Public Health Reports

Vol. 63 • DECEMBER 3, 1948 • *No. 49*

—Editorial—

Antigenic Sensitivity and Pulmonary Infiltrations of Obscure Origin

This issue carries a study by Drs. Lydia B. Edwards, Ira Lewis, and Carroll E. Palmer in which certain types of pulmonary infiltration are correlated closely with skin sensitivity to histoplasmin, and other types of infiltrates are correlated with sensitivity to tuberculin.

This study, suggesting a relationship between specific etiological pulmonary lesions seen and respective antigen sensitivities, is an outgrowth of 6 years of investigation on tuberculosis in nurses conducted by staff members of the Tuberculosis Control Division of the Public Health Service in cooperation with the National Tuberculosis Association. For some years the National Association has been interested in the development of a comprehensive investigation of the problem of minimal tuberculosis and the circumstances responsible for tuberculous infection and progression to advanced disease. The personnel, facilities and organization of the Public Health Service were well adapted for carrying out such an undertaking among a large number of nurses, and a nation-wide program of investigation in this group is now well under way. The initial stimulus, counsel and continued interest of the Committee on Medical Research of the National Tuberculosis Association, supplemented by specific financial support from the association, have enabled the Tuberculosis Control Division of the Service to conduct the study in a most effective manner.

Reports from various sources have shown that many persons with pulmonary scarring and calcified nodules, which a few years ago would have been interpreted as residues of healed primary tuberculous infection, fail to react to tuberculin, but do react to a comparable antigenic material derived from the micro-organism *Histoplasma capsulatum*. This coincidence suggests that the healed lesions might be end products of an old histoplasmic or related infection rather than of healed tuberculous infection, but the inference would not be justified without much further study. The investigation is now directed toward discovery of earlier pulmonary lesions of a progressive infiltrative character which may later proceed to scarring and calcifi-

cation. In the meantime, this exact and extensive investigation of antigenic sensitivity in relation to pulmonary infiltrations of obscure origin is of great value.

Among the thousands of nurses under study were many with X-ray evidence of old pulmonary infection. The size of the group and their wide geographic distribution made an analysis of the antigenic sensitivity of these nurses of unusual significance. As the study progressed and many correlations were made on the basis of the pulmonary findings present at the time of the initial X-ray examination, a noteworthy association became apparent between a nodular type of infiltration, which tended to be widely distributed throughout the lungs, and reactivity to histoplasmin. An equally striking association of a poorly circumscribed type of infiltration, tending to be somewhat restricted to the apical portions of the lung, with sensitivity to tuberculin was found. Further evidence indicated that the nodular lesions were more prone than the poorly circumscribed to calcify.

However, caution should be observed in the interpretation of the evidence presented. It is corroborative but not final. Nevertheless, it represents an important step in elucidating the difficult diagnostic problem posed by frequent finding of certain types of pulmonary lesions, once universally accepted as tuberculous, in persons not reactive to tuberculin. Further study will show whether the lesions encountered in the reactors are actually lesions of histoplasmosis.

A valuable contribution of the paper lies in its discussion of specificity of antigens and the definition of that specificity. The following clear and concise statement appears: "In order to establish that level of sensitivity to tuberculin which may be regarded as specific for infection with tuberculosis, one attempts to determine that dosage of the antigen to which the greatest proportion of infected individuals and the smallest proportion of uninfected individuals give the specified minimum reaction." In this study the authors found a reaction of five or more mm. of definite induration to 0.0001 mg. of the standard PPD tuberculin to be effective.

It is to be hoped that the investigation will continue to be fruitful, and that more correlations will be discovered as it progresses. The work will stimulate investigators who are in a position to see clinically active cases of histoplasmosis. The results to date suggest the great desirability of skin testing with both tuberculin and histoplasmin to establish a diagnosis in cases of pulmonary infiltration of doubtful origin, particularly in those regions where sensitivity to histoplasmin is common.

ESMOND R. LONG, M. D.,
Director, Medical Research and Therapy, National Tuberculosis Association, and *Director, Henry Phipps Institute, University of Pennsylvania.*

Studies of Pulmonary Findings and Antigen Sensitivity Among Student Nurses

III. Pulmonary Infiltrates and Mediastinal Adenopathy Observed Among Student Nurses at the Beginning of Training [1]

By Lydia B. Edwards, Ira Lewis, and Carroll E. Palmer,
Senior Surgeons, Public Health Service [2]

A study of early tuberculosis was begun in 1943 as a joint project of the National Tuberculosis Association and the Public Health Service. Student nurses were chosen for study since they constitute a large group of highly cooperative individuals who could be observed for a prolonged period of time, and who experience varying degrees of exposure to tuberculosis in the course of their training period. Moreover, the choice of this study group permitted a fairly wide geographic coverage of the country. The program included semiannual skin testing, first with tuberculin alone, later with the addition of various fungus antigens, including histoplasmin, and semiannual X-ray examination regardless of the results of such tests. Starting with 38 schools in 6 areas, the program expanded to a peak enrollment in 1945 of more than 13,000 student nurses in a total of 76 schools located in 10 widely separated metropolitan areas throughout the country. At the present time more than 23,000 nurses have been, or are now, under study.

In studying the problem of early tuberculosis in any population group, the first step must be the analysis of the findings at the time of initial observation. This is particularly true in a study directed toward an evaluation of the earliest discernible roentgenographic changes. It is apparent that in the present group these initial findings will be of minimal clinical import since students with evidence of significant disease would not have been admitted to training. However, only when such a baseline has been established, can the study proceed to the consideration of the X-ray and other changes which develop during the period of observation.

In the course of planning the study, it was evident that much emphasis must of necessity be placed on the differential diagnosis of early tuberculosis and the diseases which may simulate tuberculosis. It was known that infection with pathogenic fungi could present abnormal X-ray findings easily confused with tuberculosis; but such

[1] Presented before the National Tuberculosis Association at the 43rd annual meeting, New York City, June 15–18, 1948. This is the third in a series of reports from this investigation. For previous publications see Palmer, C. E.: Nontuberculous pulmonary calcification and sensitivity to histoplasmin, Pub. Health Rep. **60**: 513–520 (1945); and Palmer, C. E.: Geographic differences in sensitivity to histoplasmin among student nurses, Pub. Health Rep. **61**: 475–487 (1946).

[2] From the Office of Field Studies, Tuberculosis Control Division.

infections were, in general, thought either to occur in strictly localized areas of the country, as does coccidioidomycosis, or to be of relatively infrequent occurrence. The presence of an unidentified yet prevalent pulmonary infection simulating tuberculosis was suspected because it was found that pulmonary calcification occurs with great frequency in certain portions of the country, and because a large proportion of the individuals showing such calcification did not react to tuberculin. Moreover, the areas with high tuberculosis mortality were not necessarily those where the frequency of calcification was great. Christie and Peterson (*1*) reporting from Tennessee, and Palmer (*2*), in an earlier report of the present investigation, showed that, in certain areas of the country, sensitivity to histoplasmin is common; and that these areas correspond with the regions where a high frequency of pulmonary calcification was noted. Furthermore, the individuals who showed calcification, and failed to react to tuberculin, almost uniformly reacted to histoplasmin.

Calcification is, however, an end stage of a pathological process. If the hypothesis of a subclinical pulmonary infection associated with histoplasmin sensitivity is accepted, then one would expect to find infiltrates in a precalcified stage. In studies among school children in Kansas City, one of the areas where histoplasmin sensitivity is frequently encountered, Furcolow, Mantz and Lewis (*3*) described pulmonary infiltrates and mediastinal adenopathy and their close relationship to histoplasmin sensitivity.

It was possible to study the relation of tuberculin and histoplasmin sensitivity to pulmonary calcification at a relatively early stage in the present investigation because of the frequency of such findings in roentgenograms of the chest. However, since the occurrence of infiltrates, even of small size and without apparent clinical significance, is relatively infrequent in such a highly screened population as young women accepted for nursing training, it has been necessary to wait until a much larger body of data could be collected before making a similar analysis for pulmonary infiltrates. The present paper deals with the X-ray findings, limited to parenchymal infiltrates and involvement of the mediastinal lymph nodes, observed among student nurses at the beginning of their training period, and the relationship of such findings to tuberculin and histoplasmin sensitivity.

Methods and Materials

Included in this study are all student nurses [3] who entered training in the cooperating hospitals prior to the fall of 1947 and met the following criteria. A roentgenogram and a tuberculin test must have

[3] Since the number of Negro nurses included in the program is too small for separate analysis, and since there may be racial differences in the pattern of tuberculosis, this study has been limited to white student nurses only.

been done during the first year of training and at approximately the same time. In addition a histoplasmin test must have been performed at some time during training. According to the study routine, the semi-annual X-rays are made during the month prior to the skin-testing session. In individual instances, however, films were taken somewhat earlier, or later, than this schedule. When the interval between the initial X-ray and the tuberculin test was more than 120 days, the nurse was excluded from this analysis.

Purified Protein Derivative (PPD–S), prepared by Dr. Florence Seibert, is employed in two strengths: a first dose of 0.0001 mg. and a second dose of 0.005 mg. The tests are read at 48 hours, and the measurements of erythema and induration recorded, together with a description of the type of induration present. To obtain uniformity of the readings, two individuals have separately or together read practically all the tests performed during the course of the study.

Histoplasmin is used in a dilution of 1/1000 and administered and read as is the tuberculin test, with the exception that the strongest reaction at either 48 or 96 hours after injection is used as the measure of sensitivity. The first batch of histoplasmin was obtained from Dr. Chester Emmons of the National Institute of Health. Subsequent batches have been prepared by Dr. Arden Howell, Jr. of the Tuberculosis Control Division. Since testing with histoplasmin was not begun until 1945, students entering training prior to that period received the test at some time later than their first skin-testing session.

All X-ray films of the chest have been read by the roentgenologists of the Field Studies Office without knowledge of the skin test results, and all pathological changes were described without regard to size or apparent clinical significance. In addition to individual readings, all films on a given student nurse have been reviewed in series by one of the authors (I. L.). During the process of review, the initial X-ray impression was subject to change; and such a change was made occasionally when, in the light of subsequent films, it was possible to determine the presence of a lesion on the first film, or to discard a finding that was initially thought to be an infiltrate on the basis of one film.

Since the beginning of the investigation, an attempt has been made to classify the infiltrates into several broad categories. This was done with the realization that such a grouping was a very gross one, and that there were many intermediate stages between the respective groups. The infiltrates included in this study were classified into four categories: (1) nodular infiltrates, (2) poorly circumscribed infiltrates, (3) fibrotic infiltrates, and (4) so-called "nonspecific" infiltrates. Here again, the roentgenographic descriptions were made without knowledge of the skin test results.

The most uniformly characteristic group of infiltrates are the nodular lesions. These shadows on the X-ray film are circular in outline and have clear-cut borders. They are sharply delimited and their density is usually much greater than that of the surrounding lung. Very frequently they have markedly increased densities as their core, presumably due to calcification. Illustrations of this type of infiltrate are shown in plates 1 through 7.

The poorly circumscribed infiltrates comprise a far less homogeneous group. Unlike the nodular lesions their borders are poorly defined. This type of infiltrate has no characteristic shape and is so poorly outlined and so irregular that its description is difficult. Its density is not usually as great nor as homogeneous as that of the nodular lesion. It very often lacks contrast to the surrounding lung field and merges gradually into the normal lung markings. While there may be some areas of the lesion that show fibrosis, there are always, in addition, areas that have a "soft" appearance, and it is this soft quality which is common to all lesions classified in this category. This type of infiltrate is illustrated in plates 8 through 13.

The group of infiltrates which are classified as fibrosis alone, in contrast to the mottled irregular group, have no elements which can be considered "soft." This is the pulmonary scar, which may be a single linear strand or possibly several strands. These scars are very sharply outlined and usually extend from the hilum to the lateral thoracic wall or into the apex of the lung. Occasionally, however, a compact dense irregular area is included in this category. The presence of calcification within this type of lesion is frequent. Plate 14 shows an example of a fibrotic infiltrate.

The fourth group includes the heterogeneous X-ray shadows which are, in general, considered to be of nontuberculous etiology, such as gross pneumonias, infiltrates associated with bronchiectasis, and similar pathological entities. For want of a better name, and for the sake of brevity, this type of infiltrate is referred to as "nonspecific."

On occasion, the choice of category was exceedingly arbitrary. Difficulties arose where small amounts of mottling were observed in lesions which were essentially fibrotic or where a mottled lesion tended to have circular outline. The great majority of the nodular lesions were sharply circumscribed, well defined, and clearly distinct from their surroundings and thus offered no problem of classification; but, in a few instances, the borders were not so discrete and had a tendency to fade into the surrounding tissue.

Findings

Classification of reactions to tuberculin and histoplasmin.—The nurses included in this study showed a wide range of reaction to the injection of tuberculin and histoplasmin, as may be seen in the data presented in appendix table A.

In the determination of histoplasmin sensitivity, only one strength of the antigen was used. Seventy-five percent of the nurses gave no reaction to this single test dose. Twenty-one percent gave reactions of 5 or more mm. of induration, and only 539 individuals, or 4 percent of the total group showed erythema alone, or indurations of less than 5 mm., or questionable indurations of any size.

In the determination of tuberculin sensitivity two strengths of the antigen were used. If the individual tested gave a reaction of less than 10 mm. of firm induration to the 0.0001 mg. dose, a second test using a strength 50 times greater (0.005 mg.) was given. This two-dose testing created a difficult problem of classification in that the reactions to the smaller dose had to be considered in combination with those to the larger. Thus, whereas only 4 percent of the tests with histoplasmin gave reactions between zero mm. of erythema and induration and 5 mm. of definite induration, 74 percent of the tests with tuberculin gave reactions between zero mm. of erythema and induration to the large dose and 5 mm. of definite induration to the small dose.

When a specific antigen is used to detect the presence of an infection, and a range of reactions to graded doses of the antigen results, the problem arises as to what dosage of the antigen shall be employed and the degree of reaction to that dosage which shall be interpreted as indicative of the infection.

Furcolow, Hewell, Nelson, and Palmer (*4*), in titration studies of tuberculin, showed that a relatively small dose (in the neighborhood of 0.0001 mg. of PPD) was sufficient to cause a reaction of 5 or more mm. of induration almost uniformly in those individuals tested having known tuberculosis, and in a high proportion of those giving a history of contact with tuberculosis. This dosage, on the other hand, produced relatively few reactions among children considered free of the disease and without known exposure. When, however, the dose of tuberculin was successively increased, almost all of the individuals tested eventually reacted to the antigen, including infants and young children without evidence of tuberculous infection or history of contact. It is improbable that such a high proportion of children were actually infected with tuberculosis. The explanation advanced by the authors is that, with the use of higher dosages of the antigen, nonspecific reactions appear with increasing frequency.

In order to establish the level of sensitivity to tuberculin which

should be regarded as specific for infection with tuberculosis, one would attempt to determine that dosage of the antigen to which the greatest proportion of infected individuals and the smallest proportion of uninfected individuals would give the specified minimum reaction.

The only means whereby this level of sensitivity can be determined is through correlation with other objective evidence of infection. Unfortunately, there is no measure available by which all infected individuals may be identified. In a limited number only, absolute diagnosis may be made by bacteriological means. A larger group will show X-ray findings compatible with a diagnosis of tuberculous infection; and the relationship of such findings to tuberculin sensitivity may be ascertained.

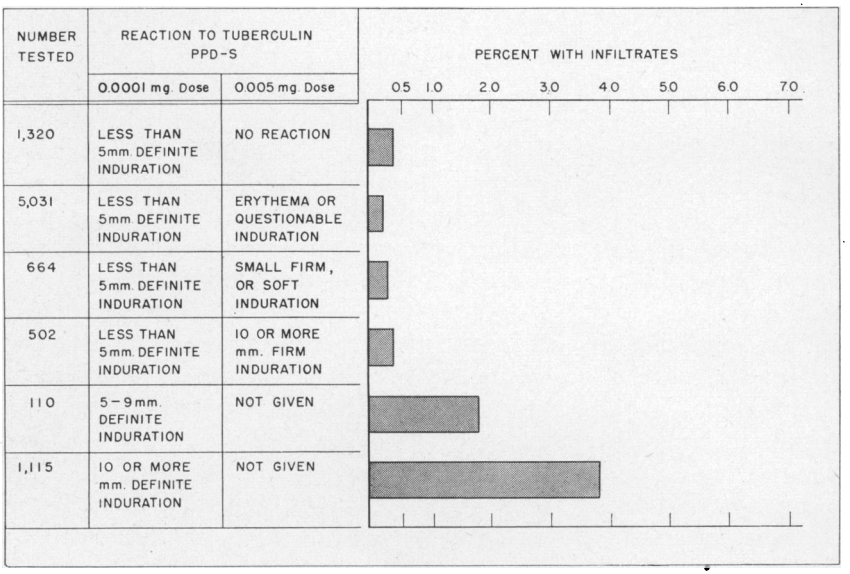


FIGURE 1. Frequency of infiltrates according to specified levels of sensitivity to tuberculin among histoplasmin nonreactors.

Among a group of students entering nursing training, it is not possible to correlate sensitivity levels of tuberculin with frank active tuberculous disease, since, as a general rule, such individuals would have been excluded from training. However, a certain number of pulmonary infiltrates were observed on the initial X-ray examination, and it is possible to relate the frequency of these infiltrates to the various levels of tuberculin sensitivity. Such infiltrates undoubtedly include those which are not related to tuberculous infection. However, it is to be expected that these nontuberculous findings will be randomly distributed throughout all levels of tuberculin sensitivity, and therefore their inclusion should not invalidate the correlation of the frequency of pulmonary infiltrates with the various levels of

tuberculin sensitivity, providing they are not numerically large in proportion to the total number of infiltrates.

The frequency distribution of infiltrates according to specified levels of tuberculin sensitivity is presented in figure 1. To eliminate the confusion that might arise from pathological changes associated with histoplasmin sensitivity, only student nurses who showed no reaction to histoplasmin have been included.

It was found that the frequency of infiltrates was constantly very low among individuals showing less than 5 mm. of definite induration to the 0.0001 mg. dose of tuberculin regardless of the degree of sensitivity demonstrated to the 0.005 mg. dose. Nurses, however, who showed 5–9 mm. of definite induration to the 0.0001 mg. dose showed a greater frequency of infiltrates; and, among those showing 10 or more mm. of induration, an even higher rate was observed.

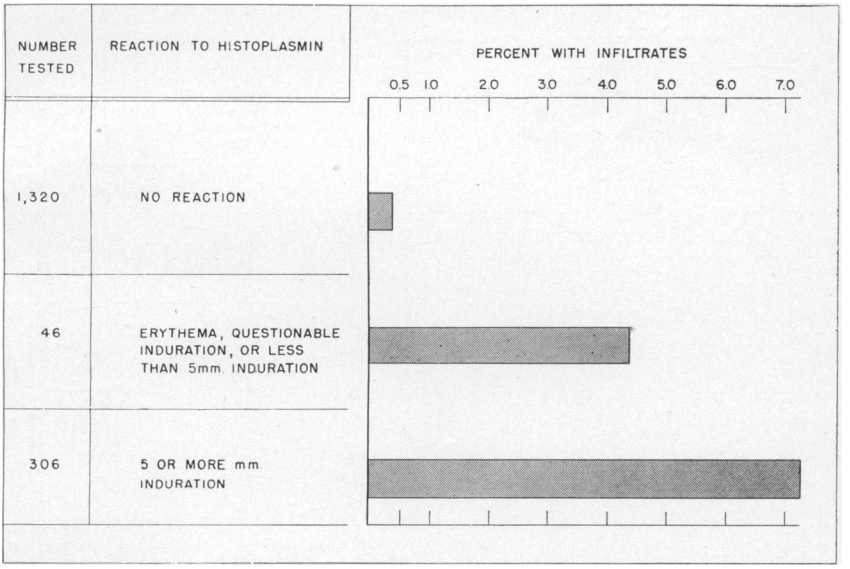


FIGURE 2. Frequency of infiltrates according to specified levels of sensitivity to histoplasmin among tuberculin nonreactors.

The relationship between histoplasmin sensitivity and the frequency of pulmonary infiltrates was studied in a similar manner, the analysis being limited to those students showing neither induration nor erythema to the 0.005 mg. dose of tuberculin.

Among nurses with no reaction to histoplasmin, the frequency of infiltrates was found to be very low, whereas the rate was significantly higher among those showing definite induration of 5 or more mm. to the antigen. Among the small group of individuals who showed only small or questionable indurations or erythema alone, there was also a significantly higher frequency of infiltrates than among the negative group. This parallels the findings in a previous report (*2*) from this

investigation, in which the frequency of pulmonary calcification among individuals giving doubtful reactions was shown to approximate closely the rate of such findings among positive reactors to the antigen—in contrast to the very low rate of calcification observed among those nurses who had no reaction to the test.

For the purpose of this paper, therefore, a tuberculin reactor is defined as an individual showing 5 or more mm. of definite induration to the 0.0001 mg. dose of PPD–S. Histoplasmin reactors include those individuals showing 5 or more mm. of definite induration to the test, and also the very small group of persons showing erythema alone, or questionable or small indurations.

Frequency of infiltrates among reactors and nonreactors to tuberculin and histoplasmin.[4]—Among the 12,803 student nurses included in this study, 224 showed pulmonary infiltrates.

Table 1. *Pulmonary infiltrates observed on X-ray among student nurses at beginning of training according to tuberculin and to histoplasmin reaction*

Reaction group	Total student nurses tested	Student nurses with infiltrates	
	Number	Number	Percent
T−, H−	8,358	22	0.26
T−, H+	2,729	136	4.98
T+, H−	1,225	43	3.51
T+, H+	491	23	4.68
Total	12,803	224	1.75

When these infiltrates were considered in relation to the skin test group in which they were observed, the association with sensitivity to histoplasmin or tuberculin was impressive. The rate among nonreactors to either antigen (T−, H−) was 0.26 percent in contrast to 3.51 percent among tuberculin reactors (T+, H−), 4.98 percent among histoplasmin reactors (T−, H+), and 4.68 percent among reactors to both antigens (T+, H+). When one takes into account that, by our extremely rigid definition of a tuberculin reactor the great mass of the population tested were classified as nonreactors to this antigen, it is striking that the prevalence of infiltrates among nonreactors is so low.

The frequencies observed present certain anomalies of sufficient interest to warrant mention, although adequate explanation cannot be offered on the basis of the material available at present. Although the over-all frequency of pulmonary infiltrates among the histoplasmin reactors is slightly higher than among tuberculin reactors, the difference in rate between the two reactor groups is not significant. This

[4] The following symbols are used throughout the text and tables:
T−, nonreactor to tuberculin T+, reactor to tuberculin
H−, nonreactor to histoplasmin H+, reactor to histoplasmin

is in contrast to the findings reported in the first paper (*2*) of this series, in which it was shown that the occurrence of pulmonary calcification was approximately three times more frequent among histoplasmin reactors than among tuberculin reactors. It is of interest also to note that the frequency of infiltrates in the group reacting to both antigens is slightly lower than the frequency observed among nurses reacting to histoplasmin alone; whereas one would expect a higher frequency of infiltrates among a group of individuals who have evidence of two infections which may be causative factors in the production of such infiltrates.

Frequency of occurrence of various types of infiltrates.—The relationship between antigen sensitivity and the presence of infiltrates has been shown. The material was further analyzed to determine the correlation between the respective types of infiltrates and specific antigenic sensitivity.

Table 2. *Pulmonary infiltrates of specified type observed on X-ray among student nurses at beginning of training according to tuberculin and to histoplasmin reaction*

Reaction group	Total student nurses tested	Student nurses with specified types of infiltrates							
		Nodular		Poorly circumscribed		Fibrotic		Nonspecific	
	Number	Number	Percent	Number	Percent	Number	Percent	Number	Percent
T−, H−	8,358	4	0.05	3	0.03	6	0.07	9	0.10
T−, H+	[1] 2,729	94	3.44	12	0.44	26	0.95	5	0.18
T+, H−	[2] 1,225	5	0.41	23	1.88	15	1.22	1	0.08
T+, H+	[3] 491	11	2.24	8	1.63	7	1.43	---	---

[1] One nurse had a pneumonic and a nodular infiltrate.
[2] One nurse had a nodular and a fibrotic infiltrate.
[3] Two nurses had nodular and fibrotic infiltrates; one had a poorly circumscribed and a fibrotic infiltrate.

Among the 224 nurses showing infiltrates on X-ray at the beginning of the training period, 219 showed a single type of infiltrate according to the classification herein described, while 5 showed more than one type of infiltrate.

Examples of each type of infiltrate were observed in each skin reaction group, but the frequency with which they occurred, with the exception of the group of nonspecific infiltrates, varied markedly according to the specific sensitivity demonstrated.

Of the four types, the nodular was the most frequently observed. One hundred fourteen nurses showed such infiltrates on X-ray. A close relationship between histoplasmin sensitivity and these nodular infiltrates was found to exist. Among nurses who reacted to histoplasmin alone the rate was 3.4 percent; whereas, among tuberculin reactors who failed to react to histoplasmin, the rate was 0.4 percent. Among those nurses who reacted to neither antigen, the rate was 0.05 percent.

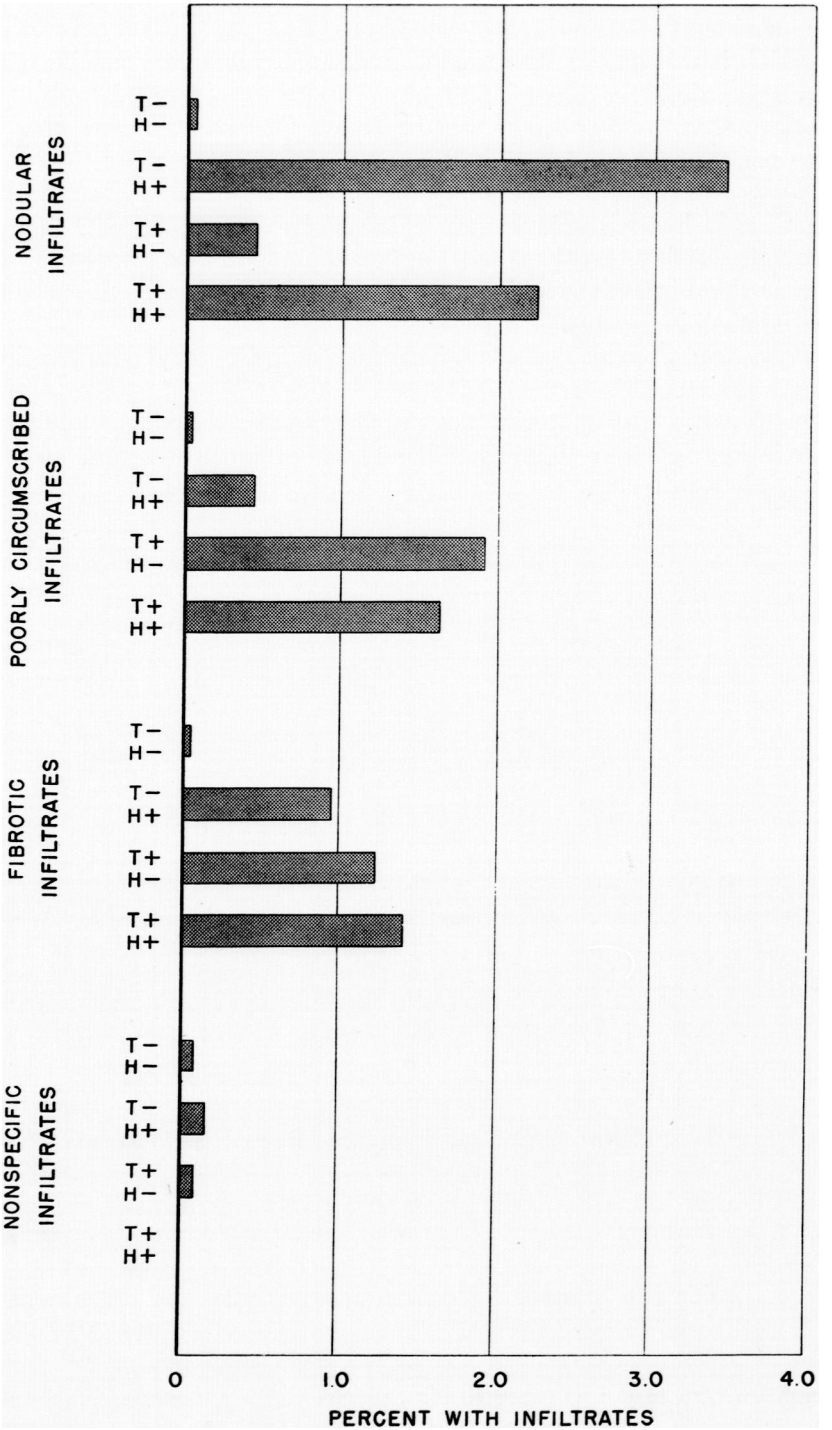


FIGURE 3. Percentage of student nurses with specified types of pulmonary infiltrates observed on X-ray at beginning of training according to tuberculin and to histoplasmin reaction.

Forty-six nurses showed infiltrates of the poorly circumscribed type, which were observed almost five times as frequently among tuberculin reactors as among histoplasmin reactors. Of the nurses reacting to tuberculin alone, 1.9 percent showed such infiltrates, as compared with 0.4 percent among those reacting to histoplasmin alone. Only 0.03 percent of those reacting to neither antigen showed infiltrates of this character.

Fifty-four nurses showed fibrosis alone. Such findings were infrequent among nonreactors to either antigen (T−, H−), but were related to both tuberculin and histoplasmin sensitivity.

Table 3. *Percentage of pulmonary infiltrates (exclusive of the nonspecific group) observed among student nurses at beginning of training, and percentage of histoplasmin and of tuberculin reactors in each study area, ranked by the frequency of infiltrates in each area*

Study area	Percentage		
	Pulmonary infiltrates	Histoplasmin reactors	Tuberculin reactors
Columbus, Ohio	3.8	60.1	11.2
Kansas City, Kans. and Mo	3.0	59.8	13.6
Detroit, Mich	2.3	14.3	12.8
Baltimore, Md	1.8	25.5	16.1
New Orleans, La	1.5	28.6	12.7
Denver, Colo	1.2	8.8	14.4
Philadelphia, Pa	0.9	14.5	18.1
Minneapolis and St. Paul, Minn	0.8	7.5	7.0
Los Angeles, Calif	0.6	14.9	16.4
San Francisco, Calif	0.3	9.3	14.5
Total	1.6	24.2	12.6

Fifteen nurses showed infiltrates that were classified as nonspecific. No relation was apparent between either tuberculin or histoplasmin sensitivity and this type of infiltrate, the frequency being essentially the same in all skin reaction groups. Since no correlation was found between the nonspecific group and skin sensitivity to tuberculin or to histoplasmin, further analysis will be confined to the three categories of infiltrates in which such correlation exists.

Relationship of infiltrates to tuberculin and to histoplasmin sensitivity by separate study areas.—There are marked differences in the frequency of infiltrates and in the frequency of tuberculin and histoplasmin, reactors in the ten study areas.

As shown in table 3, the rates for infiltrates vary from 3.8 percent in Columbus to 0.3 percent in San Francisco. The frequencies of histoplasmin reactors (T−, H+ and T+, H+) vary from a high of 60.1 percent in Columbus to a low of 7.5 percent in the metropolitan area of Minneapolis and St. Paul; the rates for tuberculin reactors (T+H− and T+H+) show less variation, ranging from 18.1 percent in Philadelphia to 7.0 percent in Minneapolis and St. Paul.

Table 4 gives the percentage distribution of pulmonary infiltrates in each study area, according to tuberculin and histoplasmin reaction.

Table 4. *Percentage distribution of pulmonary infiltrates (exclusive of the nonspecific group) according to tuberculin and to histoplasmin reaction in each study area*

Study area	Student nurses with infiltrates	Reaction group			
		T−, H+	T+, H−	T+, H+	T−, H−
	Number	*Percent*	*Percent*	*Percent*	*Percent*
Columbus, Ohio	44	81.8	9.1	6.8	2.3
Kansas City, Kans. and Mo	49	73.5	4.1	16.3	6.1
Detroit, Mich	25	44.0	40.0	12.0	4.0
Baltimore, Md	26	69.2	19.2	3.8	7.7
New Orleans, La	16	62.5	18.8	18.8	0.0
Denver, Colo	10	20.0	60.0	0.0	20.0
Philadelphia, Pa	13	61.5	15.4	15.4	7.7
Minneapolis and St. Paul, Minn	17	41.2	35.3	11.8	11.8
Los Angeles, Calif	8	50.0	25.0	12.5	12.5
San Francisco, Calif	2	0.0	100.0	0.0	0.0
Total	210	62.9	20.0	10.9	6.2

As would be expected with the variations in the prevalence of such sensitivity noted in table 3, this percentage distribution shows marked variation from one area to another.

In view of the very close association of infiltrates with sensitivity to tuberculin or to histoplasmin in the total group studied, it is of interest to determine whether significant differences exist in this association in the separate study areas which show such marked variation in levels of tuberculin and histoplasmin sensitivity. Data bearing on this point are given in tables 5 and 6. (The figures on which the rates presented in these tables are based are given in appendix table B.)

Table 5. *Percentage of student nurses in each reaction group at beginning of training, in each study area*

Study area	Student nurses tested	Reaction group							
		T−, H+		T+, H−		T+, H+		T−, H−	
	Number	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Columbus, Ohio	1,147	612	53.4	51	4.5	77	6.7	407	35.5
Kansas City, Kans. and Mo	1,628	837	51.4	85	5.2	137	8.4	569	35.0
Detroit, Mich	1,084	131	12.1	115	10.6	24	2.2	814	75.1
Baltimore, Md	1,468	317	21.6	179	12.2	57	3.9	915	62.3
New Orleans, La	1,164	287	24.7	102	8.8	46	4.0	729	62.6
Denver, Colo	807	55	6.8	100	12.4	16	2.0	636	78.8
Philadelphia, Pa	1,455	161	11.1	213	14.6	50	3.4	1,031	70.9
Minneapolis and St. Paul, Minn	1,966	123	6.3	112	5.7	25	1.3	1,706	86.8
Los Angeles, Calif	1,285	144	11.2	164	12.8	47	3.7	930	72.4
San Francisco, Calif	799	62	7.8	104	13.0	12	1.5	621	77.7
Total	12,803	2,729	21.3	1,225	9.6	491	3.8	8,358	65.3

Table 5 shows the relative proportion of nurses, from each study area, in each of the four reaction groups. Table 6, which is similar to the basic tabulation of table 1, shows the frequency of infiltrates for each reaction group and for each separate study area.

Inspection of the latter table indicates that the pattern of frequency of infiltrates in the separate reaction groups for the different study

areas is grossly similar to that of the total group studied. Among nonreactors to either antigen (T−, H−) the frequency of infiltrates is uniformly low. Among reactors, however, there are significant deviations from the expected pattern. Among histoplasmin reactors (T−, H+), there is no significant departure from the mean rate for all areas, although the lowest rate observed (San Francisco) is significantly different from the highest (Detroit). Among tuberculin reactors (T+, H−) the rates of infiltrates vary significantly from area to area, as well as from the general mean for all areas. In addition, there is a definite indication that the frequency of infiltrates among tuberculin reactors varies inversely with the prevalence of tuberculin reactors in the separate study areas. Another rather surprising finding is that the frequencies of infiltrates among reactors to tuberculin alone and to histoplasmin alone seem to follow the same pattern. For example, while the over-all rate of infiltrates among reactors is approximately 4 percent, in Detroit 8.4 percent of histoplasmin reactors and 8.7 percent of tuberculin reactors have infiltrates. On the other hand, in San Francisco, the frequency of infiltrates in histoplasmin reactors is zero and in tuberculin reactors is only 1.9 percent.

Table 6. *Percentage of pulmonary infiltrates (exclusive of the nonspecific group) among student nurses according to tuberculin and to histoplasmin reaction, in each study area*

Study area	Reaction group			
	T−, H+	T+, H−	T+, H+	T−, H−
Columbus, Ohio	5.9	7.8	3.9	0.2
Kansas City, Kans. and Mo	4.3	2.4	5.8	0.5
Detroit, Mich	8.4	8.7	12.5	0.1
Baltimore, Md	5.7	2.8	1.8	0.2
New Orleans, La	3.5	2.9	6.5	0.0
Denver, Colo	3.6	6.0	0.0	0.3
Philadelphia, Pa	5.0	0.9	4.0	0.1
Minneapolis and St. Paul, Minn	5.7	5.4	8.0	0.1
Los Angeles, Calif	2.8	1.2	2.1	0.1
San Francisco, Calif	0.0	1.9	0.0	0.0
Total	4.8	3.4	4.7	0.2

A complete explanation cannot be given for the variations observed among the separate study areas in the relationship of infiltrates and sensitivity to the two antigens. However, it may be postulated that the screening of the candidates through X-ray examination before acceptance for training constitutes a major contributing factor.

Other characteristics of infiltrates.—The infiltrates were studied to determine if there were distinguishing characteristics within each category which would differentiate the lesions associated with tuberculin sensitivity from those associated with histoplasmin sensitivity. Specifically, location within the lung field, size of the infiltrate, tendency toward calcification, and general description were investigated.

Composite charts of the distribution of infiltrates in the lung fields have been drawn giving the anatomical location of the changes

observed in nurses who reacted to tuberculin alone, and to histoplasmin alone, according to type of lesion.

Among tuberculin reactors, the infiltrates are found to be localized in the upper portion of the chest. Among histoplasmin reactors, the infiltrates are scattered generally throughout the lung fields. This distribution in the latter group is, however, mainly due to the widespread scattering of the nodular infiltrates, which comprise the majority of changes seen among the histoplasmin reactors. The fibrotic and poorly circumscribed infiltrates in histoplasmin reactors, as in

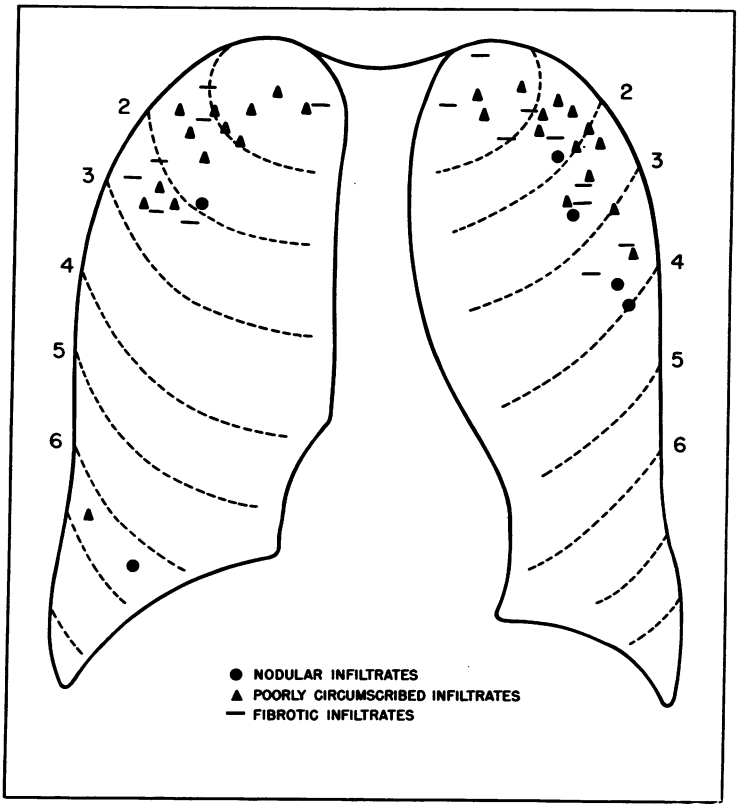


FIGURE 4. Anatomical location of infiltrates in lung fields among tuberculin reactors, histoplasmin nonreactors.

tuberculin reactors, tend to be concentrated in the middle and upper portions of the lung fields.

The size of the nodular and poorly circumscribed infiltrates was determined for each skin reaction group. Since the fibrotic infiltrates were composed essentially of strands alone and measurement of diameter would be meaningless, they were not analyzed in a similar manner. Ninety-seven percent of the nodular infiltrates were less than 15 mm. in diameter; whereas only 24 percent of the poorly circumscribed

infiltrates were less than this in diameter. The over-all size of infiltrates occurring among the histoplasmin reactors (T−, H+) was much smaller than those occurring among tuberculin reactors (T+, H−), as would be expected when the closer association of the nodular infiltrate with histoplasmin sensitivity and of the poorly circumscribed infiltrate with tuberculin sensitivity is taken into account. Within each category of infiltrates, however, there was a tendency for those associated with histoplasmin sensitivity to be somewhat smaller than those observed associated with tuberculin sensitivity.

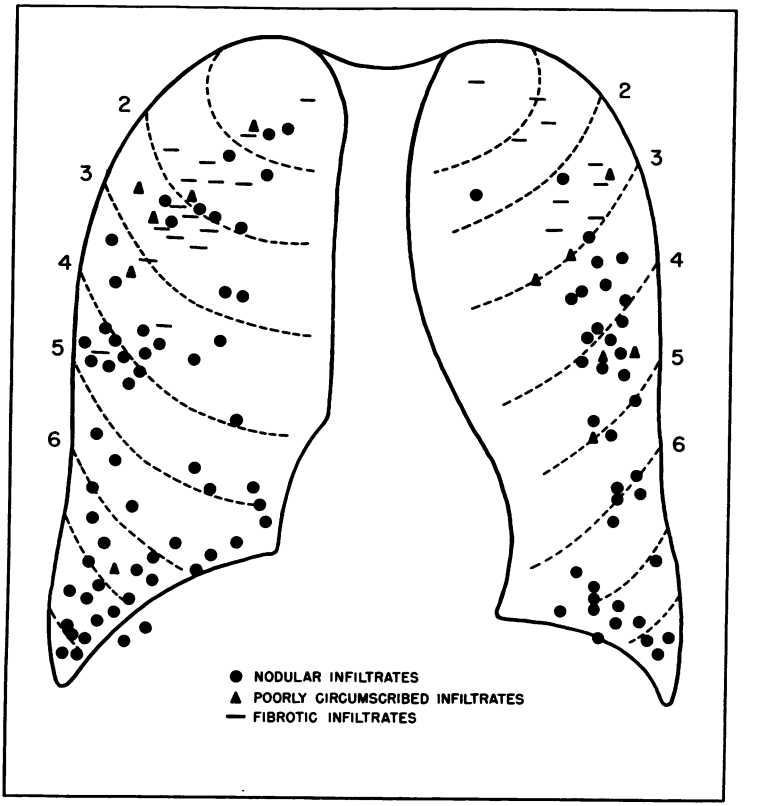


FIGURE 5. Anatomical location of infiltrates in lung fields among tuberculin nonreactors, histoplasmin reactors.

A large proportion of the infiltrates described in this study showed partial calcification at the time of the initial observation, this finding being most common among the nodular and least common among the poorly circumscribed infiltrates.

The frequency of calcification in nodular and fibrotic infiltrates was somewhat higher among histoplasmin reactors (T−, H+) than among tuberculin reactors (T+, H−). On the other hand, none of the poorly circumscribed infiltrates showed calcification unless associated with a positive tuberculin test.

Table 7. *Comparative size of poorly circumscribed and nodular infiltrates according to tuberculin and to histoplasmin reaction*

Type of infiltrate	Reaction group	Size of infiltrate				Total Number
		Less than 15 mm.		15 or more mm.		
		Number	Percent	Number	Percent	
Poorly circumscribed	T−, H−	1	33.3	2	66.7	3
	T−, H+	5	41.7	7	58.3	12
	T+, H−	5	21.7	18	78.3	23
	T+, H+	0	0.0	8	100.0	8
	Total	11	23.9	35	76.1	46
Nodular	T−, H−	4	100.0	0	0.0	4
	T−, H+	92	97.9	2	2.1	94
	T+, H−	4	80.0	1	20.0	5
	T+, H+	11	100.0	0	0.0	11
	Total	111	97.4	3	2.6	114

No qualitative differences in the appearance of the lesions were observed between the nodular infiltrates associated with histoplasmin sensitivity and the few such infiltrates occurring in association with tuberculin sensitivity. Among the poorly circumscribed infiltrates, the softer appearing, more mottled tended to be more closely associated with tuberculin sensitivity; whereas those showing more homogeneous density and approaching the nodular form tended to be more frequently associated with histoplasmin sensitivity. Among the

Table 8. *The percentage of infiltrates showing partial calcification by type of infiltrate and according to tuberculin and to histoplasmin reaction*

Reaction group	Student nurses with specified types of infiltrate					
	Nodular		Poorly circumscribed		Fibrotic	
	Number	Percent with calcification	Number	Percent with calcification	Number	Percent with calcification
T−, H−	4	50.0	3	0.0	6	0.0
T−, H+	94	67.0	12	0.0	26	69.2
T+, H−	5	40.0	23	8.7	15	26.7
T+, H+	11	81.8	8	12.5	7	71.4
Total	114	66.7	46	6.5	54	50.0

infiltrates classed as fibrosis, the combination of fibrotic strands associated with a single round nidus of calcium or hilar calcification tended to occur more frequently among histoplasmin reactors. However, in the majority of instances, within each category it was not possible to differentiate the infiltrates associated with sensitivity to one antigen or the other.

Involvement of the mediastinal lymph nodes.—In this study, involvement of the mediastinal lymph nodes was observed on the initial roentgenogram of 38 nurses. Thirty-one reacted to histoplasmin

alone, 4 to both histoplasmin and tuberculin, and 3 to neither antigen. None reacted to tuberculin alone.

The three who did not react to either antigen showed bilateral involvement. There was no associated parenchymal infiltrate, and no calcification was observed within the enlarged nodes. Of the remainder, partial calcification was noted in the majority of cases, and 20 of the 35 showed an associated parenchymal infiltrate, most frequently of the nodular type.

Table 9. *Mediastinal adenopathy observed on X-ray among student nurses at beginning of training according to tuberculin and to histoplasmin reaction*

A. ASSOCIATION WITH PARENCHYMAL INFLITRATES

Reaction group	Number student nurses with mediastinal adenopathy	Number associated with specified types of infiltrates		
		Nodular	Poorly circumscribed	Fibrotic
T−, H−	3			
T−, H+	31	12	3	2
T+, H−				
T+, H+	4	2		1
Total	38	14	3	3

B. PRESENCE OF CALCIUM WITHIN THE NODE

Reaction group	Number student nurses with mediastinal adenopathy	Number with partial calcification within the node
T−, H−	3	
T−, H+	31	16
T+, H−		
T+, H+	4	4
Total	38	20

C. SITE OF INVOLVEMENT

Reaction group	Number student nurses with mediastinal adenopathy	Number with bilateral involvement	Number with unilateral involvement	
			Of the right side	Of the left side
T−, H−	3	3		
T−, H+	31	2	20	9
T+, H−				
T+, H+	4	2	2	
Total	38	7	22	9

Among the nurses who reacted to histoplasmin alone, bilateral involvement occurred only twice, whereas unilateral involvement was observed in 29 instances. Among the four reactors to both antigens who showed adenopathy on the initial X-ray examination, two showed enlargement of the lymph nodes on both sides, and in two the process was limited to one side only. In the 29 instances where the adenopathy was unilateral, the right side was involved more than twice as frequently as the left.

Course.—It is not within the scope of the present paper to describe the X-ray and clinical changes that develop among this group of student nurses during the period in training. However, a brief preliminary statement of the course observed to date seems warranted for those showing pulmonary infiltrates and mediastinal adenopathy at the initial X-ray examination. Nurses showing these X-ray abnormalities have been observed for varying lengths of time subsequent to the initial examination; 88 percent have been followed for at least 1 year, and 66 percent for at least 2 years. On the average, the length of follow-up was the same for all skin reaction groups and for all types of infiltrates.

No gross change was observed in any of the group of infiltrates classed as fibrosis alone, nor in the group of nodular infiltrates—with one exception. In this instance, an infiltrate occurring in a histoplasmin reactor remained unchanged until 36 months after the initial film, at which time there was a transitory increase in the size, with a rapid return to its original dimensions the following month. In three histoplasmin reactors tuberculin nonreactors, where nodular infiltrates were observed on the initial film, the subsequent appearance of new pathological changes on the X-ray was accompanied by conversion to tuberculin. One nurse developed mediastinal adenopathy, two developed infiltrates of the poorly circumscribed type. These X-ray changes, developing coincidentally with tuberculin sensitivity, were considered as new lesions associated with the onset of tuberculous infection, and not as the spread of a pre-existing infection.

The progressions observed in this study all occurred in individuals showing infiltrates of the poorly circumscribed type associated with tuberculin sensitivity. Of 23 such infiltrates observed among nurses reacting to tuberculin alone, 7 showed definite increase in the size of the infiltrate, developed new lesions, were hospitalized, or had to discontinue training because of their disease. One of the infiltrates observed among nonreactors to tuberculin, occurring in a nurse who was in the process of converting to tuberculin at the time she was first observed, should properly be considered in this group. In her case, also, progression of the lesion occurred, and sanatorium care was eventually necessary. (This case is described in more detail in the discussion.) The two remaining infiltrates of the poorly circumscribed type observed among nonreactors to either antigen (T−, H−) showed no change in the X-ray findings during the period of observation.

In contrast to the progression observed in the poorly circumscribed infiltrates when associated with tuberculin sensitivity, the changes observed among the 12 such cases associated with histoplasmin sensitivity (T−, H+) were limited to resolution, a sharpening of the borders, or in some instances a change to the nodular type of infiltrate.

No progression or spread was observed. The same was true for the eight instances where such infiltrates were associated with sensitivity to both tuberculin and histoplasmin.

Subsequent X-rays on nurses showing mediastinal adenopathy associated with sensitivity to histoplasmin alone or to both histoplasmin and tuberculin occasionally showed slight decrease in the size of the node or increase in the deposition of calcium within the node, but, in general, the X-ray picture remained essentially the same as on the initial examination. Of the three nonreactors to either antigen (T—, H—) who showed mediastinal adenopathy, one remained unchanged during the period of observation, one showed a rapid decrease in the size of the nodes with essentially normal findings 5 months after the initial film, and one showed a slow increase in involvement during the subsequent 2-year period.

Discussion

The present study of student nurses at the time of beginning training presents the X-ray and skin test findings in a given population at a given point in time. From this study, an indication of the relative frequency of infiltrates associated with tuberculin and histoplasmin sensitivity is obtained in a specified population group.

In evaluating our findings, however, it must be realized that this is not a random population sample. Any choice of areas for study inevitably introduces a geographic factor in selection. More important, the choice of student nurses as a study population implies a selection by sex, age, race,[5] the factors involved in their choice of profession, and the pre-entrance physical examination. Criteria for acceptance of individuals showing abnormalities on chest X-ray examination are not necessarily the same in all training schools. It would be expected that the prognostic import attributed to the presence of the infiltrates classed as poorly circumscribed would lead to the exclusion of candidates showing such shadows more frequently than would be true of candidates with the nodular or fibrotic types of infiltrates. Moreover, this group of poorly circumscribed infiltrates is a heterogeneous one, and, while infiltrates of a "soft" character would usually be considered a contraindication to training, small infiltrates showing a maximum of fibrosis and a minimum of the "soft" quality would be more difficult to evaluate as potential risks. Since the poorly circumscribed infiltrates have been shown to correlate more closely with tuberculin than with histoplasmin sensitivity, the screening process may have resulted in a more selective exclusion, which was subject to more variation, of those infiltrates associated with tuberculin sensitivity than would be true of the infiltrates associated with histo-

[5] See footnote 4.

plasmin sensitivity. In other population groups, one would expect to find differences in the frequency distributions and in the roentgenological characteristics of the abnormalities observed.

It must be assumed that the roentgenological abnormalities observed in this group of student nurses are, in general, either those which were missed, or considered to be of no clinical significance at the time of pre-entrance examination, or which developed in the interim between the pre-entrance examination and the first film in our study. Many of these lesions are of borderline status roentgenologically. The aberrations from the limits of normal are slight. Nevertheless, the likelihood that those shadows categorized as infiltrates represent pathological changes, is attested to by the correlation of such infiltrates with specific skin sensitivity. This is true even though a high proportion of the nurses in this study are classified as being nonreactors to either tuberculin or histoplasmin (T—, H—).

In considering the relationship between types of infiltrate and specific antigen sensitivity, it must be remembered that for the infiltrates described neither the duration of the infiltrate itself nor the age of the individual at the time the infiltrate developed was known. It is extremely likely that these factors affect the morphology of pulmonary infiltrates. For example, such findings as the generalized distribution throughout the lung fields of the pulmonary infiltrates observed among histoplasmin reactors, or the preponderance of nodular types among such infiltrates, may be a function of the age at which infection occurred, rather than a characteristic of the infection itself. Similarly, it may be that any fresh pulmonary infiltrate appearing in a young adult tends to be poorly circumscribed and irregularly shaped without regard to the causative agent. This is supported by the fact that very few of the poorly circumscribed infiltrates showed evidence of calcification, whereas more than half of both the nodular and the fibrotic types showed such changes.

Special mention should be made of the 22 instances in which infiltrates were observed among those student nurses who were classified as nonreactors to either tuberculin or histoplasmin (T—, H—). Nine of these fell into the category that has been called "nonspecific." This accounts for 41 percent of the total number of infiltrates observed among the nonreactors; whereas, among reactors to either tuberculin or histoplasmin or to both, 3 percent or less of the total number of infiltrates observed fell into this category. Six of the remaining 13 infiltrates in the nonreactors were limited to fibrosis, which could represent the healing of any one of a wide variety of pathological processes within the lung. One nurse with a nodular infiltrate reacted to coccidioidin; another, with a poorly circumscribed infiltrate, was in the process of developing tuberculin sensitivity. At her first tuber-

culin test this student failed to react to the 0.0001 mg. dose of PPD-S but gave a strong reaction to the 0.005 mg. dose. The X-ray, taken 3 weeks later, showed an apical infiltrate; and, at the time of the next skin testing (6 months later), a strong reaction to the 0.0001 mg. dose of PPD-S was obtained.

The tuberculin test among histoplasmin nonreactors, was found to be highly specific in identifying individuals with infiltrates when a reaction was defined as 5 or more mm. of induration to the 0.0001 mg. dose of PPD-S. It is of interest that, of the small number of individuals who showed pulmonary infiltrates on the initial X-ray, and who gave reactions of 5–9 mm. of induration to the 0.0001 mg. dose, or 10 or more mm. of firm induration to the 0.005 mg. dose, all showed at least 10 mm. of firm induration to the 0.0001 mg. dose at the next retest. These findings suggest that in the testing of any large group of individuals, a certain number may be observed in the process of developing sensitivity; and, included in this group, may be those who already show roetgenographic evidence of pulmonary infection. A subsequent retest with the 0.0001 mg. dose of tuberculin will identify those individuals who are in the process of developing sensitivity to the antigen.

Although the findings may be weighted by the choice of areas selected for study and the possibility of selective preentrance screening of infiltrates associated with tuberculin sensitivity, more infiltrates were associated with histoplasmin sensitivity (T−, H+) than were associated with tuberculin sensitivity (T+, H−) in 8 of the 10 study areas.

The relative relationship of histoplasmin and tuberculin sensitivity to mediastinal adenopathy in the present material is even more marked. Of particular interest are those individuals showing adenopathy and associated parenchymal infiltration. In spite of the fact that this combination has been considered to be the characteristic picture of primary tuberculosis, all of the 20 cases with these findings in this study reacted to histoplasmin, 17 of them reacting to histoplasmin alone and 3 to both tuberculin and histoplasmin.

Summary

1. An analysis is presented of the pulmonary infiltrates and mediastinal lymph node enlargement observed among 12,803 student nurses at the beginning of training, and of the relationship of these findings to tuberculin and to histoplasmin sensitivity.

2. Definitions of reactors to tuberculin and to histoplasmin were primarily based upon that reaction which proved efficient in identifying individuals with pulmonary infiltrates. For tuberculin, therefore, a reactor is defined as one having 5 or more mm. of definite indura-

tion to the 0.0001 mg. dose of PPD-S, and for histoplasmin a reactor is defined as one showing any erythema or palpable induration.

3. Among the 12,803 student nurses, 224 showed pulmonary infiltrates on the initial X-ray film. The rate among the very large group which did not react to either tuberculin or histoplasmin (T−, H−) was only 0.26 percent, in contrast to 3.51 percent among tuberculin reactors (T+, H−), 4.98 percent among histoplasmin reactors (T−, H+), and 4.68 percent among reactors to both antigens (T+, H+).

4. All infiltrates were classified into four broad categories: (1) nodular infiltrates, (2) poorly circumscribed infiltrates, (3) fibrotic infiltrates, and (4) so-called "nonspecific" infiltrates.

The nonspecific group, which included pneumonias, infiltrates associated with bronchiectasis, and similar pathologic entities, showed no correlation with tuberculin or histoplasmin sensitivity, whereas the other three types of infiltrates did show such a correlation.

The rate of nodular infiltrates among reactors to histoplasmin alone (T−, H+) was 3.44 percent in contrast to 0.41 percent among reactors to tuberculin alone (T+, H−), and 0.05 percent among nonreactors to both antigens (T−, H−).

The rate of poorly circumscribed infiltrates was 1.88 percent among reactors to tuberculin alone, in contrast to 0.44 percent among reactors to histoplasmin alone, and 0.03 percent among nonreactors to both antigens.

The rate of fibrotic infiltrates was 1.22 percent among reactors to tuberculin alone and 0.95 percent among reactors to histoplasmin alone, in contrast to 0.07 percent among nonreactors to either antigen.

5. There were marked differences in the frequency of infiltrates and in the frequency of tuberculin and histoplasmin reactors in the 10 study areas. Among histoplasmin reactors (T−, H+), there was no significant departure from the mean rate for all areas, although the lowest rate observed was significantly different from the highest. Among tuberculin reactors (T+, H−), the rates of infiltrates varied significantly from area to area as well as from the general mean for all areas. The rates of infiltrates among nonreactors to both antigens (T−, H−) were uniformly low throughout all areas.

6. There was a tendency for the infiltrates associated with tuberculin sensitivity (T+, H−) to occur in the upper portions of the lung fields, whereas those associated with histoplasmin sensitivity (T−, H+) were observed in all areas of the lung. This was essentially due to the widespread distribution of the nodular infiltrates which comprised a high proportion of the lesions observed among histoplasmin reactors.

7. Of the 38 nurses showing mediastinal adenopathy, 31 reacted to histoplasmin alone, 4 reacted to both tuberculin and histoplasmin, and 3 reacted to nether antigen. The combination of mediastinal adenopathy and associated parenchymal infiltrate, the so-called "primary complex" of tuberculosis was observed 17 times in this series; 14 times in individuals who reacted to histoplasmin alone, and 3 times in reactors to both tuberculin and to histoplasmin. In no instance was it observed in an individual reacting to tuberculin alone.

8. The only progressions observed to date among student nurses showing infiltrates on the initial X-ray examination, have been among those showing a poorly circumscribed infiltrate associated with tuberculin sensitivity (T+, H−). Seven of the 23 nurses with this type of infiltrate showed definite increase in the size of the infiltrate, developed new lesions, were hospitalized, or had to discontinue training because of their disease.

9. In evaluating the above findings, the selection involved in the choice of student nurses as a study population must be taken into account.

ACKNOWLEDGMENT

The authors acknowledge their deep indebtedness to the staff of the Field Studies Office, past and present, who have worked with them on this investigation. Special recognition is given to Miss Margaret Allen and Mrs. Martha Bruyere for their advice and assistance in the statistical analysis of the material presented; and to Miss Jennie Goodard, Dr. Charlotte Silverman, Mrs. Virginia Trevett, Dr. Henry Zwerling, and Surgeon Eugene Gillespie for their painstaking work in the collection and interpretation of the basic data upon which this study is based.

Special thanks are due to the members of the Medical Research Committee of the National Tuberculosis Association for their continued interest, counsel and support. Most of all, the authors make most grateful acknowledgment to the thousands of student nurses whose loyal cooperation has made this program possible.

REFERENCES

(*1*) Christie, Amos, and Peterson, J. C.: Pulmonary calcification in negative reactors to tuberculin. Am. J. Pub. Health. **35:** 1131 (1945).

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

(*3*) Furcolow, M. L., Mantz, H. L., and Lewis, I.: The roentgenographic appearance of persistent pulmonary infiltrates associated with histoplasmin sensitivity. Pub. Health Rep. **62:** 1711 (1947).

(*4*) Furcolow, M. L., Hewell, B., Nelson, W. E., and Palmer, C. E.: Quantitative Studies of the Tuberculin Reaction. I. Titration of tuberculin sensitivity and its relation to tuberculous infection. Pub. Health Rep., **56:** 1082 (May 23, 1941).

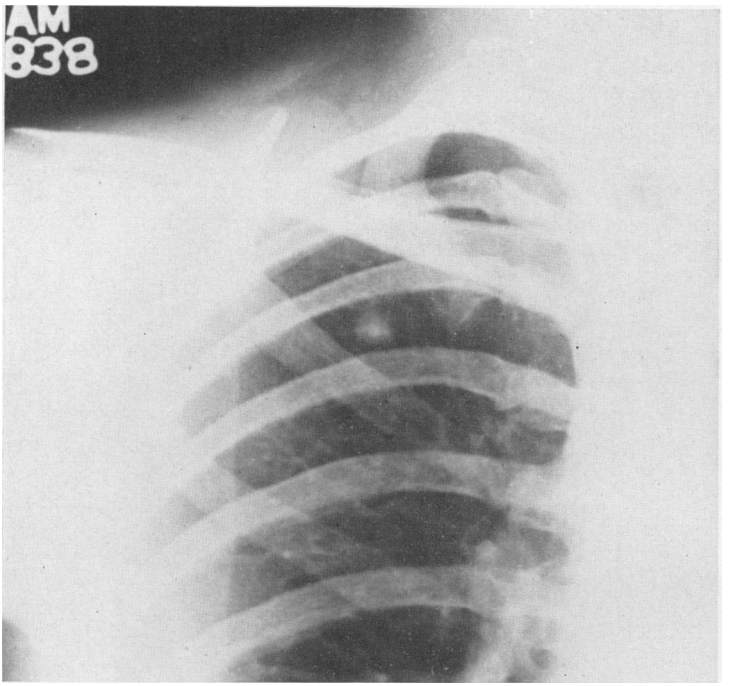


PLATE 1. Nodular infiltrate in the right first interspace. Unchanged over a period of 34 months. Tuberculin nonreactor, histoplasmin reactor.

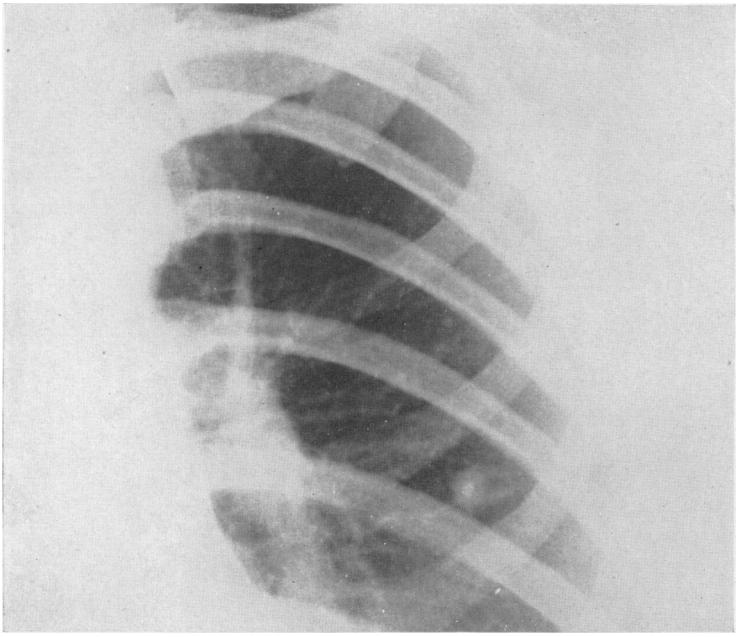


PLATE 2. Nodular infiltrate in the left third interspace associated with hilar adenopathy. Unchanged during 18 months of observation. Tuberculin nonreactor, histoplasmin reactor.

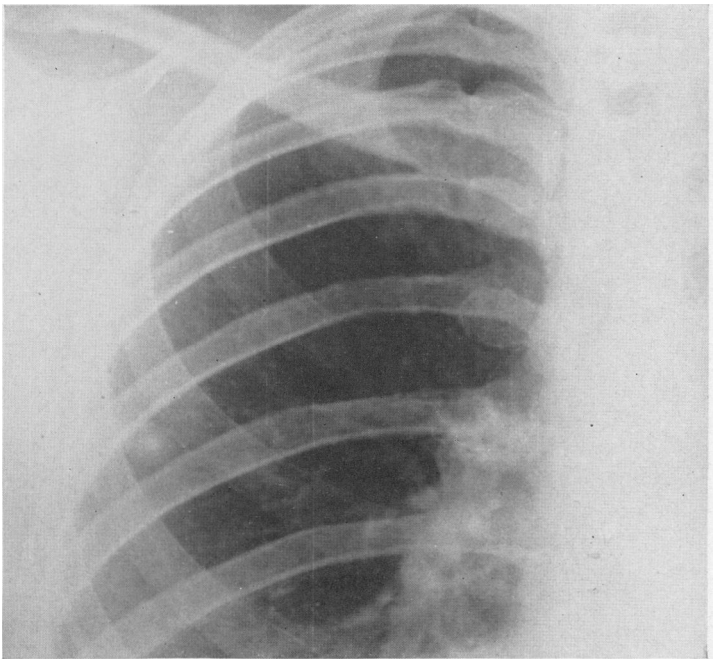


PLATE 3. Nodular infiltrate at the periphery of the right third interspace. Unchanged during 33 months of observation. Tuberculin nonreactor, histoplasmin reactor.

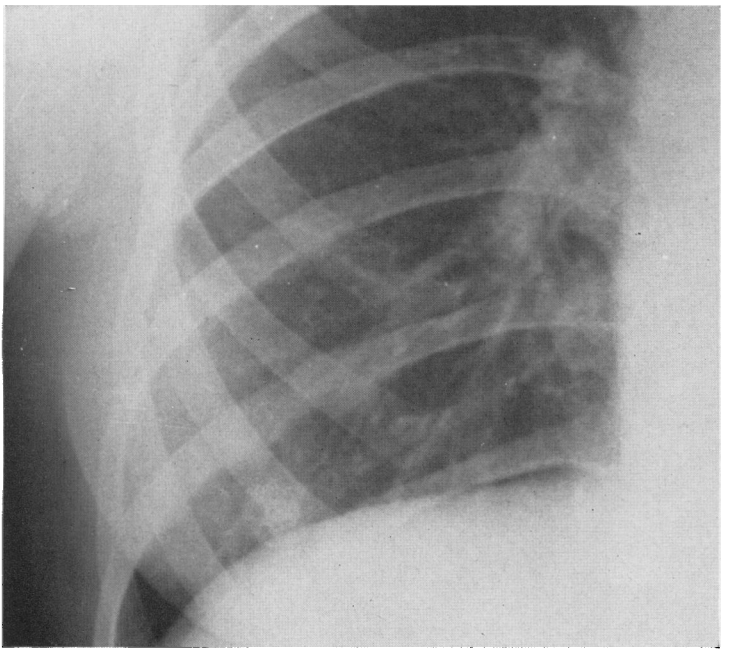


PLATE 4. Nodular infiltrate just above the dome of right diaphragm. Unchanged over period of 1 year. Tuberculin nonreactor, histoplasmin reactor.

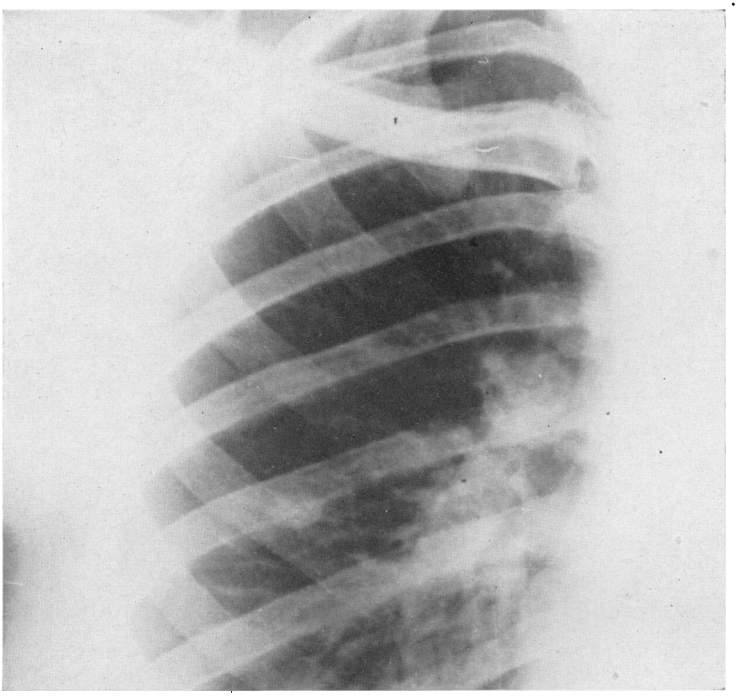


PLATE 5. Nodular infiltrate in the right midlung associated with hilar adenopathy. Unchanged over period of 1 year. Tuberculin nonreactor, histoplasmin reactor.

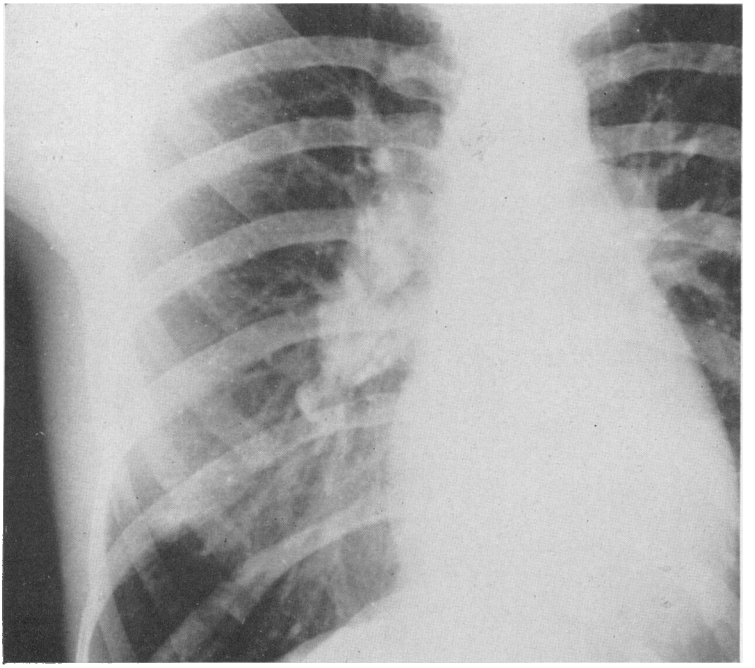


PLATE 6. Nodular infiltrate partially obscured by the 9th posterior rib associated with regional adenopathy. No change during more than 2 years of observation. Tuberculin nonreactor, histoplasmin reactor.

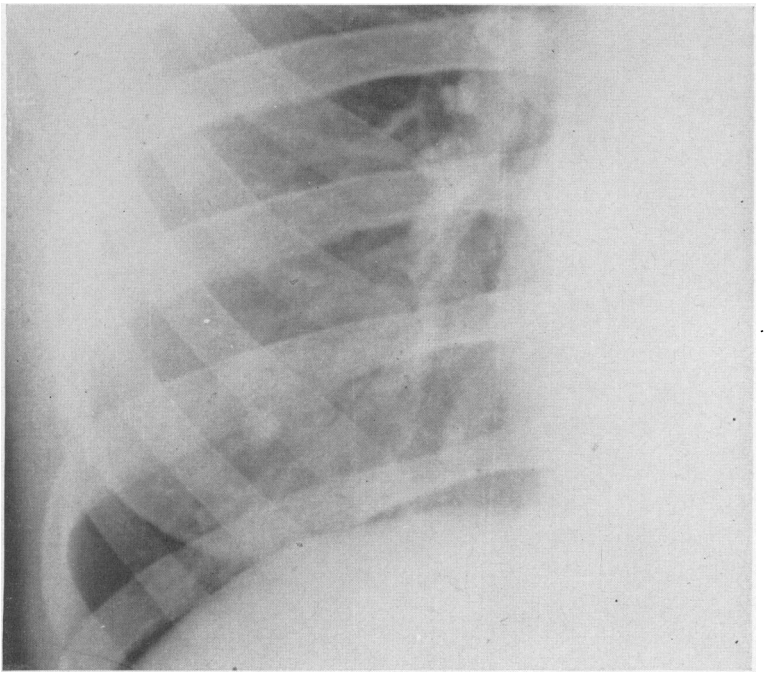


PLATE 7. Nodular infiltrate in the right lower lung. No follow-up. Tuberculin reactor, histoplasmin nonreactor.

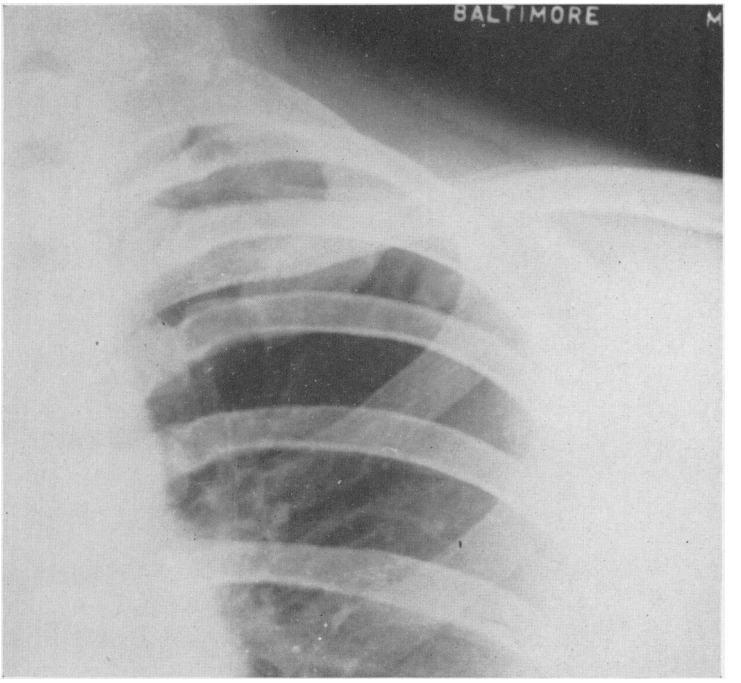


PLATE 8. Poorly circumscribed infiltrate in the left apex and first interspace. Later showed spread and contralateral involvement. Tuberculin reactor, histoplasmin nonreactor.

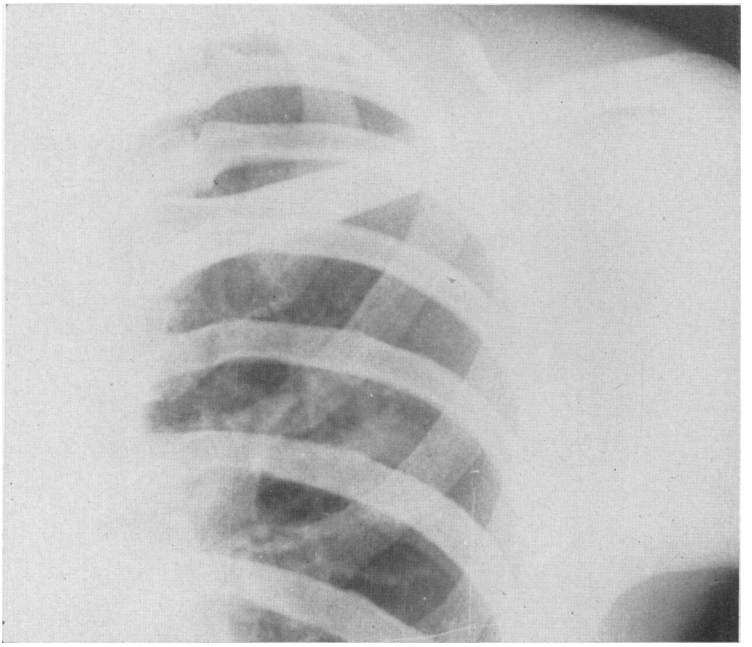


PLATE 9. Poorly circumscribed infiltrate in the left second interspace. Resolved, leaving residual fibrosis. Tuberculin reactor, histoplasmin nonreactor.

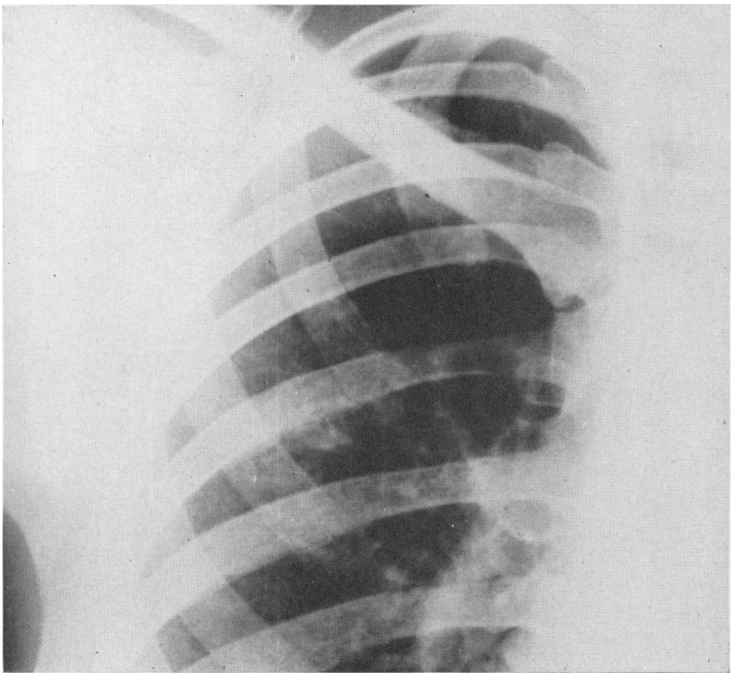


PLATE 10. Poorly circumscribed infiltrate in the right second interspace. Student discontinued training because of tuberculosis. Tuberculin reactor, histoplasmin nonreactor.

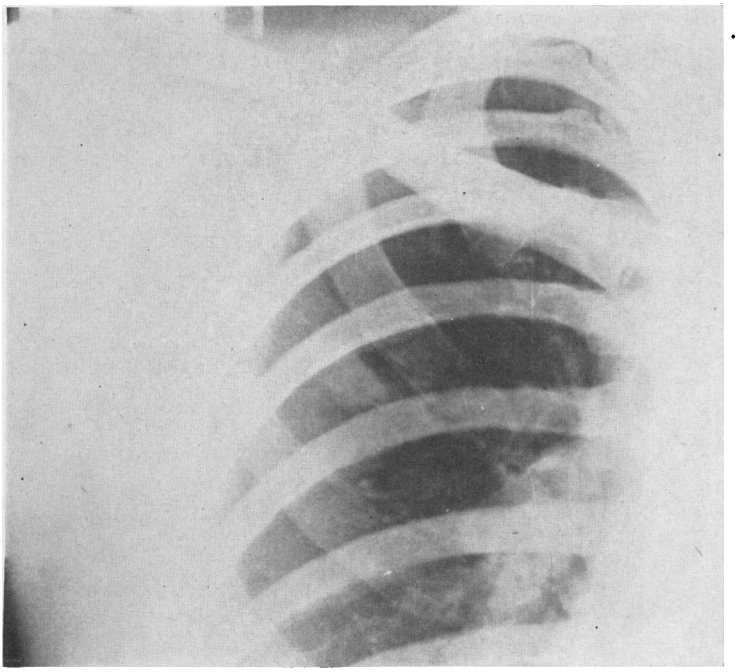


PLATE 11. Poorly circumscribed infiltrate in the right second interspace. After partial resolution, finally became a sharply circumscribed nodule. Tuberculin nonreactor, histoplasmin reactor

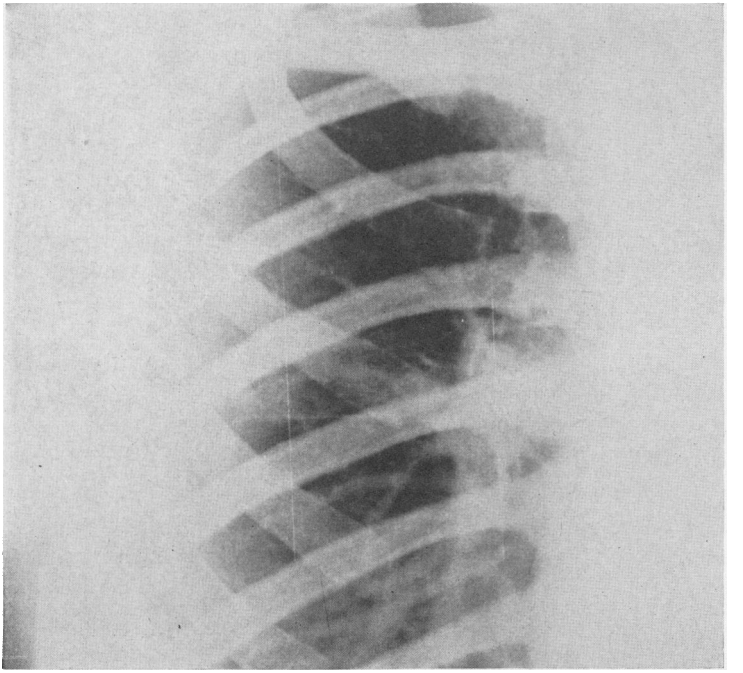


PLATE 12. Poorly circumscribed infiltrate in the right third interspace which went on to eventual fibrosis. Tuberculin nonreactor, histoplasmin reactor.

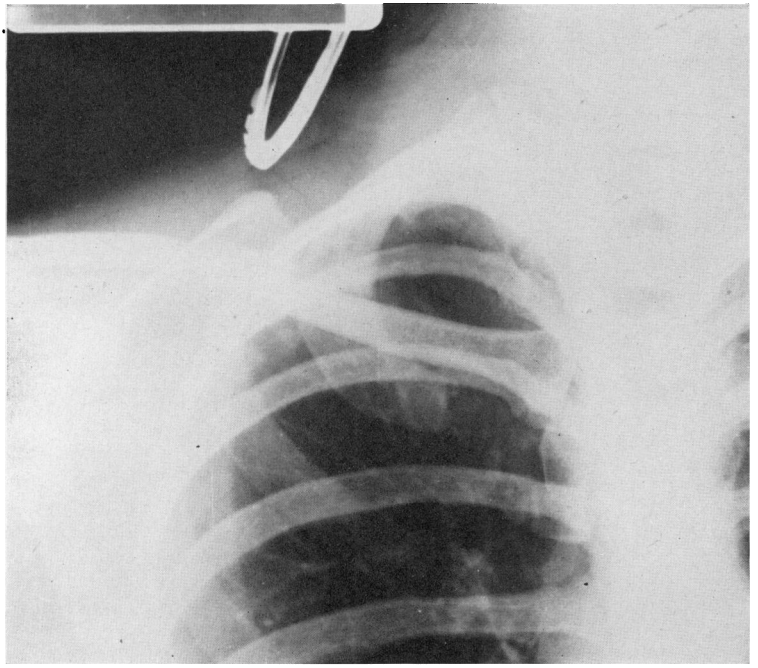


PLATE 13. Poorly circumscribed infiltrate in the right apex and right first interspace. Unchanged during 2 years of observation. Tuberculin nonreactor, histoplasmin nonreactor.

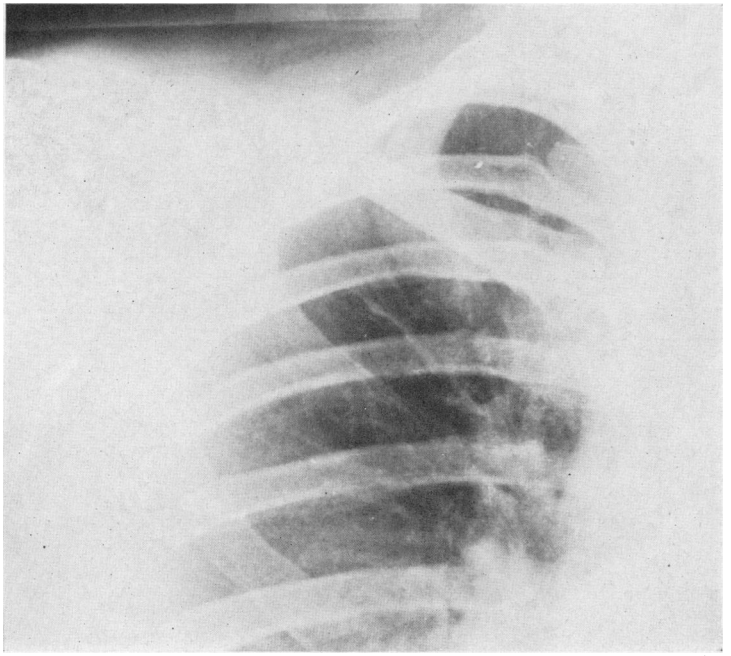


PLATE 14. Fibrosis in the right first interspace. No change in ensuing 16 months. Tuberculin nonreactor, histoplasmin nonreactor.

Appendix Table A. *Pulmonary infiltrates observed on X-ray among student nurses at beginning of training according to specified levels of sensitivity tuberculin and to histoplasmin*

Reaction to tuberculin		Reaction to histoplasmin									Total		
		No reaction			Erythema, questionable induration, or small definite induration			5 or more mm. definite induration					
		Total student nurses tested	Student nurses with infiltrates		Total student nurses tested	Student nurses with infiltrates		Total student nurses tested	Student nurses with infiltrates		Total student nurses tested	Student nurses with infiltrates	
0.0001 mgm. dose of PPD-S	0.005 mgm. dose of PPD-S		Number	Percent		Number	Percent		Number	Percent		Number	Percent
Less than 5 mm. definite induration	No reaction	1,320	5	0.38	46	2	4.3	306	22	7.2	1,672	29	1.7
	Erythema or questionable induration	5,031	12	0.24	258	3	1.2	1,450	90	6.2	6,739	105	1.6
	Small firm induration or soft induration	664	2	0.30	43	0	0.0	221	6	2.7	928	8	0.9
	10 or more mm. firm induration	502	2	0.40	30	0	0.0	143	5	3.5	675	7	1.0
	0.005 mgm. dose not administered	841	1	0.12	59	0	0.0	173	8	4.6	1,073	9	0.8
5–9 mm. definite induration		110	2	1.82	13	1	7.7	38	1	2.6	161	4	2.5
10 or more mm. definite induration		1,115	41	3.67	90	1	1.1	350	20	5.7	1,555	62	4.0
Total		9,583	65	0.68	539	7	1.3	2,681	152	5.7	12,803	224	1.75

Appendix Table B. *Pulmonary infiltrates (exclusive of the nonspecific group) observed on X-ray among student nurses at beginning of training according to tuberculin and histoplasmin reaction in each study area*

Study area	Total		Reaction group							
			Tuberculin nonreactors, histoplasmin reactors		Tuberculin reactors, histoplasmin nonreactors		Tuberculin reactors, histoplasmin reactors		Tuberculin nonreactors, histoplasmin nonreactors	
	Number tested	Number with infiltrates	Total number	Number with infiltrates	Total number	Number with infiltrates	Total number	Number with infiltrates	Total number	Number with infiltrates
Columbus, Ohio	1,147	44	612	36	51	4	77	3	407	1
Kansas City, Kans. and Mo.	1,628	49	837	36	85	2	137	8	569	3
Detroit, Mich.	1,084	25	131	11	115	10	24	3	814	1
Baltimore, Md.	1,468	26	317	18	179	5	57	1	915	2
New Orleans, La.	1,164	16	287	10	102	3	46	3	729	0
Denver, Colo.	807	10	55	2	100	6	16	0	636	2
Philadelphia, Pa.	1,455	13	161	8	213	2	50	2	1,031	1
Minneapolis and St. Paul, Minn.	1,966	17	123	7	112	6	25	2	1,706	2
Los Angeles, Calif.	1,285	8	144	4	164	2	47	1	930	1
San Francisco, Calif.	799	2	62	0	104	2	12	0	621	0
Total	12,803	210	2,729	132	1,225	42	491	23	8,358	13

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 NOVEMBER 13, 1948

A net decline of 285 (approximately 43 percent) was reported in the incidence of poliomyelitis for the current week, from 954 cases to 669. The 5-year (1943–47) median is 314, and in 1946, 490 cases were reported for the corresponding week, the highest figure for a corresponding week of the past 5 years. No State reported currently more than 30 cases except California, 198 (last week 276) and South Dakota, 90 (last week 111). Utah was the only State which reported an increase of more than 6 cases (from 8 to 26). The total for the year to date is 25,041, as compared with 23,431 for the corresponding period of 1946 and a 5-year median of 12,672. The average weekly decline during the past 8 weeks has been 10.9 percent, as compared with 13.6 percent for the corresponding weeks of 1946.

The net increase in the incidence of measles (from 2,384 cases last week to 2,761 currently, 5-year median 1,544) was largely accounted for in the reports of Massachusetts (522, last week 359), New York (192, last week 110), Michigan (170, last week 98), and Texas (261, last week 227). No other State reported more than 147 cases. The total since September 3, approximate average date of seasonal low incidence, is 13,740; the corresponding 5-year median is 8,562.

The incidence of influenza declined from 2,053 cases reported last week to 1,890 for the current week, of which Virginia reported 250 (last week 459), South Carolina 278 (last week 363), and Texas 1,004 (last week 856). The total since July 31 is 19,276 cases, 5-year median of 14,461.

Two cases of Rocky Mountain spotted fever were reported, 1 each in South Carolina and Alabama and 2 cases of anthrax, 1 each in Massachusetts and Arizona. One case of rabies in man was reported, in Louisiana. No case of smallpox was reported during the week.

Deaths recorded during the week in 93 large cities in the United States totaled 8,539, as compared with 8,991 last week, 9,342 and 8,691 for the corresponding weeks of 1947 and 1946, and a 3-year (1945–47) median of 8,836. The total for the year to date is 421,356, as compared with 421,332 for the corresponding period last year. Infant deaths totaled 625, as compared with 667 last week and a 3-year median of 721. The cumulative figure is 30,559, same period last year 33,884.

Telegraphic case reports from State health officers for week ended November 13, 1948

(Leaders indicate that no cases were reported)

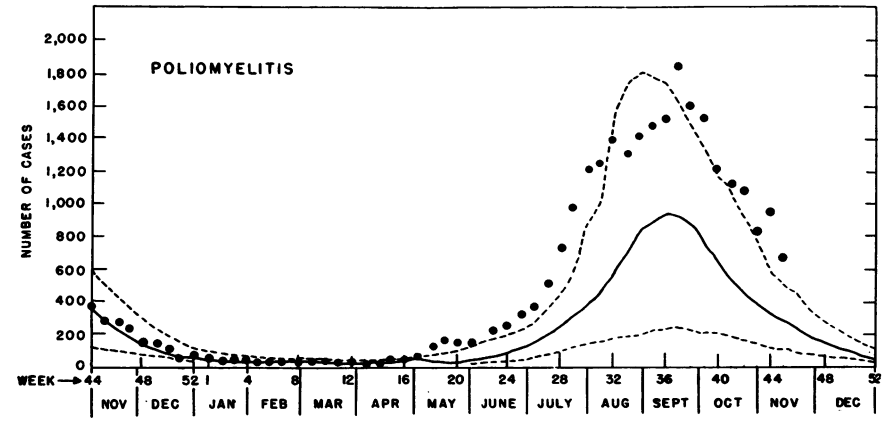
Division and State	Diphtheria	Encephalitis, infectious	Influenza	Measles	Meningitis, meningococcal	Pneumonia	Poliomyelitis	Rocky Mt. spotted fever	Scarlet fever	Smallpox	Tularemia	Typhoid and paratyphoid fever [d]	Whooping cough	Rabies in animals
NEW ENGLAND														
Maine	1			147	2	5			13				28	1
New Hampshire				1	1	1			4				8	
Vermont				55					5				5	
Massachusetts	10	2		522	1	22	1		84				62	
Rhode Island	1			13		4			[c] 6				3	
Connecticut			1	67	1	40	1		17			1	10	
MIDDLE ATLANTIC														
New York	3	3	[b] 4	192	6	152	20		[c] 98			2	112	15
New Jersey	1		3	68	5	64	15		44			1	39	2
Pennsylvania	9	1	(b)	96	3		13		91			1	77	1
EAST NORTH CENTRAL														
Ohio	4		2	46	2	33	19		163			1	32	13
Indiana	7		24	18		15	5		33		1		9	13
Illinois		1	1	19	3	85	19		75			1	28	1
Michigan [a]	4			170		36	21		115		1	3	29	
Wisconsin			1	135		10	20		19				18	
WEST NORTH CENTRAL														
Minnesota	2			6	1	11	30		41		1	2	1	
Iowa	3			13		2	28		27				1	
Missouri	6		2	19	1	9	8		21				4	
North Dakota	3			10	1		2		5				1	
South Dakota				2		1	90		1				1	
Nebraska			9	11	1	3	11		23				1	
Kansas	3		4	9	1	8	10		28			1	2	
SOUTH ATLANTIC														
Delaware				1					2					
Maryland [a]		1	1	64	3	41	[f] 5		14				23	
District of Columbia				6		11	2		5					
Virginia	8		250	57	3	52	12		18				21	1
West Virginia	10		10	23	1	1	3		[c] 25				25	
North Carolina	15			18	1		[f] 20		41			3	7	
South Carolina	10		278	5	1	64	4	1	8			2	7	
Georgia	19		9	5		17			24			8	1	3
Florida	9	1	4	9	1	19	8		11			2		10

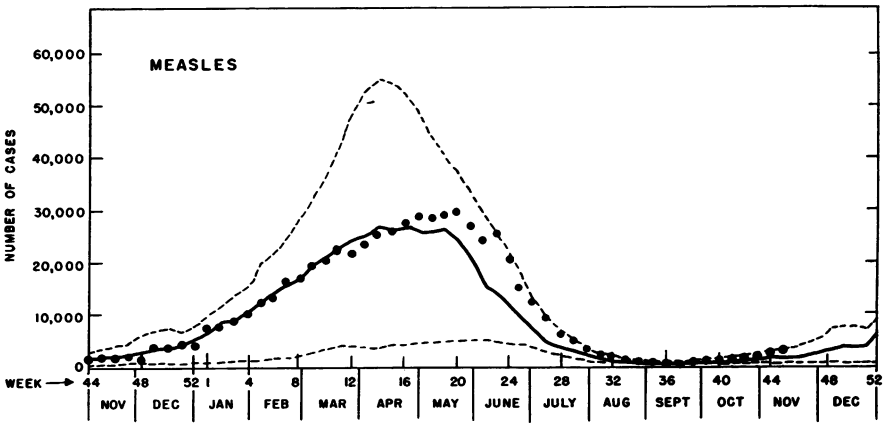
EAST SOUTH CENTRAL													
Kentucky	17			37	2	18	2		53			39	21
Tennessee	15		22	26	2	37	5		70		4	29	
Alabama	15		18	35		21	2	1	19	1	1	4	2
Mississippi [a]	8		11	3		12	1		8	2	2	5	
WEST SOUTH CENTRAL													
Arkansas	4		57	7	1	24	3		1		2	10	1
Louisiana	4	1	1	3	1	16			2		1		
Oklahoma	3		45	23	2	14	5		27			1	2
Texas	26		1,004	261	5	157	27		33	1	6	46	26
MOUNTAIN													
Montana			13	3		1	1		15		1	11	
Idaho			8	3		3	2		[c] 9			2	
Wyoming			6	102		2	2		2	1			
Colorado	1		27	61		12	2		6			2	
New Mexico	1		3	15		6	2		4		8	6	
Arizona	1		56		1	7	7						
Utah [a]	3			101		3	26		3	2		11	
Nevada				1			1						
PACIFIC													
Washington			2	50		2	7		20	1		5	
Oregon	7		7	101	1	6	9		14			9	
California	5	2	7	122	4	23	198		63		8	49	4
Total	238	12	1,890	2,761	58	1,070	669	2	1,410	11	61	785	
Median, 1943–47	405	12	1,683	1,544	104		314	3	2,609	4	8	76	2,299
Year to date, 45 weeks	8,220	502	158,091	565,154	2,823		[f] 25,041	512	65,595	54	831	3,203	67,312
Median, 1943–47	11,513	576	204,658	557,876	7,207		12,672	460	118,943	317	708	4,466	109,239
Seasonal low week ends	(27th) July 10		(30th) July 31	(35th) Sept. 4	(37th) Sept. 18		(11th) Mar. 20		(32d) Aug. 14	(35th) Sept. 4		(11th) Mar. 20	(39th) Oct. 2
Since seasonal low week	3,610		19,276	13,740	387		[f] 24,691		9,979	4		2,730	4,389
Median, 1943–47	5,249		14,461	8,562	712		12,275		18,893	37		3,842	11,703

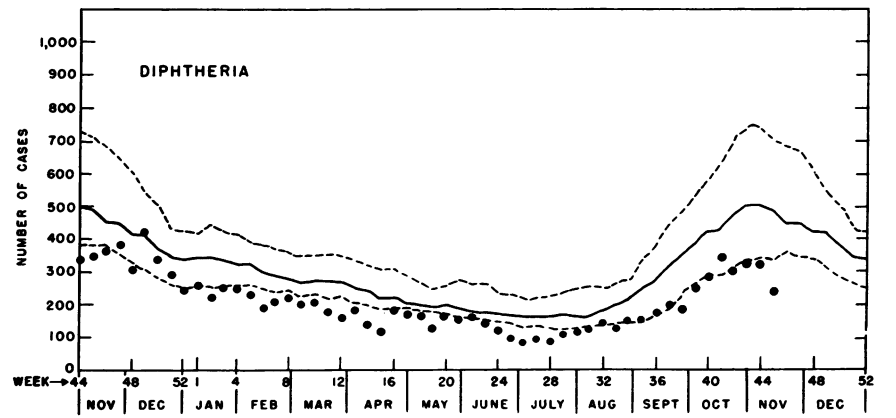
[a] Period ended earlier than Saturday.
[b] New York City and Philadelphia only, respectively.
[c] Including cases reported as streptococcal infections and septic sore throat.
[d] Including paratyphoid fever, reported separately, as follows: Connecticut 1; Michigan 1; Georgia 4; Texas 1; California 3.
[f] Corrections: Poliomyelitis, North Carolina, August, 177 cases (instead of 179); Maryland, October, 1 case deducted; Rocky Mt. spotted fever, Oklahoma, 2 cases delayed
Anthrax: Massachusetts 1; Arizona 1.
Rabies in man: Louisiana 1.
Alaska: No cases reported.
Territory of Hawaii: Measles 143.

Communicable Disease Charts

All reporting States, November 1947 through November 13, 1948







The upper and lower broken lines represent the highest and lowest figures recorded for the corresponding weeks in the 7 preceding years. The solid line is the median figure for the 7 preceding years. All three lines have been smoothed by a 3-week moving average. The dots represent numbers of cases reported for the weeks of 1948.

DEATHS DURING WEEK ENDED NOVEMBER 6, 1948

[From the Weekly Mortality Index, issued by the National Office of Vital Statistics]

	Week ended Nov. 6, 1948	Corresponding week, 1947
Data for 93 large cities of the United States:		
Total deaths	8,991	8,638
Median for 3 prior years	8,663	
Total deaths, first 46 weeks of year	412,817	411,990
Deaths under 1 year of age	667	688
Median for 3 prior years	688	
Deaths under 1 year of age, first 46 weeks of year	29,934	33,163
Data from industrial insurance companies:		
Policies in force	70,827,848	67,082,670
Number of death claims	10,319	9,359
Death claims per 1,000 policies in force, annual rate	7.6	7.3
Death claims per 1,000 policies, first 46 weeks of year, annual rate	9.2	9.2

TERRITORIES AND POSSESSIONS

Panama Canal Zone

Notifiable diseases—September 1948.—During the month of September 1948, certain notifiable diseases were reported in the Panama Canal Zone and terminal cities as follows:

Disease	Residence [1]									
	Panama City		Colon		Canal Zone		Outside the Zone and terminal cities		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Chickenpox	5		4		1		4		14	
Diphtheria	2		3		1		2		8	
Dysentery:										
Amebic			1				2		3	
Bacillary					4				4	
Hepatitis, infectious					2				2	
Influenza		1								1
Malaria [2]	3			1	11		191	1	205	2
Measles	1				1		2		4	
Meningitis, meningococcal			1	1	2		1		4	
Mumps	1				19				20	
Pneumonia		7		1	17			2	[3] 17	10
Relapsing fever							1		1	
Tuberculosis		12		3	5	1		7	[3] 5	23
Typhoid fever							4		4	
Typhus fever (murine)	1		1						2	
Whooping cough					3				[3] 3	
Yaws	1						1		2	

[1] If place of infection is known, cases are so listed instead of by residence.
[2] 5 recurrent cases.
[3] Reported in the Canal Zone only.

Puerto Rico

Notifiable diseases—5 weeks ended October 30, 1948.—During the 5 weeks ended October 30, 1948, cases of certain notifiable diseases were reported in Puerto Rico as follows:

Disease	Cases	Disease	Cases
Chickenpox	15	Syphilis	361
Diphtheria	46	Tetanus	5
Dysentery, unspecified	4	Tetanus, infantile	1
Gonorrhea	348	Tuberculosis (all forms)	565
Influenza	2,783	Typhoid fever	18
Malaria	81	Typhus fever (murine)	1
Measles	437	Whooping cough	98
Poliomyelitis	3		

Virgin Islands of the United States

Notifiable diseases—July–September 1948.—During the months of July, August, and September 1948, cases of certain notifiable diseases were reported in the Virgin Islands of the United States as follows:

Disease	July	August	September	Disease	July	August	September
Cancer	3		3	Pellagra		1	
Chickenpox		1	1	Pneumonia		1	
Gonorrhea	6	9	9	Schistosomiasis	1		1
Hookworm disease	2	2	1	Syphilis	26	20	13
Influenza	9	6		Trachoma		1	
Measles		1	1	Tuberculosis	3	1	6
Mumps	10	5					

FOREIGN REPORTS

CANADA

Provinces—Communicable diseases—Week ended October 23, 1948.—During the week ended October 23, 1948, cases of certain communicable diseases were reported by the Dominion Bureau of Statistics of Canada as follows:

Disease	Prince Edward Island	Nova Scotia	New Brunswick	Quebec	Ontario	Manitoba	Saskatchewan	Alberta	British Columbia	Total
Chickenpox		34		211	258	42	31	68		644
Diphtheria				5	5	4		1		15
Dysentery:										
Amebic						3				3
Bacillary				5						5
Encephalitis, infectious					1					1
German measles				7	7		3	2		19
Influenza		18			11	2				31
Measles		78	1	203	81	21	20	7		411
Meningitis, meningococcal				3	4					7
Mumps		11		134	101	38	4	3		291
Poliomyelitis			1		19	3	1	16		40
Scarlet fever		3	2	76	60	5	3	2		151
Tuberculosis (all forms)		4	11	126	22	19	5			187
Typhoid and paratyphoid fever				8						8
Undulant fever		1		6	2					9
Venereal diseases:										
Gonorrhea	1	10	12	106	105	26	20	32		312
Syphilis		5	14	79	53	9	2	7		169
Whooping cough				79	6	3	7	2		97

NOTE.—No report was received from British Columbia for the above period.

MADAGASCAR

Notifiable diseases—September 1948.—Notifiable contagious diseases were reported in Madagascar and Comoro Islands during September 1948 as follows:

Disease	September 1948			
	Aliens		Natives	
	Cases	Deaths	Cases	Deaths
Bilharziasis	0	0	149	0
Cerebrospinal meningitis	0	0	14	
Diphtheria	0	0	1	0
Dysentery, amebic	7	0	210	0
Erysipelas	1	0	14	0
Influenza	25	0	3,589	58
Leprosy	0	0	35	0
Malaria	513	2	32,330	257
Measles	0	0	101	0
Mumps	0	0	147	0
Plague	0	0	13	12
Pneumonia, broncho	0	0	310	55
Pneumonia, pneumococcic	6	0	726	145
Poliomyelitis	0	0	9	0
Puerperal infection	0	0	7	0
Trachoma	0	0	3	0
Tuberculosis, pulmonary	4	1	125	21
Typhoid fever	1	0	7	
Whooping cough	0	0	126	

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

Note.—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

India.—Cholera has been reported in Madras City, India, as follows: Week ended October 23, 1948, 94 cases, 14 deaths; week ended October 30, 49 cases; 7 deaths, week ended November 6, 29 cases. For the week ended October 16, 1948, 16 cases with 2 deaths were reported in Masulipatam, and for the week ended October 23, 70 cases with 31 deaths were reported in Calcutta.

Pakistan—Chittagong.—During the week ended November 6, 1948, 6 cases of cholera with 3 deaths were reported in Chittagong, Pakistan.

Plague

Belgian Congo—Stanleyville Province.—On October 23, 1948, 1 fatal case of plague was reported in the village of Bi, west of Blukwa, in Stanleyville Province, Belgian Congo.

British East Africa—Tanganyika.—During the week ended October 9, 1948, 3 cases of plague and 4 deaths (including 1 death which occurred the preceding week) were reported in Central Province, Tanganyika Territory, British East Africa.

Indochina (French).—Plague has been reported in French Indochina as follows: In the state of Annam—For the week ended September 25, 1948, 14 cases, 8 deaths; for the period October 1–31, 30 cases, 15 deaths; in the Mountain Provinces of South-Indochina—week ended October 16, 1948, 3 cases, 1 death; week ended October 23, 4 cases, 2 deaths; week ended October 30, 3 cases.

Java—Jokjakarta Residence.—During the period September 5–26, 1948, 139 fatal cases of plague were reported in Jokjakarta Residence, Java.

Union of South Africa—Orange Free State.—During the week ended October 30, 1948, 2 cases of plague were reported at Verdeeld Farm, Kopies District, in the Orange Free State, Union of South Africa.

Smallpox

British East Africa—Nyasaland.—Smallpox has been reported in Nyasaland as follows: Week ended October 16, 1948, 161 cases, 26 deaths, including 57 cases, 10 deaths in Fort Johnston, and 18 cases, 6 deaths in Blantyre; week ended October 23, 114 cases, 17 deaths, of which 50 cases, 6 deaths were reported in Blantyre, and 29 cases, 10 deaths in Fort Johnston.

Iran.—During the week ended October 9, 1948, 37 cases of smallpox with 12 deaths were reported in Iran.

Italy—Milan.—During the month of October 1948, 4 cases of smallpox were reported in the city of Milan, Italy—1 case imported from the Orient and 3 contacts.

Syria.—During the week ended October 23, 1948, 38 cases of smallpox were reported in Syria.

Togo (French).—During the period October 11–20, 1948, 16 cases of smallpox with 1 death were reported in French Togo.

Typhus Fever

Canada—Toronto—Correction.—The report of 1 case of typhus fever in Toronto, during the week ended October 15, 1948 (Public Health Reports November 12, 1948, p. 1505) was in error. Later information stated that it was a case of typhoid fever.

NOTE: No reports received on yellow fever.

×