many details on the methods and data collected.

From a practical public health viewpoint, the cooperative BCG project was regarded simply as a routine vaccination service program for all of the school children in a small homogeneous rural area in Jutland, Denmark. From a technical standpoint, the program was

carried out according to rigid scientific standards. The tests and vaccinations were done by a special research field team operating under a carefully prepared protocol. Each separate operation was assigned to a single person on the team in order to avoid differences due to personal bias. Tuberculin reactions were carefully and objectively measured. All records were made and handled by clerical personnel particularly trained for the work. In addition to the usual routine data on tests and vaccinations, the names of the father and mother of each child were obtained in order to permit the grouping of the children into family aggregates.

The total enrollment of 4,200 children in 90 rural municipal schools constitutes the base population for the study. Of this number of registered children, 3,270 fulfilled the following requirements: They were not previously vaccinated, had a negative prevaccination tuberculin reaction, were vaccinated and had a completed postvaccination tuberculin test 10 weeks later. More than 99 percent of the children were between 7 and 14 years of age, and 50.5 percent were males. Among the 3,270 children, 1,751 belonged to 738 families, each consisting of 2 to 5 vaccinated children.

The intradermal Mantoux, using 10 and 100 T. U. (0.0002 and 0.002 mg. of PPD), was given for both the prevaccination and postvaccination tuberculin test. Readings of the reactions were made on either the 3d or the 4th day and included the careful measurement in millimeters of the widest transverse diameter of both erythema and induration and, as well, the classification of reactions into four types according to the density of induration. Children were vaccinated if their reactions did not exceed 6 millimeters of induration to the 10 T. U. test.

BCG vaccine, batch No. 869, prepared by the State Serum Institute in Copenhagen for routine vaccination work in Denmark and in the International Tuberculosis Campaign was used; 0.1 cc. was given by the intradermal method. Thirty-five different samples of the vaccine were actually used, graduated with respect to dosage, age of vaccine after preparation, and temperature of storage. Each of the 35 samples was used on approximately the same number of children attending one to four schools. The designed variations in the 35 samples of vaccine, while making the analysis slightly more complex, have been taken into account by the method of analysis.

Method

The vaccinations in this project probably should be regarded as somewhat unusual in one respect: after 10 weeks almost every child had become allergic to tuberculin to the extent that he showed 6 or more millimeters of induration to the 10 T. U. Mantoux test. It is believed the particular batch of BCG used was a rather potent one.

Although the BCG infection apparently produced a fairly high level of allergy in all children, marked differences in postvaccination tuberculin reactions were recorded. It is usual to assume that such differences reflect differences in the degree of allergy attained—that is, that the larger and more severe the reaction, the greater the allergy. This assumption, explicitly accepted in the present analysis, may be simply stated as follows: Within the limitations of considerable experimental error, the transverse diameter of induration of the tuberculin reaction is a quantitative measure of the degree or level of postvaccination allergy.

Use of the size of the tuberculin reaction as an index of the allergy of an individual permits a quantitative analysis of the data and immediately raises a question as to which of a number of statistical methods is best suited to investigate whether children of different families exhibit different "familial" capacities to become allergic after BCG vaccination.

The technique known as the "analysis of variance" was chosen as the most appropriate for the purpose. Since many interested in the results of the study may not find a technical statistical presentation very satisfactory, a very general and somewhat oversimplified discussion will be given here, and the technical details reported in an appendix.

For present purposes, it may suffice to say that the term "variance" is used to denote a numerical measure of the differences that occur in a series of observations. Or, variance may be regarded as a kind of average, not of measurements themselves, but of the differences among them. Since one measurement may be larger or smaller than another for some particular reason, an "analysis of variance" becomes a determination of how much of the average difference, or variance, may be accounted for by one or more pertinent reasons.

Application of the analysis of variance to the present problem leads at once to a consideration of the particular reasons why the measured size of a tuberculin reaction in one child may differ from that of another. Two main categories of causes are readily visualized. The first is common to all scientific work and is generally referred to as experimental or observational error. Thus, reactions may appear to be different simply because we are not accurate enough in the technical procedures of vaccinating and of making and reading tuberculin tests. In one child a whole series of small errors may contribute to his apparently having a large postvaccination tuberculin reaction. In another child, who may actually have exactly the same allergy, the errors may be reversed with the result that he may show a considerably smaller reaction. Those who have had much experience in BCG work will know that observational errors are relatively large, even under the most exacting conditions, and will expect that a

substantial share of the average difference or the variance of tuberculin reactions will be due to this unavoidable but measurable cause.

The second major cause of differences is generally referred to as biological variation and it is the contribution of this factor to the variance of postvaccination tuberculin reactions that is of greatest interest here. It may be well to point out, again, the potential advantage of studying the question in BCG infections rather than in naturally occurring tuberculous infections. In the latter, sensitivity to tuberculin has been determined for many hundreds of thousands of persons and, although marked differences in the sensitivity of individuals are always found, it has never been possible to do more than to guess as to the reasons for these differences. This statement is patently true despite many published reports which imply, at least, that the primary factors responsible for producing differences in levels of allergy are virulence of the infecting organism, intimacy and duration of exposure, etc. BCG-produced allergy, obviously, can be affected to only a very small extent by similar influences. Except for experimental errors in vaccinating and tuberculin testing, BCG allergy primarily reflects an individual's allergenic capacity and a way is thus opened to study the biological causes of variation in allergy.

Enough has been written above to indicate that we shall be concerned here chiefly with the technical problem of separating biological variation in tuberculin sensitivity into two portions: that due to *differences among children within the same family* and that due to *differences among families* in their capacity to develop allergy.

Results

The first requirement in the analysis is a determination of the experimental error in measuring postvaccination allergy, obtained by accepting certain assumptions and by using a somewhat indirect but quite satisfactory procedure. In many problems it is possible, by repeating the same procedures on the same persons, often at the same time, to estimate the experimental error in terms of the differences between what are essentially independent duplicated observations. Obviously, vaccinations cannot be independently duplicated on the same person. A fairly close approximation to this can be accomplished, however, by simultaneously vaccinating identical twins, under the assumption that differences in their responses will be due largely to variations in the techniques of vaccinating and tuberculin testing and to some degree, of course, to their individual differences.

From our whole series of BCG vaccine investigations results are available from vaccinating 61 pairs of like-sexed twins. This is not as large a number of pairs as would be desirable, nor are they all identical twins, which would be more suitable; nevertheless, as is indicated in

the later more technical section of the paper, the estimate of experimental error based on the study of these 61 pairs of twins is probably reasonably satisfactory for this purpose.

Application of this estimate of the experimental error to the variance of the total group leads to the conclusion that experimental error accounts for approximately one-half and biological variation the other half of the total variance found in measuring the postvaccination allergy of the 3,200 children in the study.

The second and more critical result of the study consists of the separation of the biological source of variation into the two components, a little more than half contributed by within-family differences and something less than half which arises because of between-family differences. In approximate and rather general terms, it is possible to conclude from this analysis, first: That the total observed differences between children are about equally due to experimental error and biological differences; and, second, that of the total biological variation in the present population, about one-half may be accounted for by factors which children share with their brothers and sisters, the other half by factors which children possess independent of their siblings.

Discussion and Summary

The paper has two purposes: First, to point out the great possibilities of learning about tuberculosis through careful research done as part of public health service programs, for example, the extensive BCG vaccination programs being carried out in many places in the world today. Second, as an illustration of the possibilities of these ready-made research facilities, to show that the capacity to develop allergy to tuberculin after BCG vaccination is about as much a familial as an individual characteristic.

Material for the study was derived from a service BCG vaccination program carried out according to strict scientific standards on the population of about 4,000 registered school children living in a small homogeneous rural area in Jutland, Denmark.

The statistical technique of analysis of variance was applied to observations on the measured diameter of induration of postvaccination tuberculin reactions, the assumption being made that this measurement of the reaction would serve, within the limits of experimental error, as a quantitative index of the allergenic capacity of an individual child. One step in the analysis is based upon the result of vaccinating like-sexed twins. Such pairs, it was assumed, are sufficiently alike with respect to both heredity and environment to permit the interpretation that differences between their responses to vaccination will constitute a reasonably satisfactory estimate of the experimental error of vaccinating and tuberculin testing. By starting with

the assumption that the biological differences between like-sexed twins is zero, it was found that biological differences between brothers and sisters in the same family would be represented by a variance value of 3.1. When the population is extended to include all children in all of the different families studied, the variance nearly doubles, to reach a value of 5.4. This result was interpreted in general terms to mean that a very substantial share, nearly one-half, of the variation in a child's capacity to become allergic after vaccination is due to familial factors.

The most immediate practical value of this finding may be its bearing on the problem of revaccination. At present, one or more revaccinations are often given routinely if a person fails to develop a certain degree of tuberculin allergy. This is a reasonable procedure if dosage and technique of vaccination are the decisive factors. But if a lack of postvaccination allergy is caused by the individual's allergy-producing capacity, the whole matter of revaccination must be approached from an entirely new point of view.

As for its contribution to fundamental knowledge of tuberculosis, the significance of this study most probably will depend on the nature of the relationship between the capacity to develop allergy and susceptibility to tuberculous disease. The present study, of course, contributes no information on this point. On the other hand, tuberculosis is certainly concentrated in family groups, and this investigation strongly suggests that the capacity to become allergic to tuberculin is markedly influenced by familial factors. On general grounds it is difficult to believe that further research will show these two familial characteristics to be independent. And . . . *if* allergy and immunity are related, particularly in terms of common familial factors, BCG vaccination may be of as much importance as a technique for selecting "resistant" and "susceptible" individuals as for prophylaxis against the disease.

A number of investigations may be visualized immediately to study the relationship between allergenic capacity and immunity to tuberculosis. One investigation is already under way. From the group of 738 Danish families studied here, two subgroups have been selected, one in which the children developed a high degree of allergy, the other only a low degree. By studying the past history of tuberculosis morbidity and mortality in the adult members of these two family subgroups, it should be possible to learn something of the relationship of allergy and immunity if one exists. At the present time, we can only guess as to whether "good" allergenic capacity is associated with resistance to the disease, or whether the reverse might be the case. Denmark offers a remarkable opportunity for such an investigation because of its highly efficient system of diagnosis and reporting of tuberculosis morbidity and mortality. Because the

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prevalence of tuberculosis in Denmark at present is extremely low, it would not appear profitable to attempt to follow all the vaccinated children, or members of their families, to determine future tuberculosis rates. Such an approach to the problem might, however, be undertaken in other countries where the prevalence of tuberculosis is greater.

In this study, as in most of those which deal with familial characteristics, it is not possible to separate the influences of heredity and environment. Experimental tuberculosis in laboratory animals, however, clearly indicates that hereditary factors can be of enormous significance in the development and course of the disease. Also, there is much general evidence from observations on human tuberculosis to indicate, for example, that certain races apparently are highly susceptible to the disease while others appear to be relatively much more resistant. Similar studies on white persons and Negroes living under similar environmental conditions in the United States should be relatively easy to carry out and might be very informative on this point.

It is difficult to speculate as to how far the findings reported here may be generalized. The rural Danish population under study probably represents almost as homogeneous a group of people, from the standpoint of heredity and environment, as will be found anywhere in the world today. When the present inquiry was first planned it was expected that familial differences in allergenic capacity would be very small in such a homogeneous population, even though large differences might exist among different races having widely different hereditary and environmental backgrounds. To find that children from these Danish families differ as much as they apparently do, accentuates the need for, and value of, coordinated public health research carried out on an international basis.

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APPENDIX

Statistical Methods

The principal question to be investigated is whether, with respect to post-vaccination tuberculin reactions, children in the same family tend to resemble each other more than do children belonging to different families. By an analysis of variance, one can test the hypothesis that the observed tuberculin reactions of siblings are random samples out of the total population of reactions of all the children. If this hypothesis can be rejected it would follow that the allergy producing capacity of an individual is in part a familial characteristic.

Suppose that in a population of vaccinated children there are k sibling groups, or families, each having at least two vaccinated children. Let n_i denote the number of vaccinated children in the i^{th} family, and x_{ij} the size of the reaction in the j^{th} child in this family. The number of children in all k families is

$$n=\sum_{i=1}^{k} n_i$$

The arithmetic mean of the reactions in the i^{th} family is

$$\bar{x}_i=\frac{1}{n_i}\sum_{j=1}^{n_i} x_{ij} \text{ and}$$

the mean for all children in the k families is

$$\bar{x}=\frac{1}{n}\sum_{i=1}^{k} n_i\bar{x}_i$$

The variance of reactions of all children is

$$s^2=\frac{1}{n-1}\sum_{i=1}^{k}\sum_{j=1}^{n_i}(x_{ij}-\bar{x})^2$$

The variance *between* families is

$$s_1^2=\frac{1}{k-1}\sum_{i=1}^{k} n_i(\bar{x}_i-\bar{x})^2$$

and the variance *within* families is

$$s_2^2=\frac{1}{n-k}\sum_{i=1}^{k}\sum_{j=1}^{n_i}(x_{ij}-x_i)^2$$

If family membership does not influence the reactions, s^2, s_1^2 and s_2^2 will all have the same expected value. If there are characteristic variations between families which do not prevail within families, s_1^2 will generally be greater than s_2^2. Large values of the ratio s_1^2/s_2^2 will consequently be rare if there are no character-

istic variations between families. Under certain conditions, including normal distribution of the reactions, it is possible through use of the z-test to determine whether a certain observed value of s_1^2/s_2^2 is compatible with the hypothesis of no family variations, or whether this hypothesis should be rejected. In the latter case the difference between s^2 and s_2^2 will afford an estimate of the variance of the mean values characterizing the individual families.

In the present analysis we have preferred to substitute for s^2 another estimate of the variance of reactions of all children, S^2, computed from the whole population studied which includes children who did not have vaccinated siblings.

The variance of postvaccination reactions of pairs of twins may be computed according to the formula:

$$s_T = \frac{1}{2k}\sum_{j=1}^{k}(X_{i1} - X_{i2})^2$$

where k denotes the number of pairs and X_{i1} and X_{i2} the sizes of reactions of the two members of the i^{th} pair. The same formula may be used to determine the variance of experimental errors of the tuberculin test, X_{i1} and X_{i2} denoting in this case the results of independent duplicate tests performed on a series of k persons.

Determination of Variances Within and Between Families, by Size of Induration of Postvaccination Reactions

The material for the present study was taken from an investigation (*2*) primarily designed to determine the influence of variations in dosage, age, and temperature of storage on the allergy producing capacity of BCG vaccine. Altogether, 3,270 children attending 90 rural schools were vaccinated with 35 vaccine samples, each sample differing somewhat with respect to the three variables under study. Therefore, the analysis of variance must be made separately for the 35 different groups of children given the different types of vaccine.[1] Moreover, several factors, such as use of the same ampule of vaccine, uniform conditions for reading tests, etc., which may produce some uniformity of results within each school, led to a decision to make the analysis of variance *separately for each school.* The exclusion of 6 schools, in each of which there was only 1 family, reduced the material for the analysis to 84 schools, including 1,739 children in 732 families.

The details will not be reproduced here but the values for s_1^2, s_2^2 and the ratios s_1^2/s_2^2 were obtained for each of the 84 schools. Because of the small number of families in many schools, considerable random variation was apparent but there was an obvious predominance of large ratios at the expense of small ones. By weighting the variances from each school by the number of degrees of freedom,[2] the following average values were obtained:

$$\bar{s}_1^2 = 13.4,\ \bar{s}_2^2 = 8.9,\ \text{and}\ \bar{s}_1^2/\bar{s}_2^2 = 1.50$$

According to the z-test, the probability of finding a ratio as large as 1.50 is less than 0.0005. This test of the statistical significance of the average ratio would be suitable if the variances from the separate schools were constant except for sampling variation. Although this condition is not completely satisfied, the result strongly suggests, nevertheless, the existence of differences among families in allergy-producing capacity.

An additional and slightly different approach was made to the problem of

[1] Reference (*2*) gives details, not reproduced here, of the actual frequency distributions of size of postvaccination reactions for the separate groups of children given different samples of the vaccine. It is shown that the frequency distributions are approximately normal and that the standard deviations of the distributions vary from a constant value only slightly more than would be expected by sampling errors.

[2] The degrees of freedom for $\bar{s}_1^2$ was 731, for $\bar{s}_2^2$ it was 1738–731 = 1007.

determining the statistical significance of the variations in the ratios, s_1^2/s_2^2. Table 1 shows the observed and theoretical distributions of the probabilities corresponding to the ratios found for the 84 separate schools. Assuming that there are no family variations, an average of 8.4 observations would be expected in each 10 percent interval, as indicated in the table. A chi square test reveals a highly significant difference between observed and expected distributions, corresponding to P of less than 0.0005. This result also justifies the rejection of the hypothesis of no characteristic variations between families.

Table 1. *Variance ratios from 84 schools distributed according to corresponding probability fractiles (on the assumption of no family variations)*

Probability fractiles for observed values of the variance ratios (percent)	Number of observed ratios in each interval	Expected number of ratios in each interval (on the assumption of no family variations)
0–10	19	8.4
10–30	25	16.8
30–50	15	16.8
50–70	15	16.8
70–90	7	16.8
90–100	3	8.4
Total	84	84.0

An estimate of total variance, $\bar{s}^2=10.8$, was obtained by weighting by the number of degrees of freedom and averaging the 84 values of s^2 for the separate schools. This average is not significantly different from $\bar{S}^2=11.2$, obtained from all vaccinated children including those with no siblings in the school BCG program. Since the latter is computed from a larger number of observations (3,270) it is assumed to be a better estimate of the total variance and has been preferred to $\bar{s}^2$ for establishing the variance of the mean values characterizing individual families. Thus:

$$\bar{S}^2-\bar{s}_2^2=11.2-8.9=2.3$$

Random errors of sampling applicable to both $\bar{S}^2$ and $\bar{s}_2^2$ are not large and the value 2.3 may be considered quite well established. Thus it is evident that approximately 20 percent of the total variance of postvaccination reactions can be attributed to differences between families.

Before proceeding with a further analysis of other contributions to the total variance, it is necessary to consider whether certain factors, such as sex, age, and prevaccination tuberculin sensitivity, may account for the variance between families.

Differences in reactions in the two sexes cannot be responsible for the result, since, as shown in table 2, sibling groups can be regarded as random samples with respect to sex.

It can be shown also that the uniformity of reactions within families is not due to an agreement in the age of siblings. Table 3 gives the average size of postvaccination reactions by age, sex, and major subdivisions of the material according to dosage and temperature of storage of the vaccine used. As the table shows, the difference in the average size of induration varies within the relatively narrow range of about 1.5 millimeters over the whole age span of from 7 to 14 years. The variance of the mean indurations characterizing the individual age groups then will not exceed 0.19, assuming a rectangular distribution of the age component. In addition, an analysis of the records has shown that the age dispersion is gener-

Table 2. *Distribution of 738 families according to number and sex of 1,751 children included in family groups*

Composition of family group tested	Number of families	Number of children	Composition of family group tested	Number of families	Number of children
2 child families	525	1,050	4 child families—Continued		
			3 males, 1 female	8	
2 males	128		2 males, 2 females	17	
1 male, 1 female	268		1 male, 3 females	12	
2 females	129		4 females	1	
3 child families	162	486	5 child families	11	55
3 males	24		5 males	0	
2 males, 1 female	59		4 males, 1 female	2	
1 male, 2 females	53		3 males, 2 females	3	
3 females	26		2 males, 3 females	3	
			1 male, 4 females	2	
4 child families	40	160	5 females	1	
4 males	2		Total	738	1,751

ally greater within families than in the whole population studied. This means that, on the average, the factor of age would cause slightly greater differences in reactions within each family than in the total material.

Table 3. *Mean size of induration in mm. of Mantoux 10 T. U. reactions 10 weeks after BCG vaccination according to sex and year of birth for 3,270 children vaccinated in November 1949*

Year of birth	Standard vaccine stored at 2-4° C.		Standard vaccine stored at 20° C.		4 times standard vaccine stored at 2-4° C.	
	M	F	M	F	M	F
42-41	15.85	14.98	14.66	14.31	17.23	16.59
40-39	15.72	14.56	13.77	13.70	16.12	16.24
38-37	15.70	14.30	14.18	12.84	16.86	15.84
36-35	15.87	14.22	13.79	12.00	16.30	15.18

Children selected for vaccination in this study were those whose prevaccination tuberculin reaction was less than 6 millimeters of induration to the Mantoux 10 T. U. test. This criterion is generally considered adequate to eliminate all of those previously infected. It is possible, however, that the requirement for a negative reaction was not sufficient and that there might be some previously infected children among those vaccinated. If this occurred with greater frequency among children of the same family, it could cause an agreement in their postvaccination reactions.

It is obvious, however, that this possibility will be of little quantitative importance in the present material, since the prevalence of reactors to Mantoux 10 T. U. is only 7 percent. The number of naturally infected individuals developing allergy too weak to produce a reaction of 6 millimeters of induration to 10 T. U. usually constitutes only a very small fraction of all the infected individuals and it is evident that this number will be insignificant as compared to the number of noninfected children. Furthermore, in order to effect an agreement in postvaccination reactions, the few children infected without developing a conspicuous allergy would have to belong to the same families.

In addition, if this were true, agreement between pre- and post-vaccination reactions should be expected. As shown in table 4, however, practically no correlation is obtained when the families are distributed according to their average

reactions to Mantoux 10 T. U. before and after vaccination (the postvaccination reactions being expressed as the deviations from the mean value of the corresponding vaccination group). A similar result, table 5, is obtained when prevaccination sensitivity is based on reactions to the Mantoux 100 T. U. test. In both cases there is a slight increase in the average size of postvaccination reactions for the families having the highest levels of prevaccination sensitivity but the number of families having these levels is too small to affect significantly the agreement between siblings. Although the details are not shown here, the correlation between prevaccination and postvaccination reactions with the person (not the family) as the unit gives corresponding results.

Table 4. *Distribution of 738 families by mean size of induration in mm. of Mantoux 10 T. U. reactions before and 10 weeks after BCG vaccination (induration of postvaccination reaction expressed as deviation from group mean)*

Postvaccination	Prevaccination					
	4.5	3.5	2.5	1.5	0.5	Total
−6.5		1			1	2
−5.5				6	3	9
−4.5			2	11	5	18
−3.5		1	6	9	25	41
−2.5		6	10	27	27	70
−1.5	2	3	20	49	45	119
−0.5		5	16	36	44	101
+0.5	4	10	21	45	49	129
+1.5		3	13	30	41	87
+2.5	1	2	16	16	39	74
+3.5	1	5	6	11	20	43
+4.5		1	3	7	12	23
+5.5			2	5	3	10
+6.5		1		4	2	7
+7.5		1		1	1	3
+8.5		1		1		2
Total	8	40	115	258	317	738
Mean of arrays	+0.62	+0.68	+0.20	−0.10	+0.17	+0.11

Table 5. *Distribution of 714 families by mean size of induration in mm. of Mantoux 100 T. U. reactions before and Mantoux 10 T. U. reactions 10 weeks after BCG vaccination (induration of postvaccination reaction expressed as deviation from group mean)*

Postvaccination	Prevaccination									
	8.5+	7.5	6.5	5.5	4.5	3.5	2.5	1.5	0.5	Total
−6.5									2	2
−5.5							2	4	3	9
−4.5							5	3	10	18
−3.5	1					3	4	8	25	41
−2.5		2				3	7	16	38	66
−1.5	1		2		2	10	14	44	45	118
−0.5	1			2	3	9	15	32	36	98
+0.5	2	1		5	6	9	12	29	58	122
+1.5			2		3	3	15	19	39	81
+2.5	1		3	1	1	6	13	16	31	72
+3.5	1		2	1	2	2	6	14	14	42
+4.5				1		2	4	5	11	23
+5.5					1		3	6		10
+6.5				1				2	4	7
+7.5								2	1	3
+8.5								1	1	2
Total	7	3	9	11	18	47	100	201	318	714
Mean of arrays	+0.21	−1.5	+1.61	+1.68	+1.00	+0.05	+0.23	+0.19	−0.12	+0.11

From the above review it seems justifiable to exclude similarity in sex, age, and prevaccination tuberculin sensitivity as significant factors responsible for the agreement among siblings (differences among families) in postvaccination tuberculin reactions.

Determination of the Variance Within Pairs of Twins

Sixty-one pairs of twins, each consisting either of two males or two females, were BCG-vaccinated and retested after 10 weeks; 18 pairs were part of the sibling material already described, while 43 pairs were included in subsequent series of similar vaccine studies (*4*). In these latter projects children from the same family, or twins from the same pair, in some cases belonged to different groups which were given quite different BCG vaccines. In order to eliminate differences resulting from the use of different vaccines, each postvaccination reaction has been computed as a deviation from the mean value of the corresponding vaccination group.

Table 6 shows the correlation between reactions for the 61 pairs of twins. The variance within the pairs, calculated according to the formula given above, is:

$$s_T^2 = 5.8$$

This estimate of variance, being based on a small number of observations, has a relatively large standard error of approximately 1.0.

Table 6. *61 pairs of twins distributed by size of induration in mm. of both members to Mantoux 10 T. U. reactions 10 weeks after BCG vaccination (induration of each reaction expressed as deviation from the mean of corresponding vaccination group)*

Reaction in second twin	Reaction in first twin															Total
	−9.5	−8.5	−3.5	−2.5	−1.5	−0.5	+0.5	+1.5	+2.5	+3.5	+4.5	+5.5	+6.5	+7.5	+8.5	
+7.5													1			1
+6.5								1								1
+5.5									1							1
+4.5				1		2	1				2		1			7
+3.5										1		1				2
+2.5					1	2	2	1							1	7
+1.5			2	1		1			2	1		1	1			9
+0.5						2	1	1	2			1				7
−0.5				1	1	1		1	1							5
−1.5				1	2	3	1	1			2					10
−2.5		1		1			2	1	1							6
−3.5							1				1					2
−4.5							1									1
−5.5			1													1
−10.5	1															1
Total	1	1	3	5	4	11	9	6	7	2	5	3	3		1	61

Determination of the Variance of Tuberculin Tests Performed on the Same Person

Since the variance between the reactions of twins is used as an estimate of the experimental error of the combined procedure of vaccinating and tuberculin testing, and since that variance cannot be considered as quantitatively well established, it has seemed worthwhile to include here some additional information on the experimental error of the more limited procedure of simply giving and reading a tuberculin test. During the past year, we have collected data on the results of duplicate tuberculin tests carried out with great care on several thousand persons. The material consists partly of BCG-vaccinated persons, partly of non-

vaccinated persons. Some groups were tested with Mantoux 5 T. U., others with 10 T. U. The personnel of the present study gave and read the tests.

The detailed results of these studies are to be published elsewhere, but it may be reported here that the variance of the experimental error of tuberculin testing is approximately 4.0, or a little less, without a distinct relationship to the level of tuberculin sensitivity, to the dose of tuberculin (5 or 10 T. U.), or to whether the allergy is from a natural or BCG infection. This finding is useful in evaluating our estimate of the variance between twins.

When duplicate tuberculin tests are performed on the same person at the same time, differences in the results can be attributed primarily to two sources; first, variations involved in the injection of the tuberculin into the skin, and second, variations arising from the process of reading (measuring) the reaction. When children are vaccinated, and later given a tuberculin test, differences in post-vaccination reactions can be attributed to three principal technical errors, the two that affect the tuberculin test plus the error of giving the vaccine. According to our studies, the variance of the errors of giving and reading tuberculin tests, at least in our material, is quite well established by a value of approximately 4.0 or a little less. To this value something must be added to obtain the variance of the combined procedure of tuberculin testing plus vaccinating. From observations on twins we find that the variance increases from about 4.0 to 5.8. Obviously, this probably over-estimates the total experimental error, since only a part of the group of twins can be considered monozygotic and a part of their variance may be due to environmental differences. Nevertheless, taking all of the available evidence into account, it would seem that the estimate of 5.8 as the variance of experimental error of vaccinating and tuberculin testing probably represents a reasonably satisfactory upper limit for our material.

Summary of the Components of Total Variance of Postvaccination Reactions

The above analyses represent an attempt to determine the principal components of the total variance in the size of induration of postvaccination tuberculin reactions. Of basic importance is the simple subdivision of the variance into two parts: first, variation due to random errors of observation and second, variation due to the operation of biological factors. Unfortunately, the separation of these two main components of total variance is probably less well established than are other subdivisions of the variance. However, using the variance, $s_T^2=5.8$, as the estimate of observational error, the variance due to biological factors may be estimated as:

$$\bar{S}^2-s_T^2=11.2-5.8=5.4$$

where S^2 is the previously estimated variance among all the children. In general terms, this indicates that of the total variance of postvaccination allergy about one-half is due to experimental error and one-half to biological influences.

With respect to biological factors, variance due to differences among families can be considered well established from the observations on the vaccination of children in over 700 families. Thus,

$$\bar{S}^2-\bar{s}_s^2=11.2-8.9=2.3$$

which permits the conclusion that somewhat less than half of the total biological variance is contributed by differences between families and somewhat more than half to differences between siblings in the same family.

The following tabulation summarizes the subdivision of the total variance:

Source of variance	Variance	Percent of total variance
Experimental error		
Total	5.8	51.8
Due to tuberculin testing	4.0	35.7
Due to vaccinating	1.8	16.1
Biological variation		
Total	5.4	48.2
Within families	3.1	27.7
Between families	2.3	20.5
Total	11.2	100.0

Agreement Within Families in Type of Induration of Postvaccination Reactions

In addition to the measurement of the diameter of induration, postvaccination reactions were classified into 4 types according to density of the induration: Type I represents the most dense, types II and III intermediate categories, and type IV the soft, indefinite kind of induration. To a considerable extent, density of induration is independent of diameter and it seemed worth while to determine whether children in the same family tend to resemble each other with respect to the character of induration of their reactions. In this connection, as indicated in table 7, it is important to note that sex, age, and vaccine sample have considerable influence on the type of postvaccination induration.

TABLE 7. *Percentage frequency of type I induration of Mantoux 10 T. U. reactions 10 weeks after BCG vaccination according to sex and year of birth for 3,270 children vaccinated in November 1949*

Year of birth	Standard vaccine stored at 2-4°C		Standard vaccine stored at 20°C		4 times standard vaccine stored at 2-4°C	
	M	F	M	F	M	F
42-41	54.4	60.5	36.1	46.5	70.7	74.2
40-39	47.7	55.1	27.9	30.4	54.9	68.2
38-37	46.5	46.8	26.0	23.7	58.5	62.8
36-35	45.1	39.1	9.8	12.9	43.6	51.4

In order to investigate whether siblings show agreement with respect to type of reaction, an index case has been chosen in each family, and the families have been divided into four classes in accordance with type of reaction (I to IV) of the index case. Thereafter the remaining siblings in each class have been distributed according to their type of reaction.

It is essential that the choice of index case be independent of type of reaction and that the sex and age distribution of siblings of the index cases be approximately uniform in all four classes. In order to attain these conditions the child whose date of birth was closest to July 1, 1939, (the mean age for all the children) was chosen as the index case in each family. The sex and age distribution of their siblings, separately for classes I, II, and III, are shown in tables 8 and 9; in class IV the number of children is too small to reproduce the distribution. It will be seen that the distributions are very similar in classes I and II; in class III, however, the frequency in the highest age group is a little lower than in I and II.

Table 8. *Percentage distribution by sex of siblings to index cases of types I–III*

Index case type I		Index case type II		Index case type III	
M	F	M	F	M	F
48.8	51.2	47.4	52.6	45.8	54.2

Table 9. *Percentage distribution by sex and year of birth of siblings to index cases of types I–III*

Year of birth	Index case type I		Index case type II		Index case type III	
	M	F	M	F	M	F
1942–41	33.8	33.5	32.2	29.9	29.6	29.7
1940–39	9.3	5.5	10.0	7.7	20.4	26.6
1938–37	27.1	20.3	27.1	22.6	40.7	37.5
1936–35	29.3	39.8	30.1	38.5	9.3	6.2
Other years	.5	.9	.6	1.3		
Total	100.0	100.0	100..0	100.0	100.0	100.0

Table 10 shows the 738 families distributed in four classes according to the type of reaction of the index case, and in each class the siblings are distributed according to their type of reaction. A comparison of the distributions in the four classes seems to indicate a familial resemblance; for example, the frequency of type I reactions in the siblings is higher in class I, in which the reaction of the index case is of type I, than in class II, in which the reaction of the index case is of type II. It is clear, however, that a simple comparison of the totals of the vaccination groups will involve some bias since the 35 vaccination groups are not equally represented in the four classes. For example, the children who have been given vaccine stored at 2–4° C. are most heavily represented in class I, whereas the classes II, III, and IV, successively, will comprise more children who have been given vaccine stored at 20° C.

Table 10. *Distribution of 738 families according to type of reaction of index case. Siblings of index case in each class distributed by their type of reaction*

Type of reaction of index case	Number of index cases	Total number of siblings of index cases	Number of siblings having specified type of reaction			
			I	II	III	IV
Type I	344	461	264	178	15	4
Type II	301	420	160	209	46	5
Type III	83	118	27	61	25	5
Type IV	10	14	1	5	7	1
Total	738	1,013	452	453	93	15

Since the usual way of eliminating the effect of the differing compositions of populations is unsatisfactory because of the small number of children in many of the vaccination groups, a slightly different method will be used to test the significance of differences in the frequency of a certain type of reaction in two classes. The procedure may be illustrated as follows: The number of siblings observed in the k^{th} vaccination group of classes I and II is indicated by m_k and

n_k, respectively. The numbers among these which are of type I are indicated by x_k and y_k. The observed frequencies of type I will then be

$$p_k=\frac{x_k}{m_k} \text{ and } q_k=\frac{y_k}{n_k}$$

The difference between the two corresponding observed frequencies p_k-q_k, will then have a standard deviation which will not in any case be greater than

$$\sigma_k=\frac{1}{2}\sqrt{\frac{1}{m_k}+\frac{1}{n_k}}$$

the sum:

$$U=\sum_{k=1}^{35}\frac{p_k-q_k}{s_k}$$

will have an approximately normal distribution with a standard deviation which will not, at any rate, be greater than $\sqrt{35}=5.91$. If there are no differences between the frequencies of classes I and II, U will have a mean value of 0.

A computation for the frequencies of type I in classes I and II results in

$$U=10.6$$

which is slightly less than twice the standard deviation.

A similar computation for the frequencies of type I in classes I and III yields:

$$U=16.3$$

which is about three times the standard deviation. In this case the latter is not more than $\sqrt{30}=5.47$ because no observations are available in five vaccination groups of class III.

This analysis, although less extensive than that dealing with the size of post-vaccination reactions, furnishes additional evidence of the existence of differences between families in the allergy produced by BCG vaccination.

Resistance to Streptomycin of Tubercle Bacilli Isolated From Patients Treated With Streptomycin

By SHIRLEY H. FEREBEE, A.B. and FREDERICK W. APPEL, Ph.D.*

The advent of chemotherapy in the treatment of tuberculosis has been accompanied by a tremendous amount of laboratory investigation centering around the phenomenon of drug resistance. Much has been written about the nature and mechanism of the effect on the pathogenic organism resulting from chemotherapy and equally great discussion concerns the implications of drug resistance for the clinical management of the tuberculous. The present paper deals with one aspect of these problems; it concerns the results of *in vitro* tests for streptomycin resistance of tubercle bacilli in cultures obtained from patients observed in cooperative studies sponsored by the Public Health Service. The clinical and laboratory investigations on the use of streptomycin in the treatment of tuberculosis were planned and coordinated by the Tuberculosis Study Section of the Division of Research Grants and Fellowships of the National Institutes of Health. Investigators from several sections of the country participated in the cooperative studies with the aid of grants from the Division of Research Grants and Fellowships. Preliminary results of the clinical investigation were reported in an earlier paper.[1]

The necessity for uniformity of observations in the laboratory, as well as the clinical phase of these studies, led the Tuberculosis Study Section to designate the facilities of three bacteriological investigators as central laboratories for the study of streptomycin resistance of tubercle bacilli. Each clinical investigator sent cultures obtained from patients in the pulmonary tuberculosis studies to one of the three central laboratories. Results of the resistance testing were sent by the laboratories to a central office for analysis and correlation, as well as to the clinical investigator responsible for the management of the patient. The laboratory investigators were: Dr. Emil Bogen, Olive View Sanatorium, Olive View, Calif.; William Steenken, Jr., The Trudeau Laboratory, Trudeau, N. Y.; and Dr. Guy P. Youmans, Northwestern University Medical School, Chicago, Ill.

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[1] Long, E. R. and Ferebee, Shirley H.: A controlled investigation of streptomycin treatment in pulmonary tuberculosis. Pub. Health Rep. 65: 1421 (1950).

Material and Methods

Sanatorium Laboratory Procedure

Resistance tests were sought for all patients receiving the prescribed 91-day regimen, 20 milligrams of streptomycin per day per kilogram of body weight, given in three equal doses. They were to be made on cultures from specimens taken the week before streptomycin treatment, during the 5th and 9th weeks of therapy, and during certain weeks after the discontinuance of streptomycin (the 14th, 27th, 40th, 53d, and 66th week from the beginning of therapy). The cooperating hospitals and sanatoria followed their usual techniques in the isolation and cultivation of tubercle bacilli, or the standard methods recommended by the National Tuberculosis Association. The cooperating clinical institutions used concentrated 24 hour sputum samples whenever possible, and gastric lavage specimens if sputum cultures were negative. Cultures, planted on whatever egg-yolk medium had proved satisfactory in past experience in the various tuberculosis hospitals, were sent to one of the central laboratories.

Central Laboratory Test Procedures and Interpretation

A standard procedure was established by the laboratory investigators for the uniform performance of the tests. From the primary cultures received by the sanatoria, subcultures were made in Dubos' liquid medium. When growth reached measurable density in the Dubos' cultures, the flasks were shaken vigorously to produce a uniform suspension for use as the source of inocula for the tests. For the resistance tests, a modified Herrold's egg-yolk agar medium was used.

In each test there were four cultures, one on a medium containing no streptomycin and three on media containing different concentrations of streptomycin. Initially, the concentrations were 1, 10, and 100 micrograms per milliliter of medium. Later a 3-microgram was substituted for the 1-microgram concentration. Tests were read at 14, 21, 28, and 35 days; the amount of growth in each culture tube was estimated on a 1+ to 4+ scale.

The level of bacterial sensitivity has been defined, for present purposes, as the highest concentration of streptomycin (mcg./ml.) in which significant growth appeared within 1 week of the date on which maximum growth had been achieved in the control tube. In general, growth in the control tube was rapid, usually reaching a maximum by the 21st day. In the present analysis, only three levels of sensitivity are distinguished: strongly resistant as evidenced by growth in the 100-microgram culture, moderately resistant as shown by growth in the 10-microgram culture, and sensitive.

Occasionally tests had to be repeated, especially those which failed to show rapid and abundant growth in the control culture, those exhibiting the same amount of growth in two or more concentrations, and those in which contamination or free moisture interfered with evaluation.

The time interval between receipt of a culture and performance of the sensitivity testing in the central laboratory was not uniform. The nature or extent of changes occurring during this interval is not known but the test results may have been influenced by this factor.

Selection of Tests for Analysis

According to the plan of the study, there should have been a complete series of seven sensitivity tests for each patient who received the scheduled dose of streptomycin (per kilo of body weight) for 91 days including the entire group of 270 patients treated in the pulmonary control study and 21 patients on this regimen in the pulmonary comparative regimens study. However, the combination of a variety of human, bacteriological, and mechanical factors resulted in the loss of a considerable number of the expected cultures. A large number of patients who left the hospital during the year's observation were lost to effective bacteriological observation at the proper intervals. Failure in some instances of the hospital laboratories to furnish properly prepared and uncontaminated cultures resulted in the loss of still others. In one instance, for example, the mechanical failure of a deep freeze unit resulted in the loss of a considerable number of cultures.

In addition, the precision and interpretation of the test itself was not nearly so clear-cut as had been assumed by those not working directly with the test but concerned only with its application in clinical management; equivocal and even contradictory test results were not infrequently obtained. Since the first tests included in this study were made in the fall of 1947, many refinements in technique have been introduced.

Test results from the Trudeau Laboratory and from the Northwestern University Laboratory have been combined for this presentation because of the close agreement obtained when identical cultures were tested in different laboratories. Since the results from Olive View Laboratory were somewhat different, it appeared that a different system of interpretation would be required for them. For the preparation of special cultures used for the equivalence tests, acknowledgment is made to Frank G. Petrik, bacteriologist at the Homer Folks Tuberculosis Hospital, Oneonta, N. Y. Mr. Petrik prepared a series of identical cultures which were sent to the three participating laboratories for sensitivity testing. The series, in which cultures were identified only by number, contained some duplicates, and this gave

some measure of the reproducibility of results within each laboratory as well as the agreement between laboratories.

Although the program produced a large number of sensitivity tests, the yield was disappointingly small in terms of the number of patients for whom a relatively complete series of tests was obtained. Of a total of 291 patients under study, sufficient data was secured for this analysis on only 157, or 54 percent. In other words, many of the tests were isolated observations with very few earlier or later results available for the same patient.

It is obviously necessary that all observation periods include cultures from the same patients. Otherwise, the inclusion of isolated tests would give a different patient population at each point of observation and it would be impossible to make sure that these shifting populations were comparable with respect to factors which may effect the emergence of resistance to streptomycin.

It should be mentioned that 18 patients were excluded from the analysis because cultures taken before the beginning of the study showed resistance to streptomycin. Inquiry into the previous management of these cases revealed that 5 had received streptomycin prior to this study, but for the remaining 13 no evidence of previous streptomycin therapy could be found.

In this report the analysis has been restricted to results from cultures of 157 patients represented at almost every scheduled observation period. The group includes some patients for whom estimates for equivocal or missing test results could be made with reasonable certainty on the basis of a level of sensitivity clearly indicated by tests given before and after the missing one in the series. In order to utilize as many off-schedule tests as possible, each "due" week prescribed in the protocol has been treated as the median of a class interval, containing approximately as many early tests as late ones. In the appendix table, the individual test results are listed for the 157 patients included in the analysis.

Results

The significance of bacterial resistance to streptomycin has, in much of the literature, been considered in relation only to the population which continues to be bacteriologically positive. However, the importance of the resistance phenomenon depends not only on the frequency with which resistance develops in the positive cultures but also on how frequently cultures continue, in spite of drug therapy, to be positive. Let us suppose, for example, treatment with a new antibiotic produced resistant organisms in all positive cultures in patients treated more than 2 weeks, but that by the end of 2 weeks only 5 percent of the cultures were positive. Then, the occurrence

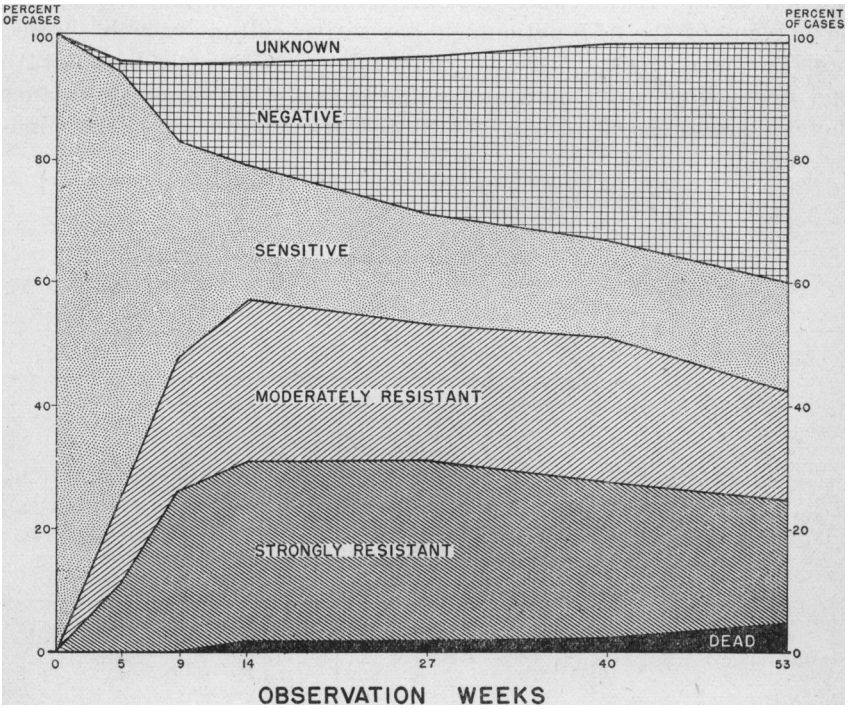
of resistance in all of the positive cultures might be of minor significance in evaluating the usefulness of a drug which could result in negative bacillary status for 95 percent of the patients treated.

Although this example is extreme, it illustrates how an erroneous interpretation may arise from a consideration of only the patients with positive cultures and explains the emphasis given in this report to a consideration of the entire distribution of the group at each observation period.

The bacteriological course for the 157 patients during the 53 weeks of observation is shown in table 1 and the chart. At the beginning of the study, the entire group had positive cultures sensitive to streptomycin. The number of cultures in which the presence of tubercle bacilli was not detected at subsequent points increased gradually throughout the period of observation until, by the end of the year, 40 percent had negative cultures. This is the group which, with respect to isolation of tubercle bacilli, reflects the most favorable action of the drug.

Seven, or 5 percent, of the 157 patients had died by the 53d week, representing the least favorable response to streptomycin therapy.

With the movement of patients during the year into these two ex-



Percent distribution of 157 patients by bacteriological status and streptomycin resistance status at specific periods of observation.

treme categories, the proportion of patients with positive cultures decreased steadily during the year from 100 percent at pretreatment to 55 percent in the 53d week. It is the cultures in this group which may be subdivided into resistant and sensitive categories at succeeding periods in time. But the dynamics of the emergence of resistant organisms involves the interchange between the sensitive and resistance groups, and the movement into the nonpositive categories, the negative, and the dead. The changing proportions with time give only the most elementary one-dimensional view of a problem which involves simultaneous movement in several directions.

Moderate resistance, that is, growth of the tubercle bacilli in the 10 microgram tubes of streptomycin-containing media, was, of course, absent in cultures of this series of patients at pretreatment, but by the 5th week of sensitivity testing, 15 percent of the 157 patients had positive cultures with moderately resistant organisms. Thereafter, the change was gradual over the remainder of the year, with a high of 26 percent at 14 weeks and a very gradual decrease to 18 percent at 53 weeks. Strong resistance had appeared in the positive cultures of 11 percent of the patients by the 5th week, with a continued rise to a high of 29 percent in the 14th week and a gradual decrease to 20 percent by the 53d week. If the two levels of resistance are considered together, 26 percent of the 157 patients had positive cultures which showed resistant bacilli by the 5th week, increasing to 55 percent by the 14th and decreasing to 38 percent by the end of the year. Resistance increased most sharply during the 13 weeks of drug therapy. Examina-

Table 1. *Distribution of 157 patients by bacteriological status and streptomycin resistance status at specified periods of observation*

Status	Observation week from beginning of therapy						
	Pretreatment	5	9	14	27	40	53
	Number						
Total	157	157	157	157	157	157	157
Negative culture	0	4	19	26	40	50	62
Positive culture	157	146	129	121	109	100	86
Sensitive	157	106	56	34	31	25	26
Moderately resistant	0	23	34	41	33	36	28
Strongly resistant	0	17	39	46	45	39	32
Patient dead	0	0	1	2	3	4	7
Unknown	0	7	8	8	5	3	2
	Percent						
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Negative culture	0	2.5	12.1	16.5	25.5	31.9	39.5
Positive culture	100.0	93.0	82.2	77.1	69.4	63.7	54.7
Sensitive	100.0	67.5	35.7	21.7	19.7	15.9	16.5
Moderately resistant	0	14.7	21.7	26.1	21.0	22.9	17.8
Strongly resistant	0	10.8	24.8	29.3	28.7	24.9	20.4
Patient dead	0	0	.6	1.3	1.9	2.5	4.5
Unknown	0	4.5	5.1	5.1	3.2	1.9	1.3

tion of the appendix table discloses only seven cases in whose cultures resistance initially appeared later than the 14th week: for five of the seven in the 27th week, and for two at 40 weeks. The material, it is true, is not large and chance fluctuation in the downward trend is obviously great but the decrease between the 14th and 53d week is not likely to be fortuitous since it occurs in both sub-groups, the moderately and strongly resistant. This must not, however, be interpreted as evidence of a reversion to streptomycin sensitive status since from the 14th week to the end of the year both categories of positive cultures, the sensitive and the resistant, decrease in size as the negative group increases. The trend of the group of patients with positive cultures sensitive to streptomycin declines sharply from 100 percent at pretreatment to 22 percent by 14 weeks and then gradually to 17 percent by the 53d week.

The question of the permanence of resistance to streptomycin cannot be determined by comparing the proportions of the group sensitive or resistant at different points in time, or even indeed by considering the entire spectrum of possible bacteriological change as shown in table 1. Such a tabulation does not show the amount or direction of movement of individuals between categories. Additional information about the bacteriological pattern of change is given in table 2, in which the status of the 157 patients at the end of the year has been correlated with the course of sensitivity of their cultures during the year. The table shows that resistance never developed in the cultures of 52 or roughly one-third of the 157 patients under study. In cultures of the remaining 106, resistance was reported at some time during the year's observation, and was maintained in the cultures of 87 of the 105 patients. Thus, in general, cultures which developed resistance did not become sensitive again within the 53-week period.

Perhaps the most significant information regarding resistance may be derived from an examination of the changes which occurred during the remainder of the year among patients classified according to their

Table 2. *Distribution of cultures of 157 patients classified by bacteriological status and streptomycin resistance status at 53 weeks, and by resistance status during previous year*

Status at 53d week	Status during year				
	Total	Never resistant	Resistance developed		
			And maintained	And lost	Variable
Total	157	52	87	12	6
Negative culture	62	34	27	1	0
Positive culture:					
Sensitive	26	16	0	10	0
Moderately resistant	28	0	25	0	3
Strongly resistant	32	0	30	0	2
Patient dead	7	2	3	1	1
Unknown	2	0	2	0	0

bacteriological status at 14 weeks. Fourteen weeks mark the end of the period of streptomycin therapy, and it is generally agreed, and also shown here, that resistance rarely develops after discontinuance of the drug. After that time, as shown in table 3, for the 27th, 40th, and 53d weeks, there is some irregular interchange of patients from one classification to another. The largest and most consistent change, however, is a progressive increase in the proportion of patients who became bacteriologically negative. Table 4 summarizes the data in this respect and shows that the rate of becoming negative after discontinuance of the drug is apparently rather remarkably influenced by the degree of sensitivity of the tubercle bacilli to streptomycin at 14 weeks. By the 53d week of observation, 38 percent of the patients with sensitive organisms, 36 percent of those with moderately resistant organisms, and only 15 percent of those with strongly resistant organisms had become bacteriologically negative. Further, although the number of cases in each category is not large, the stability of the trend in the change to negative status suggests that the differences, at least between the sensitive and strongly resistant, are not fortuitous. The development of streptomycin resistant organisms, particularly the highly resistant, may appear to prejudice the patient's chances of ceasing to produce positive cultures. However, the cause and effect relationship is not at all clear. It may well be that resistant organisms are found because the individuals do not respond well initially to therapy and, therefore, continue to excrete tubercle bacilli. The nature of relationship between sensitivity and subsequent ability to convert warrants further investigation directed specifically at this point.

Summary

Streptomycin resistance tests were made on cultures of tubercle bacilli isolated at intervals during a period of one year from 157 patients who had been treated with streptomycin for 91 days. The results show that:

(1) At the end of 53 weeks tubercle bacilli could not be cultured from the sputa of 40 percent of the patients; tubercle bacilli could be isolated, however, at this time from the sputa of 55 percent of patients. The remaining 5 percent of the patients were dead.

(2) Approximately two-thirds of the patients still excreting tubercle bacilli in their sputa at the end of 53 weeks harbored tubercle bacilli which were moderately or strongly resistant to streptomycin. The other one third were excreting tubercle bacilli which were sensitive to streptomycin.

(3) Once tubercle bacilli in a patient become resistant to streptomycin this resistance tends to persist after the cessation of treatment, although reversion to streptomycin sensitivity was observed in cultures isolated from approximately 18 percent of the patients.

Table 3. *Distribution at succeeding observation points of the status of 157 patients classified by their bacteriological status at 14 weeks from the beginning of streptomycin therapy*

Status	14-week status						
	Total	Negative	Positive culture			Dead	Unknown
			Sensitive	Moderately resistant	Strongly resistant		
Number	157	26	34	41	46	2	8
At 27 weeks:							
Negative culture	40	17	8	8	2	0	5
Positive culture:							
Sensitive	31	4	22	2	2	0	1
Moderately resistant	33	2	2	27	2	0	0
Strongly resistant	45	1	1	4	38	0	1
Patient dead	3	0	0	0	1	2	0
Unknown	5	2	1	0	1	0	1
At 40 weeks:							
Negative culture	50	22	10	8	5	0	5
Positive culture:							
Sensitive	25	2	17	1	4	0	1
Moderately resistant	36	2	4	27	3	0	0
Strongly resistant	39	0	3	4	32	0	0
Patient dead	4	0	0	0	1	2	1
Unknown	3	0	0	1	1	0	1
At 53 weeks:							
Negative culture	62	21	13	15	7	0	6
Positive culture:							
Sensitive	26	3	15	3	4	0	1
Moderately resistant	28	2	3	19	4	0	0
Strongly resistant	32	0	2	3	27	0	0
Patient dead	7	0	1	0	3	2	1
Unknown	2	0	0	1	1	0	0

Table 4. *Number and percent of negative cultures at 27, 40, and 53 weeks, from patients with positive cultures at 14 weeks, classified by streptomycin resistance status at 14 weeks*

Streptomycin resistance status of cultures positive at 14 weeks	Number	Negative at 27 weeks		Negative at 40 weeks		Negative at 53 weeks	
		Number	Percent	Number	Percent	Number	Percent
Sensitive	34	8	23.5	10	29.4	13	38.2
Resistant:							
Moderately	41	8	19.5	8	19.5	15	36.6
Strongly	46	2	4.3	5	10.9	7	15.2

(4) In the majority of patients, the development of resistance of tubercle bacilli to streptomycin occurred during the period of administration of streptomycin.

(5) Out of 18 patients who could not be included in the program because their initial cultures of tubercle bacilli were found to be resistant to streptomycin, 5 had previously received streptomycin therapy whereas the remaining 13, insofar as could be determined, had not received streptomycin therapy.

(6) The development of streptomycin resistant organisms, particularly the highly resistant, may appear to prejudice the patient's chances of ceasing to produce positive cultures. However, the cause

and effect relationship is not at all clear. It may well be that resistant organisms are found because the individuals do not respond well initially to therapy and, therefore, continue to excrete tubercle bacilli. The nature of relationship between sensitivity and subsequent ability to convert warrants further investigation.

APPENDIX

Highest concentration of streptomycin (mcg./ml.) in which significant growth appeared in positive cultures obtained from 157 patients during 53 weeks of observation

Case No.	Observation week						
	Pretreatment	5	9	14	27	40	53
1	1	*3	10	10	10	*10	*10
2	*1	1	100	100	100	Neg.	3
3	1	1	1	1	*1	*1	3
4	1	100	*100	100	100	100	100
5	1	100	*100	100	*100	100	100
6	1	10	100	100	1	100	100
7	1	1	100	*10	10	*10	10
8	*3	100	100	100	100	100	100
9	*1	1	100	100	100	100	100
10	1	1	10	1	1	100	100
11	1	N. A.	100	100	Neg.	10	0
12	1	10	100	100	100	100	*100
13	1	100	100	100	100	100	100
14	*3	10	100	100	100	100	100
15	1	1	100	100	100	1	10
16	1	100	100	100	100	100	100
17	1	*100	100	100	100	100	3
18	1	100	100	100	100	100	100
19	1	100	100	100	100	100	100
20	1	1	1	*1	*1	*1	0
21	1	1	100	100	100	*100	100
22	0	10	10	10	10	10	10
23	1	10	100	100	100	100	100
24	1	10	*10	10	10	*10	10
25	1	1	10	10	10	10	10
26	*1	1	1	*10	10	10	10
27	1	1	10	10	10	10	10
28	1	1	10	10	10	3	3
29	1	1	10	10	10	10	10
30	1	100	100	10	10	*10	10
31	3	1	3	3	10	*100	100
32	1	10	10	10	10	10	10
33	1	10	10	10	10	*10	10
34	1	1	1	10	10	10	10
35	1	100	100	100	100	100	100
36	1	1	100	100	100	100	100
37	*1	*1	1	100	100	100	100
38	1	N. A.	N. A.	100	*100	100	100
39	1	10	100	100	100	100	100
40	1	*1	Neg.	Neg.	*1	1	1
41	*1	1	*1	1	*1	1	1
42	1	100	100	100	100	100	10
43	*1	1	10	10	10	10	10
44	1	100	1	3	N. A.	10	10
45	*1	1	100	100	*100	100	100
46	3	3	10	10	10	10	10
47	1	10	10	10	10	10	10
48	1	*1	*1	1	*1	1	3
49	1	Neg.	Neg.	Neg.	Neg.	Neg.	3
50	1	1	1	1	*3	3	10
51	1	1	1	10	10	*10	*100
52	1	1	1	100	3	3	*3
53	1	1	1	*100	100	*10	10
54	1	1	*10	10	10	10	3
55	1	Neg.	10	3	3	3	3
56	1	10	Neg.	*10	*10	*10	10
57	1	1	*1	3	3	3	3
58	*3	10	10	10	10	*10	100
59	1	N. A.	N. A.	Neg.	Neg.	10	10
60	1	1	1	100	100	*100	100
61	*1	1	1	*1	3	3	3
62	1	1	1	1	*1	10	0

See footnote at end of table.

Highest concentration of streptomycin (mcg./ml.) in which significant growth appeared in positive cultures obtained from 157 patients during 53 weeks of observation—Cont.

Case no.	Observation week						
	Pretreatment	5	9	14	27	40	53
63	1	1	100	100	*100	*100	100
64	1	100	100	100	100	100	100
65	1	*1	1	0	Neg.	Neg.	3
66	1	10	3	10	3	10	*3
67	1	0	100	100	100	100	100
68	1	1	1	1	Neg.	10	*10
69	1	1	*10	10	10	10	Neg.
70	1	*1	1	*1	0	3	*3
71	1	1	100	100	10	0	Dead
72	1	1	10	10	*10	10	Neg.
73	*1	1	*1	1	*1	1	*1
74	0	1	N. A.	100	N. A.	1	Neg.
75	1	1	10	*10	100	100	Neg.
76	1	10	10	10	10	10	*10
77	1	10	10	1	1	100	Dead
78	1	1	100	100	100	100	Dead
79	1	1	1	*1	*1	3	*3
80	1	10	100	*100	100	10	Neg.
81	1	100	100	Neg.	Neg.	0	Neg.
82	*1	1	3	*3	1	3	*3
83	1	1	100	100	100	100	*100
84	1	10	*10	*10	100	100	Neg.
85	*1	*1	Neg.	1	Neg.	3	Neg.
86	1	*3	10	N. A.	3	3	*3
87	1	1	N. A.	10	10	10	Neg.
88	1	1	Neg.	10	3	10	*10
89	*3	100	100	100	100	100	*100
90	1	10	100	100	100	100	*100
91	1	0	0	Neg.	3	10	*10
92	1	Neg.	Neg.	10	Neg.	10	10
93	0	0	10	*10	100	100	100
94	0	0	10	10	100	100	Neg.
95	1	1	10	10	10	Neg.	Neg.
96	1	*1	*1	1	1	*1	*1
97	1	1	100	100	100	*100	Neg.
98	1	1	1	Neg.	100	Neg.	Neg.
99	1	1	*10	10	10	N. A.	N. A.
100	1	1	100	100	100	N. A.	N. A.
101	1	*10	100	100	100	*100	Neg.
102	1	1	1	N. A.	100	Dead	Dead
103	0	0	0	0	0	Neg.	Neg.
104	1	1	1	1	1	Neg.	Neg.
105	1	1	1	*1	10	*10	Neg.
106	1	1	1	1	1	Neg.	Neg.
107	1	1	1	1	100	Neg.	Neg.
108	*1	1	Neg.	Neg.	3	Neg.	*3
109	1	*1	*1	3	3	3	Neg.
110	1	1	1	100	100	Neg.	Neg.
111	1	Neg.	Neg.	Neg.	10	Neg.	Neg.
112	3	100	100	100	100	100	100
113	1	*10	Neg.	Neg.	10	Neg.	Neg.
114	0	3	3	Neg.	3	Neg.	Neg.
115	*3	3	10	100	10	Neg.	*10
116	1	1	1	10	Neg.	Neg.	Neg.
117	*1	1	1	1	*1	*1	*1
118	1	1	*1	1	*1	*1	Neg.
119	1	1	*10	10	Neg.	Neg.	Neg.
120	*1	1	*10	100	*100	Neg.	Neg.
121	1	N. A.	10	*10	Neg.	Neg.	Neg.
122	0	*1	Neg.	1	Neg.	Neg.	Neg.
123	1	10	*10	100	Dead	Dead	Dead
124	0	3	3	3	Neg.	Neg.	*Neg.
125	1	N. A.	N. A.	10	Neg.	Neg.	Neg.
126	1	1	1	1	Neg.	Neg.	Neg.
127	1	1	10	10	Neg.	*10	Neg.
128	1	100	*100	100	Neg.	Neg.	Neg.
129	1	1	1	1	Neg.	Neg.	Neg.
130	1	N. A.	Neg.	10	*10	Neg.	Neg.
131	3	3	*3	3	Neg.	Neg.	Neg.
132	1	*1	0	N. A.	N. A.	Neg.	Neg.
133	1	*1	1	N. A.	Neg.	*Neg.	Neg.
134	1	10	10	*10	Neg.	Neg.	Neg.
135	1	1	3	N. A.	Neg.	Neg.	Neg.
136	1	1	1	Neg.	Neg.	*Neg.	*Neg.
137	1	1	1	N. A.	Neg.	N. A.	Neg.
138	1	*1	1	Neg.	Neg.	Neg.	Neg.

See footnote at end of table.

Highest concentration of streptomycin (meg./ml.) in which significant growth appeared in positive cultures obtained from 157 patients during 53 weeks of observation—Cont.

Case no.	Observation week						
	Pretreatment	5	9	14	27	40	53
139	1	1	1	Neg.	Neg.	Neg.	Neg.
140	1	*1	1	N. A.	Neg.	Neg.	*Neg.
141	*1	1	1	Neg.	Neg.	Neg.	Neg.
142	1	1	1	Dead	Dead	Dead	Dead
143	1	1	1	Neg.	Neg.	Neg.	Neg.
144	1	1	1	N. A.	Neg.	Neg.	*Neg.
145	*0	*0	0	Neg.	Neg.	Neg.	Neg.
146	*1	1	Neg.	Neg.	Neg.	Neg.	Neg.
147	1	10	Neg.	*10	Neg.	Neg.	Neg.
148	1	1	Dead	Dead	Dead	Dead	Dead
149	*1	3	N. A.	Neg.	Neg.	Neg.	*Neg.
150	1	N. A.	Neg.	Neg.	Neg.	Neg.	Neg.
151	1	1	Neg.	Neg.	Neg.	*Neg.	*Neg.
152	1	1	Neg.	Neg.	N. A.	Neg.	Neg.
153	1	1	N. A.	Neg.	N. A.	Neg.	*Neg.
154	*1	1	N. A.	Neg.	Neg.	Neg.	*Neg.
155	1	1	Neg.	Neg.	Neg.	Neg.	Neg.
156	0	1	Neg.	Neg.	Neg.	Neg.	*Neg.
157	1	3	Neg.	Neg.	Neg.	Neg.	Neg.

* Estimated from conflicting test results or assumed from the unchanging trend in preceding and succeeding tests. N. A.—Not available.

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 February 10, 1951

Measles. The number of new cases of measles increased for the current week to 12,831 as compared with 11,030 for the previous week and the 5-year median of 10,756 cases. Data exclude Washington State for which no report was received.

Influenza. There are no indications of widespread prevalence of epidemic influenza in the United States at the present time. Localized epidemics of respiratory diseases are being reported, in some of which A-prime virus has been isolated, such as Gordo, Ala., and a few military establishments. Mortality reports of 106 major cities in the United States have shown no increase which would suggest the occurrence of the type of disease prevalent in England and characterized by a relatively high mortality in the older ages.

Reports of Epidemics

Respiratory Infections. D. H. Stevens, Maine Commissioner of Health and Welfare, has reported that an influenza-like illness caused the absence of about 200 pupils in the Waterville, Maine, schools. The type of infection has not been determined by laboratory examination.

Dr. W. L. Halverson, Director of the California Department of Public Health, has reported that mild respiratory infections are spreading to various sections of the State. School absences are reported to be 25 to 30 percent of enrollment with a high rate of infection in teachers.

NIH Influenza Information Center

The regional laboratory in the California Department of Public Health reports six cases of influenza diagnosed by hemagglutination-inhibition test. Five of these were A-prime, and the sixth, pending additional test, has been classified as indeterminate. These, like the three cases reported 2 weeks ago, have all been from the San Francisco Bay area.

The regional laboratory at Montgomery, Ala., reports that one of four throat washings collected from Gordo, Ala., January 23 yielded influenza A-prime virus.

The Naval Medical Research Unit No. 4, Great Lakes, Ill., reports

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the isolation of influenza virus tentatively identified as A-prime from four of eight throat washings from selected cases of influenza. The report states that a minor epidemic has been in progress during January but is now declining.

The Division of Preventive Medicine of the Office of the Surgeon General, Department of the Army, reports that at the Second Army Laboratory, of seven paired serum specimens obtained from Fort Knox, Ky., during January, one showed a rise in hemagglutination-inhibition titer for A, and two for A-prime influenza virus. The Sixth Army Laboratory has reported a rise in hemagglutination-inhibition titer for influenza B virus in paired sera obtained at Camp Cook, Calif., in January. During January, 42 paired samples were tested in this laboratory, and a total of 3, including 2 previously reported and 1 here reported, gave serologic evidence of influenza infection. For the week ended February 10, the Sixth Army Laboratory reported a rise in titer of a paired serum from Camp Cook to both A and A-prime influenza virus and a titer rise in two paired sera to A-prime. From the Oakland Army Base, one paired serum showed a rise in titer to virus A: from Mather Air Force Base, one showed a rise in titer to type A; from Travis, two paired sera showed an increase in titer to A-prime virus; and from Norton, one serum showed a rise in titer to B virus. No unusually large amount of respiratory disease has been reported in the military forces in the Sixth Army area.

Comparative Data for Cases of Specified Reportable Diseases: United States

[Numbers after diseases are International List numbers, 1948 revision]

Disease	Total for week ended—		5-year median 1946–50	Seasonal low week	Cumulative total since seasonal low week		5-year median 1945–46 through 1949–50	Cumulative total for calendar year—		5-year median 1946–50
	Feb. 10, 1951	Feb. 11, 1950			1950–51	1949–50		1951	1950	
Anthrax (062)	------	------	1	(1)	(1)	(1)	(1)	8	2	7
Diphtheria (055)	93	154	189	27th	[2] 3,484	5,324	7,753	[2] 577	1,053	1,395
Encephalitis, acute infectious (082)	10	17	8	(1)	(1)	(1)	(1)	56	67	45
Influenza (480–483)	3,354	3,171	3,171	30th	28,628	25,501	30,613	14,086	14,917	14,917
Measles (085)	12,831	6,564	11,260	35th	84,566	48,823	65,666	55,865	29,693	39,542
Meningitis, meningococcal (057.0)	101	94	94	37th	[3] 1,598	1,442	1,442	[3] 636	529	520
Pneumonia (490–493)	1,950	2,335	-------	(1)	(1)	(1)	(1)	10,211	13,678	-------
Poliomyelitis, acute (080)	104	117	48	11th	[2] 33,029	42,172	25,203	[2] 811	698	406
Rocky Mountain spotted fever (104)	------	------	------	(1)	(1)	(1)	(1)	2	6	3
Scarlet fever (050) [4]	2,342	1,871	2,646	32d	28,492	26,410	38,436	12,801	9,971	15,039
Smallpox (084)	------	3	4	35th	12	17	41	4	9	20
Tularemia (059)	9	23	23	(1)	(1)	(1)	(1)	93	145	145
Typhoid and paratyphoid fever (040,041) [5]	28	51	45	11th	[2] 3,151	3,641	3,657	[2] 236	268	253
Whooping cough (056)	1,446	2,881	1,921	39th	31,552	35,886	36,943	9,950	14,350	13,648

[1] Not computed. [2] Additions: Diphtheria—North Carolina, week ended Jan. 13, 1 case; poliomyelitis—Illinois, week ended Jan. 27, 1 case; paratyphoid fever—District of Columbia, week ended Jan. 27, 1 case and week ended Feb. 3, 2 cases. [3] Deduction: Meningitis—North Carolina, week ended Jan. 13, 1 case. [4] Including cases reported as streptococcal sore throat. [5] Including cases reported as salmonellosis.

NOTE.—Data exclude report from Washington State for week ended Feb. 10 for which no report was received.

Reported Cases of Selected Communicable Diseases: United States, Week Ended February 10, 1951

[Numbers under diseases are International List numbers 1948 revision]

Area	Diphtheria (055)	Encephalitis, infectious (082)	Influenza (480–483)	Measles (085)	Meningitis, meningococcal (057.0)	Pneumonia (490–493)	Poliomyelitis (080)
United States	**93**	**10**	**3,354**	**12,831**	**101**	**1,950**	**104**
New England	**2**		**70**	**643**	**8**	**62**	
Maine			67	7	2	14	
New Hampshire				6	1	1	
Vermont				147	1		
Massachusetts	2			357	1		
Rhode Island			1	3	1		
Connecticut			2	123	2	47	
Middle Atlantic	**10**	**2**	**8**	**1,704**	**18**	**242**	**11**
New York	3	1	[1] 5	529	6	107	9
New Jersey		1	3	324	3	78	1
Pennsylvania	7			851	9	57	1
East North Central	**6**	**6**	**46**	**2,990**	**13**	**170**	**3**
Ohio	4		2	1,100	7		
Indiana			20	235		15	2
Illinois		1	22	391	2	95	
Michigan	2	5	2	384	3	60	1
Wisconsin				880	1		
West North Central	**4**	**1**	**17**	**794**	**6**	**143**	**6**
Minnesota			2	100	1	28	1
Iowa				20	1	1	2
Missouri	3	1	2	319	3	1	1
North Dakota			13	50	1	102	
South Dakota				43		1	1
Nebraska							1
Kansas	1			262		10	
South Atlantic	**22**		**942**	**899**	**18**	**174**	**17**
Delaware				14	1		
Maryland	1			38	1	38	3
District of Columbia				43		16	1
Virginia	7		514	261	3	80	1
West Virginia	2		265	67		17	4
North Carolina	4			129	4		
South Carolina	2		97	5	1	7	
Georgia	6		66	290	4	16	3
Florida				52	4		5
East South Central	**14**		**728**	**224**	**12**	**68**	**7**
Kentucky	1		1	74	1	10	
Tennessee	1		43	17			1
Alabama	9		673	30	8		4
Mississippi	3		11	103	3	58	2
West South Central	**18**	**1**	**643**	**3,256**	**17**	**889**	**19**
Arkansas	2		480	222	1	51	
Louisiana		1	3	27	2	16	7
Oklahoma	3		160	413	3	84	4
Texas	13			2,594	11	738	8
Mountain	**9**		**711**	**1,298**	**4**	**113**	**6**
Montana	1		102	31	1		
Idaho				18			
Wyoming	1			97			1
Colorado	5		99	869	1	39	2
New Mexico			2	12		34	2
Arizona	2		508	208	2	40	1
Utah				63			
Nevada							
Pacific	**8**		**189**	**1,923**	**5**	**89**	**35**
Washington	[2]	[2]	[2]	[2]	[2]	[2]	[2]
Oregon	4		56	47		36	6
California	4		133	976	5	53	29
Alaska							
Hawaii			1		1		2

[1] New York City only.
[2] Report not received.

Reported Cases of Selected Communicable Diseases: United States, Week Ended February 10, 1951—Continued

[Numbers under diseases are International List numbers, 1948 revision]

Area	Rocky Mountain spotted fever (104)	Scarlet fever (050)	Smallpox (084)	Tularemia (059)	Typhoid and paratyphoid fever [1] (040, 041)	Whooping cough (056)	Rabies in animals
United States		**2,342**		**9**	**28**	**1,446**	**98**
New England		**252**		**2**	**1**	**181**	
Maine		10				44	
New Hampshire		16				4	
Vermont		16				12	
Massachusetts		173			1	67	
Rhode Island		5		2		24	
Connecticut		32				30	
Middle Atlantic		**419**			**5**	**237**	**10**
New York		[2] 225				108	9
New Jersey		53			2	57	
Pennsylvania		141			3	72	1
East North Central		**631**		**1**	**1**	**215**	**14**
Ohio		193			1	29	2
Indiana		42				36	10
Illinois		74				26	
Michigan		265		1		73	2
Wisconsin		57				51	
West North Central		**120**			**2**	**80**	**9**
Minnesota		15				9	1
Iowa		14				3	8
Missouri		35				10	
North Dakota		1				3	
South Dakota		5				4	
Nebraska		6			2	3	
Kansas		44				48	
South Atlantic		**223**		**4**	**3**	**166**	**10**
Delaware		7				1	
Maryland		21				10	
District of Columbia		10			1	8	
Virginia		49		1	1	51	4
West Virginia		5			1	23	
North Carolina		103				39	
South Carolina		6		1		5	3
Georgia		10		2		16	3
Florida		[2] 12				13	
East South Central		**79**		**1**	**4**	**68**	**22**
Kentucky		18			1	15	7
Tennessee		45			2	12	9
Alabama		12				33	5
Mississippi		4		1	1	8	1
West South Central		**150**			**8**	**348**	**33**
Arkansas		4			2	42	3
Louisiana		10			3	6	
Oklahoma		24				21	1
Texas		112			3	279	29
Mountain		**176**		**1**	**1**	**89**	
Montana		11				5	
Idaho		16				5	
Wyoming		1				2	
Colorado		17				7	
New Mexico		8				3	
Arizona		9			1	62	
Utah		[2] 114		1		5	
Nevada							
Pacific		**292**			**3**	**62**	
Washington	[3]	[3]	[3]	[3]	[3]	[3]	[3]
Oregon		68				19	
California		[2] 224			3	43	
Alaska						2	
Hawaii							

[1] Including cases reported as salmonellosis.
[2] Including cases reported as streptococcal sore throat.
[3] Report not received.

FOREIGN REPORTS

CANADA

Reported Cases of Certain Diseases—Week Ended January 20, 1951

Disease	Total	Newfoundland	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia
Brucellosis	2					2					
Chickenpox	1,486	2		18		315	605	80	135	109	222
Diphtheria	4					3			1		
Dysentery:											
Amebic	1							1			
Bacillary	8					3	1	1			3
German measles	237			25		26	107	1	18	27	33
Influenza	45			24			19	2			
Measles	2,505	12		13	2	376	1,925	132	5	12	28
Meningitis, meningococcal	5					2	1				2
Mumps	1,786			11	27	319	476	57	209	240	447
Poliomyelitis	1										1
Scarlet fever	420	3				111	65	15	14	140	72
Tuberculosis (all forms)	165			4	17	87	18	14		8	17
Typhoid and paratyphoid fever	9					3				2	4
Venereal diseases:											
Gonorrhea	326	8		15	7	66	55	29	14	38	94
Syphilis	108			12	5	30	23	4	22	2	10
Primary	10				1	2	3		3		1
Secondary	9					1	4	1		2	1
Other	89			12	4	27	16	3	19		8
Other forms	3	2									1
Whooping cough	322	1		1	1	99	138	15	7	12	48

NEW ZEALAND

Reported Cases of Certain Diseases and Deaths, by Month: October 1950–January 1951

Disease	October 1950		November 1950		December 1950		January 1951	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Brucellosis	10		2		4		8	
Diphtheria	6	1	9		8	1	7	
Dysentery:								
Amebic	8		10		4		9	
Bacillary	9		2		5		18	1
Encephalitis, infectious			1					
Erysipelas	17		13		5		6	
Food poisoning	32		3		5		31	
Hookworm					1			
Influenza	1	1	2	2				
Malaria			1				2	
Meningitis, meningococcal	6	1	10		2		9	2
Ophthalmia neonatorum			1					
Poliomyelitis	3		8		2		10	
Puerperal fever	3		5	1	4		4	
Scarlet fever	62		69		64		46	
Tetanus	6	1	5	1	4	2	4	
Tuberculosis (all forms)	203	37	176	45	162	37	146	40
Typhoid fever	6	2	13	1	7		7	

FINLAND

Reported Cases of Certain Diseases—December 1950

Disease	Cases	Disease	Cases
Diphtheria	95	Typhoid fever	10
Meningitis, meningococcal	5	Venereal diseases:	
Paratyphoid fever	32	Gonorrhea	439
Poliomyelitis	15	Syphilis	35
Scarlet fever	3,183		

REPORTS OF CHOLERA, PLAGUE, SMALLPOX, TYPHUS FEVER, AND YELLOW FEVER RECEIVED DURING THE CURRENT WEEK

The following reports include only items of unusual incidence or of special interest and the occurrence of these diseases, except yellow fever, in localities which had not recently reported cases. All reports of yellow fever are published currently. A table showing the accumulated figures for these diseases for the year to date is published in the PUBLIC HEALTH REPORTS for the last Friday in each month.

Cholera

Pakistan. During the week ended January 13, 1951, four cases of cholera were reported in Dacca. For the previous week there were three cases.

India (French). For the week ended January 6, 1951, nine cases (four deaths) of cholera were reported in Pondicherry.

Smallpox

Burma. During the week ended January 27, 1951, 18 cases of smallpox were reported in Kyaukpyu, compared with 7 and 3 cases for the weeks ended January 13 and 20, respectively.

India. During the week ended January 27, 1951, smallpox was reported in ports of India as follows: Calcutta 462 cases, Madras 67, Bombay 31, Tiruchirappalli 13, Mangalore 11, and Masulipatam 10.

Typhus Fever

Egypt. During the week ended January 13, 1951, four cases of typhus fever were reported in Egypt.

Yellow Fever

Brazil. The outbreak of jungle yellow fever in central Goiaz State is still continuing and seems to be spreading southward. For the period December 1 to January 20, 40 deaths were estimated out of a possible 200 cases.

Colombia. During January 1951, jungle yellow fever was reported in Colombia as follows: La Vega, North Santander Department, two cases; Vanegas, Moradales, and Campohermoso, Santander Department, one case each; and Montanita, Caqueta Commissary, one case.

Gold Coast. One suspected case of yellow fever was reported in Bawdua, Oda Area, on January 16, 1951.