The prevalence of tuberculin sensitivity indicates a high infection rate in the lower Yukon area. Comparison with results in two Southern States suggests that tuberculin reactions should be interpreted according to the prevalence of nonspecific sensitivity.

Tuberculin Sensitivity and Tuberculosis Among Natives of the Lower Yukon

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TUBERCULOSIS has been the major health problem of Alaska natives for a long time. Only in the past few years can it be considered to have been brought under control in the sense that facilities for diagnosis, isolation, and treatment of infectious cases are now reasonably adequate.

Aside from the obvious fact that the prevalence of tuberculous infection and disease is extremely high, little is known of the epidemiological aspects of tuberculosis among the native population. Some information regarding tuberculin sensitivity among Alaska natives was obtained during two BCG vaccination programs, one by Aronson in southeastern Alaska in 1938 (*1*) and the other by the Alaska Department of Health from 1948 to 1951 (*2*).

Because of the limited information on this subject, it appeared desirable to report the results of a tuberculin survey of the villages along the Yukon River during the spring of 1957. In addition, the relationship of the size of tuberculin reaction to the prevalence of tuberculosis in this and other populations has important implications for the interpretation of tuberculin sensitivity.

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Material and Methods

The original purpose of the tuberculin testing was to obtain baseline data regarding the prevalence of infection prior to the initiation of a controlled trial of isoniazid prophylaxis in the Bethel area of Alaska. This area included the deltas of the Yukon and Kuskokwim Rivers, and is bounded on the west by the Bering Sea, and in the interior by lines from Goodnews Bay and Unalakleet to McGrath (fig. 1). Because the testing teams were available for only a short time before the spring breakup of ice would make travel temporarily impossible, their efforts were concentrated in the villages in the northern half of the area to take advantage of the fact that breakup normally occurs a little later along the Yukon than along the Kuskokwim.

The tests were given and read by three experienced nurses from the tuberculosis program of the Public Health Service, assisted by the

staff of the ambulatory chemotherapy program of the Arctic Health Research Center. All participants were given 5 tuberculin units (T.U.) (0.0001 mg.) of PPD–S. In most instances, the tests were read on the second day; a few readings on the third day have also been included. The transverse diameters of both erythema and induration were carefully measured and recorded to the nearest millimeter.

According to the most recent village rosters, which were brought up to date at the time of the testing, 2,930 persons resided in the 19 villages selected for testing. Tests and readings were completed satisfactorily for 2,285 persons, or 78 percent of the total population, and 91 percent of those at home on the day of the tests (table 1). Many of the remaining 9 percent who did not come in for testing or reading lived far enough from the village centers that they could not come when traveling conditions were poor. The largest group of nonparticipants were those classified as "working or visiting," a large proportion of whom were away on hunting trips. It is likely that many of these persons would have participated if it had been possible to set up a definite schedule in advance of the arrival of the testing teams.

The study population has been restricted to natives of the selected villages with completed tests and identification data. In addition to nonparticipants, 72 whites have been excluded,

Table 1. Participation in the tuberculin testing survey among natives of the lower Yukon, 1957

Participation category	Number	Percent
Total population of villages	2,930	100.0
Persons with completed test	2,285	78.0
Persons with no or incompleted test	645	22.0
In village on day of test	225	7.7
Tested, no reading	75	2.6
Sick at home	16	.5
Did not come for test	129	4.4
Known refusals	5	.2
Away on day of test	420	14.3
Hospitalized	112	3.8
In boarding school	52	1.8
Working or visiting	256	8.7

Figure 1. Villages participating in the tuberculin testing survey in the Bethel area of Alaska, 1957.

as have 2 natives for whom no birth date was available. The study population thus consists of 2,211 persons, 1,777 of whom are classified as Eskimo, 429 Indian, and 5 as mixed Eskimo and Indian. Many of each race have some admixture of white blood.

Results

In order to interpret the results of any tuberculin testing survey, it is necessary to consider the problem of nonspecific tuberculin sensitivity, since it is now clear that the true extent of tuberculous infection in a population can be masked by the coexistence of tuberculin sensitivity resulting from infection with other organisms (*3*). Some evidence on this point was available prior to the survey.

First, atypical acid-fast organisms classified as photochromogens or nonphotochromogens have not been observed in specimens from patients at the Alaska Native Health Service Hospital in Anchorage, even though

scotochromogens were not uncommon. Although this sort of negative evidence is not conclusive, neither can it be entirely ignored, since it is based on work done by Alice Timpe, Alaska Native Health Service, Anchorage, a bacteriologist experienced in the recognition of atypical acid-fast bacilli (*4*). It does suggest that presently recognized and naturally occurring sources of nonspecific tuberculin sensitivity are probably not highly prevalent in this population.

We expected to find tuberculin sensitivity resulting from BCG vaccination—in some respects the prototype of nonspecific sensitivity—in this population, since BCG vaccination had been done sporadically since 1949 in the Bethel area. It was therefore necessary to identify as accurately as possible the persons in the study population who had been vaccinated and those who had not. This was accomplished by matching, for the tested villages, the tuberculin test records with the vaccination files of the Alaska Department of Health and the ambulatory chemotherapy program of the Arctic Health Research Center.

It is considered that the identification of those who were vaccinated is quite accurate, but a few persons may have been vaccinated without this fact having been recorded, while others may have been vaccinated in villages not included in the testing program. Consequently, some persons classified in this study as unvaccinated may in fact have been vaccinated. We believe that this is not an appreciable source of error except for those under 10 years of age in 1957.

The choice of antigen used for testing is also related to the subject of nonspecific sensitivity, since some antigens detect nonspecific sensitivity better than others. In this survey, the standard antigen given to everyone in the study population was 5 T.U. of PPD–S. In addition, 301 participants were also given an equivalent dose of a PPD prepared from an organism originally classified as a *Nocardia* but later found by others to resemble a *Mycobacterium* (*5*, *6*). The reactions to this antigen, PPD–C, reflect some types of nonspecific sensitivity much better than do those to PPD–S (*7*). Among the 301 persons tested with both antigens, 243 showed some induration to one or both preparations. Sixty persons reacted only to PPD–S; four reacted only to PPD–C. Of the 179 reacting to both, only 1 had a significantly larger reaction to PPD–C than to PPD–S. These findings suggest that the kind of nonspecific sensitivity detectable by PPD–C is uncommon in this population.

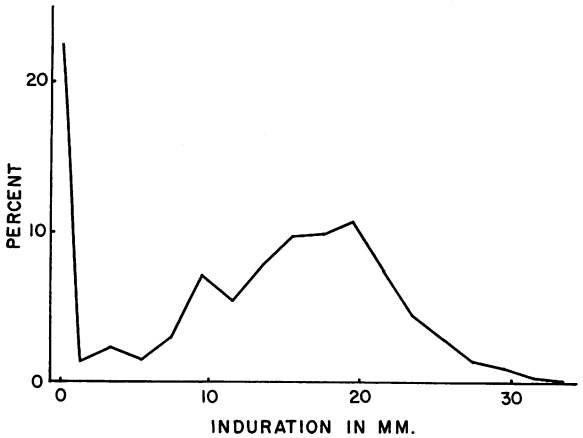
Perhaps the question of whether or not the lower Yukon natives manifest nonspecific sensitivity to the 5-T.U. dose of PPD–S is best answered by the characteristics of the frequency distributions of reaction sizes to this antigen (table 2, fig. 2). The curve of the percentage distribution for the entire study population is bimodal, with 23 percent showing no induration to 5 T.U. of PPD–S. Of those with some induration, there are more persons with very small reactions than with very large reactions. This was noted by each of the three readers and suggests that there is some nonspecific sensitivity in this population, for it seems reasonable to believe that reactions from a single, specific infection would approximate

Table 2. Distribution of sizes of reactions to 5 T.U. PPD–S among natives of the lower Yukon, 1957

Size of induration (mm.)	Total study population	0–14 years		15 years or older	
		Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
Total	2, 211	908	321	953	29
0, E [1]	501	343	129	27	2
1, 2	31	16	11	4	0
3, 4	51	23	18	9	1
5, 6	35	4	5	25	1
7, 8	67	22	7	37	1
9, 10	159	45	14	97	3
11, 12	124	38	9	75	2
13, 14	170	53	14	101	2
15, 16	217	73	22	117	5
17, 18	219	64	16	135	4
19, 20	236	90	28	115	3
21, 22	165	54	26	80	5
23, 24	100	36	7	57	0
25, 26	64	20	6	38	0
27, 28	33	11	6	16	0
29, 30	22	11	0	11	0
31, 32	9	2	1	6	0
33, 34	3	2	0	1	0
35, 36	1	0	0	1	0
37, 38	1	0	11	0	0
39, 40	2	0	1	1	0
48	1	1	0	0	0

[1] E=Erythema only.

Figure 2. Distribution of sizes of reactions to 5 T.U. PPD–S among 2,211 natives of all ages, lower Yukon area, 1957.



a normal curve of distribution, and that excess reactions of any size would very likely have been caused by something else.

It has already been mentioned that some nonspecific sensitivity resulting from BCG vaccination might be expected in this population. To investigate this possibility, it is first necessary to establish a baseline, which is provided by the distribution of reaction sizes among persons over the age of 15 years who had no history of vaccination (table 2, fig. 3).

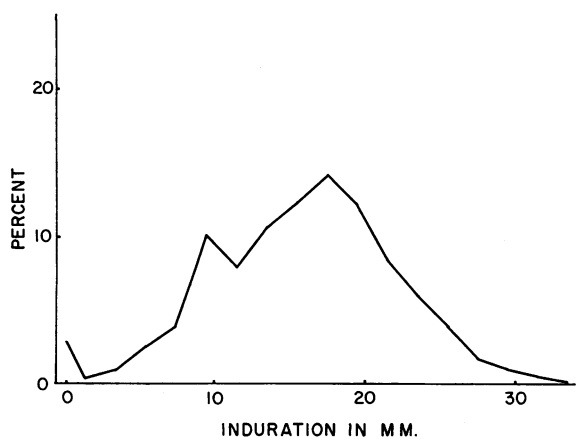
Except for a spur at 9–10 mm. of induration (which appears to be the result of terminal digit preference), the distribution closely approximates a normal one, and is consistent with the notion that the tuberculin test is measuring sensitivity to a single specific infection. Indeed, this distribution, with a mean reaction size of 15.9 mm., is almost the same as those found among patients in tuberculosis hospitals (*8*). Consequently, we have further reason to believe that there is little, if any, nonspecific sensitivity among unvaccinated persons in this area of Alaska which can be detected by the 5-T.U. dose of PPD–S.

The amount of nonspecific sensitivity resulting from previous BCG vaccination can be estimated from a comparison of the distribution of reaction sizes among vaccinated and unvaccinated persons. Because very few adults had been vaccinated, it is necessary to restrict the comparison to persons under the age of 15 years. Among both groups, the vaccinated and the unvaccinated, about 40 percent had no reaction at all to 5 T.U. of PPD–S (table 2, fig. 4). The most apparent difference between the two groups is that 9 percent of the vaccinated had reactions of 1–4 mm. in diameter, whereas only 4 percent of the unvaccinated had reactions of this size. If the comparison is limited to persons with reactions of 5 mm. in diameter or larger, the percentage distributions for the vaccinated and unvaccinated are very similar and do not differ significantly.

Since both distributions are also very similar to that for unvaccinated adults, it seems reasonable to infer that in the lower Yukon area reactions of 5 mm. or larger to the 5-T.U. dose of PPD–S reflect sensitivity resulting from natural infection. For if postvaccinal sensitivity were as strong as that resulting from natural infection, one would not expect to find an excess of very small reactions among the vaccinated without a concomitant excess of larger reactions. The most reasonable explanation of the observed finding is that vaccination in this population resulted in a low level of allergy, and that the spectrum of reactions larger than 5 mm. is probably the result of natural infection which may or may not be superimposed on postvaccinal sensitivity.

That there was in fact a low conversion rate attributable to vaccination is suggested by an examination of the proportion of those with reactions of 5 mm. or more induration among

Figure 3. Distribution of sizes of reactions to 5 T.U. PPD–S among 953 unvaccinated natives, 15 years or older, lower Yukon area, 1957.



the 350 vaccinated persons of all ages. Sixty of these persons had been vaccinated in 1956, or less than 16 months prior to testing (table 3). Only 11, or 18 percent, had reactions of 5 mm. or more in diameter. Although the proportion of reactors increases markedly as the time between vaccination and testing lengthens, this increase is about what would be expected from the natural infection rate in these communities. These findings suggest that either the vaccine used, or the conditions of vaccination, or both, resulted in a very low level of tuberculin sensitivity from vaccination.

Furthermore, aside from the low proportion of small reactions attributable to vaccination, it seems fair to conclude that there is probably no nonspecific sensitivity in this population which can be detected by the 5-T.U. dose of PPD–S. Consequently, estimates of the prevalence of tuberculous infection will not be very far wrong if they are based on reactions of 5 mm. or more in diameter. Smaller reactions may be either the result of vaccination or the "left hand tail" of the distribution of reactions from specific infection. In some respects this is a most fortunate circumstance, for had BCG vaccination been as effective in causing tuberculin conversions in this population as it has been reported to be in other vaccinated groups, the interpretation of tuberculin sensitivity would have been made much more difficult, and in some respects, impossible.

The prevalence of tuberculous infection in the study population may now be considered, defining a reactor as anyone with 5 mm. or more of induration. Females had slightly

Figure 4. Distribution of sizes of reactions to 5 T.U. PPD–S among 908 unvaccinated and 321 vaccinated natives under 15 years, lower Yukon area, 1957.

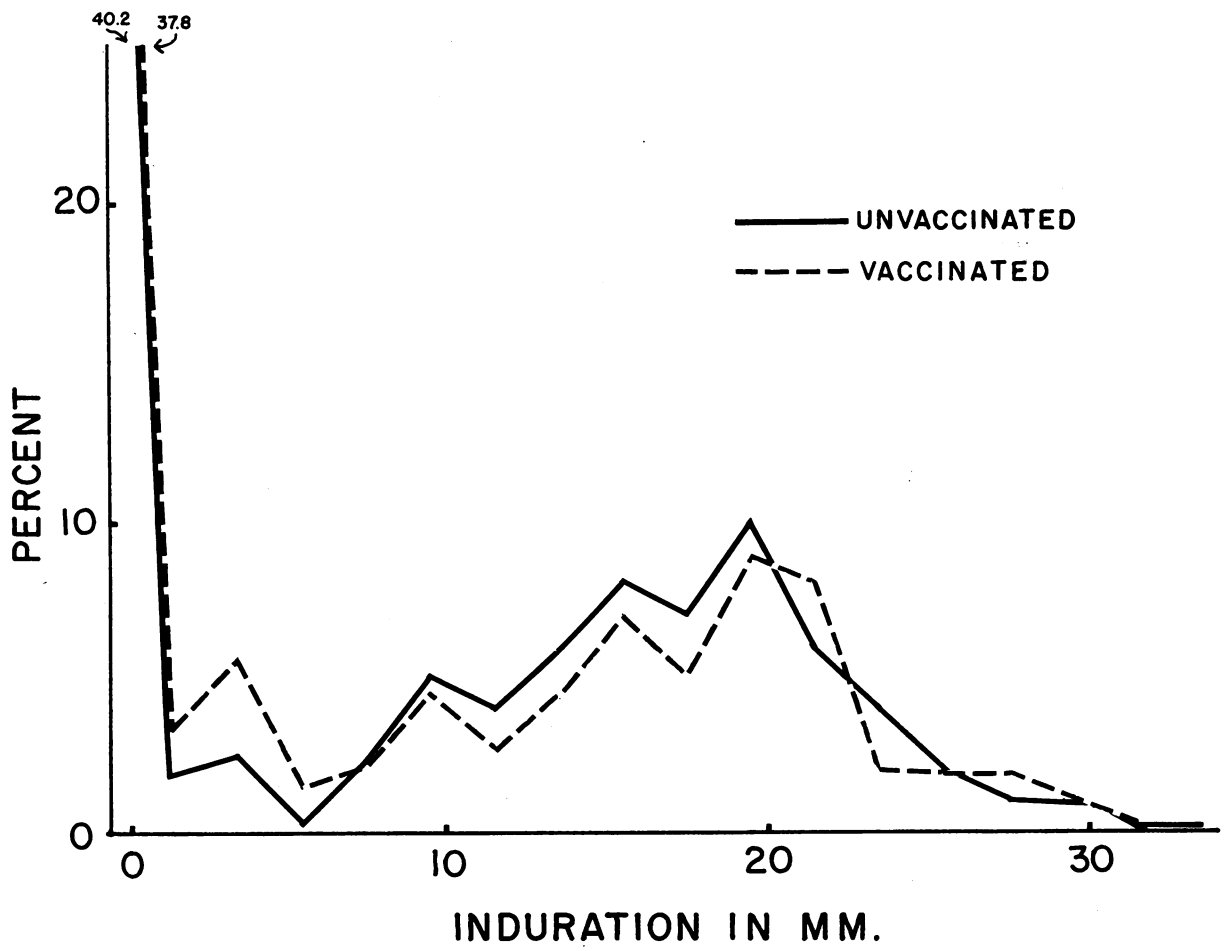


Table 3. Vaccinated natives with reactions of 5 mm. or more induration to 5 T.U. PPD–S, lower Yukon area, 1957, by year of vaccination

Year of vaccination	Total vaccinated persons	Persons with 5 mm. or more induration in 1957	
		Number	Percent
Total	350	189	54.0
1956	60	11	18.3
1955	24	6	25.0
1952	102	52	51.0
1951	17	10	58.8
1949	140	107	76.4
Other [1]	7	3	--------

[1] Includes 4 with vaccination year not stated; 1 each vaccinated in 1950, 1953, and 1954.

larger tuberculin reactions on the average than males. There were no significant differences between Eskimos and Indians, a finding in apparent disagreement with that reported by Weiss (*2*), who found somewhat lower reactor rates among interior Indians than among Eskimos of the Yukon and Kuskokwim deltas. However, his populations were drawn from a larger area than that of this study.

There were tremendous differences in tuberculin sensitivity with age (table 4, fig. 5). The prevalence of reactors was 22 percent in the age group 0–4 years, and it increased rapidly up to the age group 15–19 years, which had a prevalence of 96 percent. This high level was maintained to 65 years, with a moderate decrease among older persons. Among persons with a history of vaccination, except in the youngest age group where the prevalence among the vaccinated was slightly but not significantly higher, the prevalence of positive reactions was generally lower than among persons classified as unvaccinated. At first glance, this seems to be a disturbing finding. But when it is recalled that the vaccinated had been previously selected as negative reactors, that vaccination appears to have caused relatively little sensitivity, and that the subjects were presumably exposed thereafter to a very high natural infection rate, the differences between the vaccinated and the unvaccinated in this respect appear more reasonable.

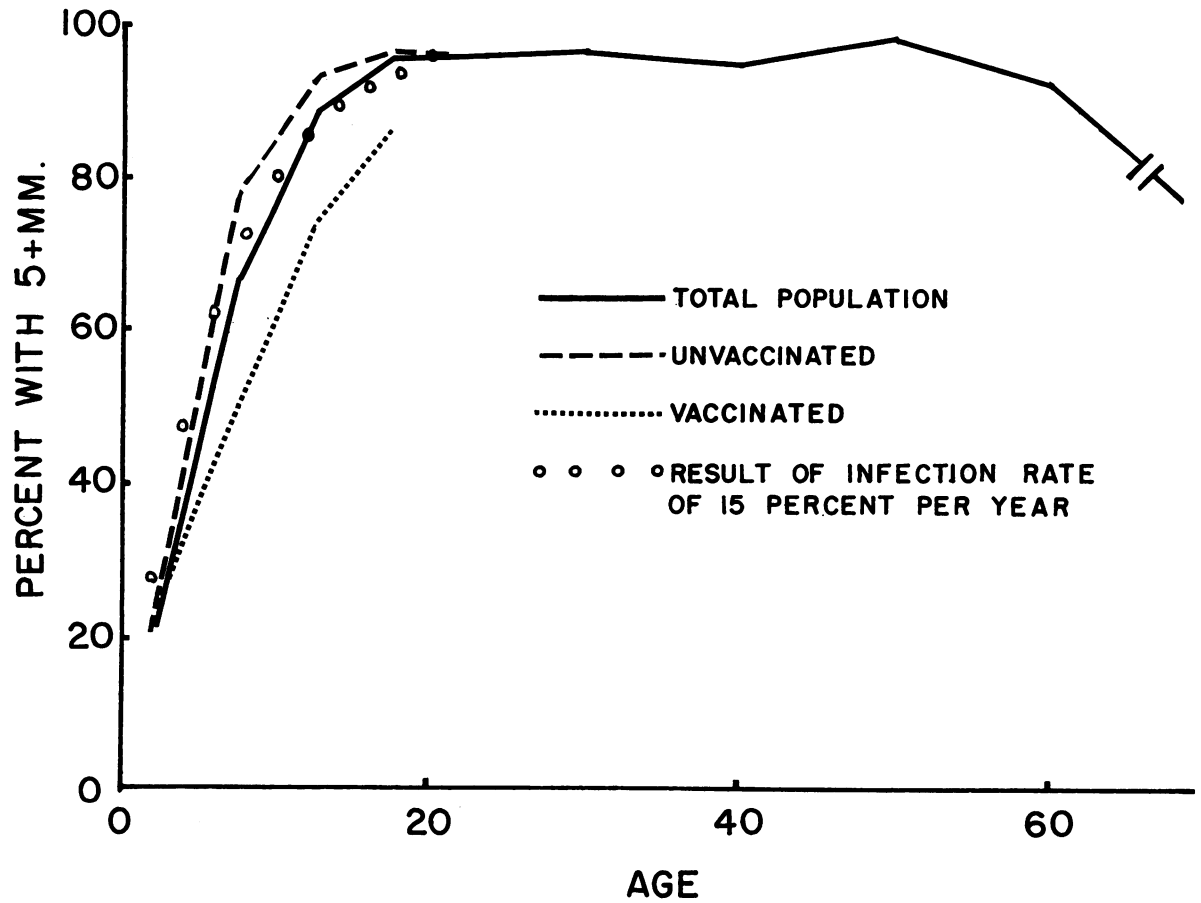
Because of vaccination, even though its effects were not great, it is impossible to ascertain with certainty the infection rate that has prevailed among this population in recent years. However, it can be shown that a prevalence ratio of 96 percent at age 20 can only be achieved by an average infection rate of 15 percent per year. The prevalence resulting from this theoretical rate is indicated by open circles in figure 5. Vaccination cannot affect this average rate since practically no one older than 20 years had been vaccinated.

The average infection rate experienced by

Table 4. Natives with reactions of 5 mm. or more to 5 T.U. PPD–S, by age and vaccination status, lower Yukon area, 1957

Age in 1957 (years)	Total			Unvaccinated			Vaccinated		
	Persons tested	5 mm. or more		Persons tested	5 mm. or more		Persons tested	5 mm. or more	
		Number	Percent		Number	Percent		Number	Percent
Total	2,211	1,628	73.6	1,861	1,439	77.3	350	189	54.0
0–4	460	99	21.5	389	81	20.8	71	18	25.4
5–9	436	293	67.2	265	207	78.1	171	86	50.3
10–14	333	297	89.2	254	238	93.7	79	59	74.7
15–19	220	211	95.9	197	191	97.0	23	20	87.0
20–24	160	154	96.2	158	152	96.2	2	2	--------
25–34	227	221	97.4	227	221	97.4	0	0	--------
35–44	167	160	95.8	166	159	95.8	1	1	--------
45–54	103	102	99.0	103	102	99.0	0	0	--------
55–64	60	56	93.3	58	54	93.1	2	2	--------
65 or over	45	35	77.8	44	34	77.3	1	1	--------

Figure 5. Natives with reactions of 5 mm. or more to 5 T.U. PPD–S, by age and vaccination status, lower Yukon area, 1957.



younger persons is more problematical. If one accepts that vaccination in this particular instance did not appreciably affect the proportion of persons with reactions of 5 mm. or more in diameter, it would be reasonable to utilize the experience of the total group as reflecting the prevalence of tuberculous infection at various ages.

In any event, since an average annual infection rate of 15 percent would produce the observed prevalence at age 20, and since the points on the observed curves fall progressively below the theoretical ratio as age decreases below 20 years, it seems likely that the infection rate 20 years ago was appreciably higher than 15 percent, and that more recently it has fallen to a much lower level, possibly in the neighborhood of 5 percent per year. This is still a much greater infection rate than that reported for the United States as a whole, which has been estimated to be about 0.1 percent per year at the present time (*9*).

The definition of a positive reactor accepted in the preceding sections was an arbitrary one, based partly on the fact that the 5-mm. level of reaction excluded the most noticeable effects of vaccination, and partly on common usage. However, for some time the wisdom of using the same definition of a positive reactor in all areas has been questioned. In areas where nonspecific sensitivity is very common, defining positive reactors as those persons with 5 mm. or more of induration to the 5-T.U. dose may classify so many persons with false positive (nonspecific) reactions among the positive group that the separation of true positives from true negatives is very unsatisfactory. On the other hand, in areas where there is little or no nonspecific sensitivity, the same definition of positive reactors may yield a relatively pure

group of truly infected persons, but the group classified as negative may also include a number of infected persons. Some evidence that this does, in fact, occur may be gathered from comparing the frequency of tuberculous disease among persons with different sizes of tuberculin reactions in two geographic areas.

The experience of Muscogee County, Ga., and Russell County, Ala., where there appears to be a great deal of nonspecific sensitivity to the 5-T.U. dose may be contrasted with that of the lower Yukon area where there appears to be very little. In the spring of 1950 a tuberculin testing and chest X-ray survey was conducted in Muscogee and Russell Counties, in which the participants received 5 T.U. of PPD (RT XIX–XXI, supplied by the State Serum Institute, Copenhagen, Denmark).

All persons classified as having suspected or definite tuberculosis on the basis of the survey followup examination had their records and films reviewed after 6 years of observation. The followup examinations were quite extensive for most of them, but for a few they consisted only of a single, large chest film. On the basis of the available evidence—extensive or scanty—but without consideration of the tuberculin sensitivity of the subjects at the time of the survey, a decision was made as to whether or not the findings appeared to have warranted classifying persons as tuberculous or suspected of having tuberculosis. Persons so classified on the basis of this retrospective review are counted as cases in the present analysis.

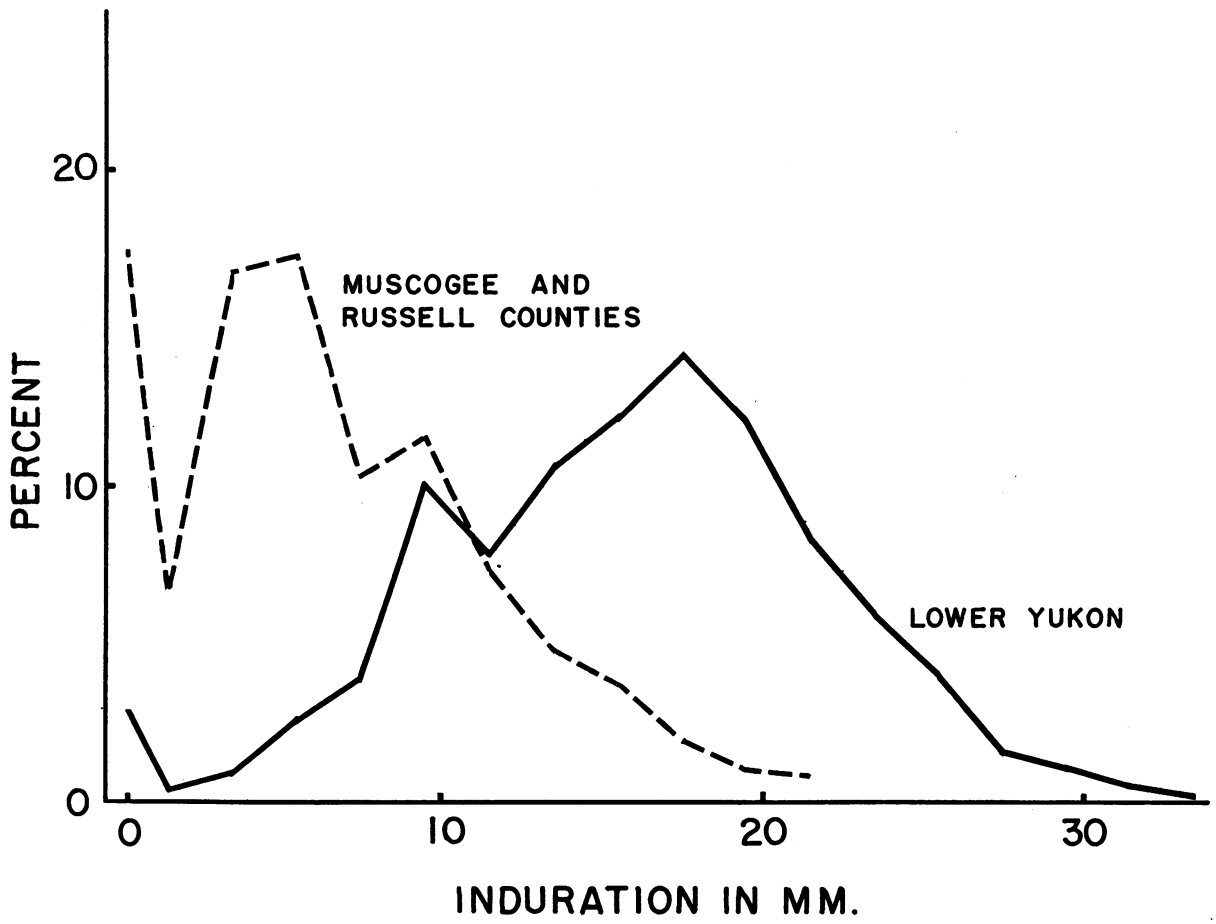
For the participants in the tuberculin testing survey along the lower Yukon, the records from the X-ray survey of the villages during the preceding year were matched against the tuberculin test cards. For those who had been tested and X-rayed, the diagnosis made by the Alaska Department of Health was utilized to define a case, accepting as such all those classified as having suspected or definite reinfection-type tuberculosis. As in the Muscogee-Russell area, this diagnosis in some instances was based on a single film; in others, it was substantiated by a long period of followup examinations, including bacteriological and clinical studies. The clinical diagnosis was independent of the tuberculin findings of the survey.

In both areas, the great majority of cases appeared to be inactive at the time of the X-ray survey. However, 24 percent of the cases in the lower Yukon area and 18 percent

Table 5. Distribution of sizes of reactions to 5 T.U. PPD among unvaccinated persons over 15 years of age in two geographic areas

Size of induration (mm.)	Lower Yukon natives, 1957		Residents of Muscogee and Russell Counties, 1950		Percent of persons with 1 mm. or more induration	
	Number	Percent	Number	Percent	Lower Yukon	Muscogee and Russell
Total	953	100.0	47,236	100.0	100.0	100.0
0, E	27	2.8	8,227	17.4		
1, 2	4	.4	3,118	6.6	.4	8.0
3, 4	9	.9	7,912	16.7	1.0	20.3
5, 6	25	2.6	8,176	17.3	2.7	21.0
7, 8	37	3.9	4,867	10.3	4.0	12.5
9, 10	97	10.2	5,499	11.6	10.5	14.1
11, 12	75	7.9	3,505	7.4	8.1	9.0
13, 14	101	10.6	2,336	4.9	10.9	6.0
15, 16	117	12.3	1,769	3.7	12.6	4.5
17, 18	135	14.2	927	2.0	14.6	2.4
19, 20	115	12.1	514	1.1	12.4	1.3
21 or more	211	22.1	386	.8	22.8	1.0
0–4	40	4.2	19,257	40.8	1.4	28.3
5–10	159	16.7	18,542	39.2	17.2	47.5
11 or more	754	79.1	9,437	20.0	81.4	24.2

Figure 6. Comparison of distributions of sizes of reactions to 5 T.U. PPD among unvaccinated persons 15 years or older in two geographic areas.



of those in the Muscogee-Russell area have had positive bacteriological findings at some time.

There is a marked difference between the two populations in the distribution of reaction sizes to 5 T.U. of PPD in unvaccinated persons over 15 years of age (table 5, fig. 6). Half of the reactions in the Muscogee-Russell area are smaller than 7 mm.; in contrast, half of the reactions in the lower Yukon area are larger than 16 mm. On the basis of unpublished studies in Muscogee and Russell Counties and studies by Nissen Meyer (*10*), only a small part of this difference can be attributed to differences in the antigens used in the two areas.

Before examining the relationship of tuberculous disease to the size of tuberculin reaction, one more difficulty must be considered. It is well known that there are definite reader differences which may enter into the problem of interpreting tuberculin sensitivity. Although several different readers participated in the Muscogee-Russell survey, it was possible to have each reader measure reactions from all major segments of the population. In the lower Yukon area, this could not be done. One reader, for instance, worked in the villages near the mouth of the Yukon; the other two farther up the river and in Unalakleet. The readings by the first reader formed a distribution about 3 mm. smaller on the average than the readings of the other two nurses. This difference appeared to have been a personal one—it did not appear to be associated with village, race, sex, age, or vaccination status—and is consistent with differences noted in the readings of these three nurses on other series of comparative readings.

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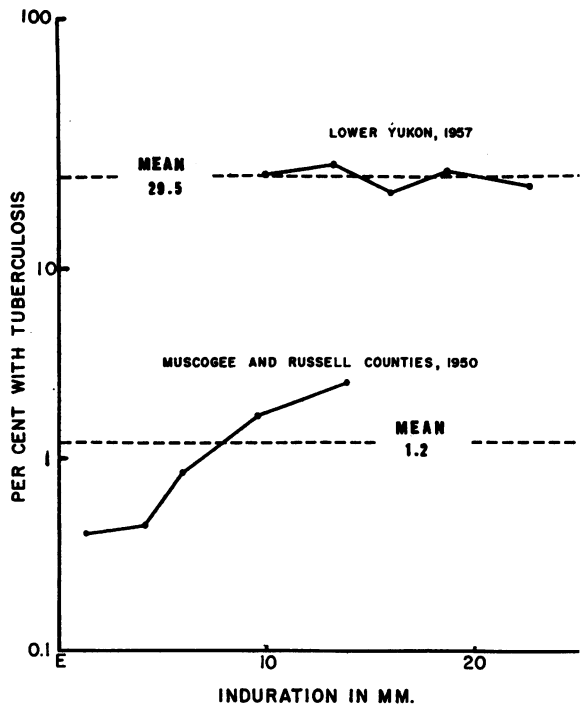
Such reader differences would not have been of critical importance except that the prevalence of tuberculosis was appreciably higher in the villages near the mouth of the Yukon, those tested by the first reader, than among the villages tested by the other two. Such a situation obviously tends to produce a "built-in" correlation between smaller reactions and increased prevalence of tuberculosis. However, when each reader's subjects were studied separately, the relationships between reaction size and frequency of tuberculosis were similar for each of the three groups.

It therefore appeared reasonable to combine the results for all three readers, but only if this could be done in such a way that the "built-in" correlation could be avoided. First, to eliminate the possible effects of vaccination, the subjects in both areas were restricted to unvaccinated persons over the age of 15 years. Then, for each reader in the lower Yukon survey, the subjects who showed some reaction (erythema or any induration) to the 5-T.U. dose were ranked by size of reaction, and each of the three groups was divided into fifths or quintiles. The quintiles from each reader's subjects with the smallest reactions were combined to form the first quintile of the total group, those with the next larger reactions were combined to form the second quintile, and so on. The subjects from the Muscogee-Russell area with some reaction to 5 T.U. of PPD were also divided into quintiles. In both areas, the populations were divided in such a way that each quintile would contain a whole number of persons; the cases were allocated on a proportionate basis which resulted in fractional numbers of cases being assigned to each quintile.

Figure 7. Prevalence of reinfection-type pulmonary tuberculosis among unvaccinated reactors 15 years of age or older in two geographic areas, by size of reaction to 5 T.U. PPD.



The total prevalence of tuberculosis among adults with some reaction to the 5-T.U. dose

Table 6. Prevalence of reinfection-type pulmonary tuberculosis among unvaccinated reactors,[1] 15 years of age or older in two geographic areas, by size of reaction to 5 T.U. PPD

Quintile	Lower Yukon				Muscogee and Russell Counties			
	Midpoint of interval	Number of persons	Persons with tuberculosis		Midpoint of interval	Number of persons	Persons with tuberculosis	
			Number	Percent			Number	Percent
Total	16. 1	692	204. 0	29. 5	6. 2	41, 893	496. 0	1. 18
1st	9. 8	138	42. 4	30. 7	1. 3	8, 378	34. 2	. 41
2d	13. 3	138	47. 1	34. 1	4. 1	8, 379	37. 7	. 45
3d	16. 1	140	34. 2	24. 4	6. 2	8, 379	71. 5	. 85
4th	18. 9	138	43. 5	31. 5	9. 3	8, 379	141. 8	1. 69
5th	22. 8	138	36. 8	26. 7	14. 0	8, 378	210. 8	2. 52

[1] Defined as all persons with some erythema or induration to the 5-T.U. dose of PPD.

was very different in the two areas, being nearly 30 percent in the lower Yukon area and only 1.2 percent in Muscogee and Russell Counties (table 6, fig. 7). In the lower Yukon area, there was no significant difference in the frequency of tuberculosis among persons with different sizes of tuberculin reactions, whereas in Muscogee and Russell Counties, there was a marked and progressive increase in the frequency of tuberculosis with increasing size of the tuberculin reaction. The same relationships were noted when the cases were restricted to bacteriologically confirmed cases from the two areas.

Previous reports have noted that there is a positive correlation between size of tuberculin reaction and subsequent incidence of tuberculosis, similar to that noted for prevalence of tuberculosis in the Muscogee-Russell area (*11–14*). For such a relationship, there could be at least two explanations. One is based on the notion that allergy to tuberculoprotein is harmful to the host, and that demonstrable disease is therefore more likely to be present among those with the highest levels of allergy. The second is that among persons with small reactions, there are many in some areas who are not infected with tubercle bacilli but with something else much less pathogenic, while persons with large reactions have almost all been infected with tubercle bacilli.

Either hypothesis is consistent with the findings from Muscogee and Russell Counties, and with the reports on incidence of tuberculosis according to the size of tuberculin reactions. However, the first hypothesis does not fit with the findings from the lower Yukon area; the second is entirely consistent. These findings therefore indicate that the degree of allergy per se does not appear to be related to the likelihood of having tuberculous disease, and provide additional support for the concept of nonspecific sensitivity (*15–17*).

Discussion

Those who are unfamiliar with the tuberculosis situation among Alaska natives may have difficulty in accepting that almost 30 percent of the adults in these 19 villages had X-ray findings compatible with past or present tuberculosis. However, there is evidence that this extraordinary prevalence of tuberculosis is not exaggerated. Historical records suggest that the arrival of the white man in Alaska was closely followed by the appearance of tuberculosis among the natives (*18*). This soon assumed the characteristics of an epidemic, which only in recent years has appeared to be subsiding. Prior to 1952, the recorded tuberculosis mortality for Alaska natives was well in excess of 500 per 100,000 (*19, 20*); for the years 1953–56, the average annual death rate for the Bethel area was 282, according to unpublished data from the Arctic Health Research Center. Also consistent with the epidemic character of tuberculosis in this population is the prevalence of tuberculin sensitivity, which is as high, if not higher, than any recorded in recent years. In the International Tuberculosis Campaign, only a few cities in Poland, Yugoslavia, and North Africa had reactor rates approaching those among natives of the lower Yukon (*21*).

In an area where tuberculosis is so common, it might be suspected that most pulmonary abnormalities would be classified as tuberculous. However, an independent reading of several hundred films from the Bethel area by Comstock yielded prevalence rates essentially the same as those derived from film readings by the Alaska Department of Health. In addition, similar findings have been noted in the Eskimo population of Greenland. Helms (*22*) reported that 41 percent of the adults in Angmagssalik during the period 1948–51 showed some X-ray evidence of pulmonary tuberculosis; and in 1956, Stein and Groth-Petersen (*23*), in a very thorough survey of the native Greenlanders, found that 29 percent of those over 15 years of age showed lung changes of a tuberculous character. On the basis of the available evidence, it is our opinion that the reported prevalence of tuberculous lesions in the present study population is entirely reasonable.

Confidence in the lack of an association between the size of the tuberculin reaction and X-ray evidence of reinfection-type tuberculosis in this study population is strengthened by the fact that the same relationship was observed when the cases were restricted to persons with a history of positive bacteriological findings.

In addition, a similar relationship was also noted for pulmonary calcifications which, with the virtual absence of histoplasmin sensitivity in this population (*24*), are likely to represent the residuals of healed primary tuberculosis.

The comparison between the findings in the lower Yukon area and those in two counties in the southeastern United States clearly illustrate the difficulties imposed on the interpretation of tuberculin sensitivity when this is attempted on the basis of a single standard for negative and positive reactions regardless of the prevalence of nonspecific sensitivity. In populations similar to the unvaccinated adult natives of the lower Yukon area, if the findings of this study can be confirmed by further investigation, it may be that any reaction to 5 T.U. of PPD–S can be considered as positive for tuberculous infection.

On the other hand, in areas like Muscogee and Russell Counties, where nonspecific sensitivity is very common, a simple dichotomy of reactions into negative and positive can never be entirely satisfactory. If the dividing line is placed fairly low on the scale of tuberculin sensitivity, say between 4 and 5 mm. of induration to the 5-T.U. dose, the negative group will contain relatively few persons infected with tubercle bacilli, but those classified as positive will include many who are infected with something else. Shifting the dividing line to 15 mm. would probably reduce the false positives to a negligible proportion, but would result in classifying many persons infected with tubercle bacilli among the negatives.

For those areas where nonspecific sensitivity is commonly encountered, a further subdivision into more categories than the two of negative and positive in common usage should be seriously considered. At the very least, it would seem wise to interpose an additional category of "doubtful" for those persons with intermediate-sized reactions of 6 to 10 mm. to the 5-T.U. dose. With such a classification, the negative reactions of 0 to 5 mm. would very largely signify the absence of tuberculous infection, and the positive reactions of 11 mm. or more of induration would very largely signify that tuberculous infection had occurred. Reactions of 6 to 10 mm. would quite properly be labeled doubtful, since in areas with more than one cause for tuberculin sensitivity, testing with the 5-T.U. dose of PPD–S alone cannot differentiate specific reactions of this size from nonspecific reactions.

The present study is only a small contribution to a long series initiated by Palmer and his associates to apply the concepts of the normal distribution of attributes in biological populations to the problem of tuberculin sensitivity in humans from many geographic areas (*15*–*17*, *25*). By using standardized antigens and careful techniques of measurement, it has been possible to show that the varied patterns of sensitivity elicited in different populations can only be explained satisfactorily by the existence of tuberculin sensitivity caused by something other than the tubercle bacillus. Although this concept has shattered the apparent simplicity of the tuberculin test as a casefinding and diagnostic tool, its application to the practical uses of tuberculin testing will result in the resolution of some of the former enigmas of tuberculin sensitivity and in a more accurate subdivision of tested populations into those who are truly infected with tubercle bacilli and those who are not.

The ability to make this subdivision with as much discrimination as possible is becoming progressively more important. For as tuberculosis declines in many areas to the point where it may be controlled, the seedbed of disease will more and more come to be those who have been infected in the distant past. These must be identified as accurately as possible if maximum progress is to be maintained toward the eradication of tuberculosis.

Summary

In 1957, tuberculin tests were given to 2,211 natives living in 19 villages along or near the lower Yukon River in Alaska. The test antigen was 5 T.U. of PPD–S, and all reactions were carefully measured by experienced nurse readers. Consideration of the distributions of reaction sizes suggests that there is little nonspecific tuberculin sensitivity detectable by this dose of tuberculin in this native population, except for some sensitivity attributable to BCG vaccination.

The prevalence of positive tuberculin reac-

tions increased markedly with age, reaching a level of 96 percent in the age group 15 to 19 years. This represents an average infection rate of 15 percent per year. It appears that the infection rate was even higher 20 years ago, and appreciably lower in recent years.

Among unvaccinated adult reactors to the 5-T.U. dose, the prevalence of active and inactive reinfection-type tuberculosis was almost 30 percent, and was essentially the same among persons with small and large tuberculin reactions. In contrast, in Muscogee County, Ga., and Russell County, Ala., where there is a great deal of nonspecific sensitivity, the prevalence among unvaccinated adult reactors was 1.2 percent, and was much higher among persons with large reactions than among those with small reactions. This finding is interpreted to signify that the prevalence of tuberculosis does not vary with the degree of allergy from specific infection, and as being consistent with the concept that there is considerable nonspecific tuberculin sensitivity in the Muscogee-Russell area and little if any in the lower Yukon area.

The problem of defining a positive tuberculin reactor is discussed, and it is suggested that the definition selected should vary according to the prevalence of nonspecific sensitivity in the area under consideration.

REFERENCES

(*1*) Townsend, J. G., Aronson, J. D., Saylor, R., and Parr, I.: Tuberculosis control among the North American Indians. Am. Rev. Tuberc. 45: 41–52 (1942).

(*2*) Weiss, E. S.: Tuberculin sensitivity in Alaska. Pub. Health Rep. 68: 23–27, January 1953.

(*3*) Edwards, L. B., and Palmer, C. E.: Epidemiologic studies of tuberculin sensitivity. I. Preliminary results with purified protein derivatives prepared from atypical acid-fast organisms. Am. J. Hyg. 68: 213–231 (1958).

(*4*) Timpe, A., and Runyon, E. H.: The relationship of "atypical" acid-fast bacteria to human disease. J. Lab. & Clin. Med. 44: 202–209, August 1954.

(*5*) Schneidau, J. D., Jr., and Shaffer, M. F.: Studies on *Nocardia* and other actinomycetales. I. Cultural studies. Am. Rev. Tuberc. 76: 770–788, November 1957.

(*6*) Shepard, C. C.: Behavior of the "atypical" mycobacteria in HeLa cells. Am. Rev. Tuberc. 77: 968–975, June 1958.

(*7*) Edwards, L. B., and Krohn, E. F.: Skin sensitivity to antigens made from various acid-fast bacteria. Am. J. Hyg. 66: 253–273 (1957).

(*8*) Palmer, C. E., and Bates, L. E.: Tuberculin sensitivity of tuberculous patients. Bull. World Health Organ. 7: 171–188 (1952).

(*9*) Report of ad hoc advisory committee on BCG to the Surgeon General of the United States Public Health Service. Am. Rev. Tuberc. 76: 726–731, November 1957.

(*10*) Nissen Meyer, S.: A method for standardization of tuberculin preparations by intracutaneous reactions in humans. Am. Rev. Tuberc. 66: 292–313, September 1952.

(*11*) Tuberculosis Vaccines Clinical Trials Committee to Medical Research Council: B.C.G. and vole bacillus vaccines in the prevention of tuberculosis in adolescents. Brit. M. J. 1: 413–427, Feb. 25, 1956.

(*12*) Palmer, C. E., Jablon, S., and Edwards, P. Q: Tuberculosis morbidity of young men in relation to tuberculin sensitivity and body build. Am. Rev. Tuberc. 76: 517–539, October 1957.

(*13*) Groth-Petersen, E., Knudsen, J., and Wilbek, E.: Konsekvensen af den aendrede epidemiologiske situation i tuberkulese-arbejdet: tuberkulosemorbiditeten i den danske befolkning og i specifikke grupper af denne. Nord. med. 58: 1361–1369 (1957).

(*14*) Value of tuberculin reactions for the selection of cases for B.C.G. vaccination and significance of post-vaccination allergy. Symposium of XIVth International Tuberculosis Conference, New Delhi, January 11, 1957. Bull. Internat. Union Against Tuberc. 27: 106–111, January–April 1957.

(*15*) Palmer, C. E., and Petersen, O. S.: Studies of pulmonary findings and antigen sensitivity among student nurses. V. Doubtful reactions to tuberculin and histoplasmin. Pub. Health Rep. 65: 1–32, Jan. 6, 1950.

(*16*) Palmer, C. E., Ferebee, S. H., and Petersen, O. S.: Studies of pulmonary findings and antigen sensitivity among student nurses. VI. Geographic differences in sensitivity to tuberculin as evidence of nonspecific allergy. Pub. Health Rep. 65: 1111–1131, Sept. 1, 1950.

(*17*) Palmer, C. E.: Tuberculin sensitivity and contact with tuberculosis. Further evidence of nonspecific sensitivity. Am. Rev. Tuberc. 68: 678–694, November 1953.

(*18*) Aronson, J. D.: The history of disease among the natives of Alaska. Tr. Coll. Phys., Phila. 8: 27–34, April 1940.

(*19*) Fellows, F. S.: Mortality in the native races of the Territory of Alaska, with special reference to tuberculosis. Pub. Health Rep. 49: 289–298, Mar. 2, 1934.

(*20*) Albrecht, C. E.: Public health in Alaska—United States frontier. Am. J. Pub. Health 42: 694–698, June 1952.

(21) Nyboe, J.: Interpretation of tuberculosis infection age curves. Bull. World Health Organ. 17: 319–339 (1957).
(22) Helms, P.: Investigations into tuberculosis at Angmagssalik. Copenhagen, Bianco Lunos Bogtrykkeri A/S, 1957.
(23) Stein, K. S., and Groth-Petersen, E.: Tuberkulosens status på Grønland. Ugesk. laeger. 119: 431–439 (1957).
(24) Comstock, G. W.: Histoplasmin sensitivity in Alaska natives. Am. Rev. Tuberc. 79: 542, April 1959.
(25) Edwards, L. B., Edwards, P. Q., and Palmer, C. E.: Sources of tuberculin sensitivity in human populations. A summing up of recent epidemiologic research. Acta tuberc. scandinav. (In press.)

Radioactivity Levels in Milk Samples

The levels of radioactivity in milk collected during February 1959 from 10 sampling stations across the country remained below the levels currently suggested as permissible by the National Committee on Radiation Protection and Measurements.

The milk sampling network of stations is part of the program of the Public Health Service for measurement of radioactivity in air, water, and food. In reporting on radioactivity levels in milk, the Service will continue to make comparisons with the permissible levels of the national committee.

The only levels thus far developed for radiation exposure for the general population are those recommended by that committee and the International Commission on Radiological Protection. Both bodies recognize that the general population should be considered separately from industrial workers exposed to radioactivity. The national committee has recently revised its 1953 recommendations for industrial workers, but left those for the general population unchanged. The international commission has made recommendations regarding radiation exposure for the general population which are being studied by the national committee.

The national committee, in a statement of April 23, 1959, considers "that undue risks to the population will not be incurred by following current policies for a while longer, during which time it is hoped that methods may be established for a meaningful analysis and control of population exposure."

Both the monthly levels and the yearly averages for all radioactivity in milk samples remained below permissible levels suggested by the national committee.

Yearly average levels [1] of radioactivity in milk samples, period ending February 1959

Area	Calcium [2]	Iodine-131 (3,000)	Strontium-89 (7,000)	Strontium-90 (80.0)	Barium-140 (200,000)	Cesium-137 (150,000)
Cincinnati, Ohio	1. 142	33	69	9. 8	24	64
New York, N.Y	1. 094	28	37	6. 7	15	62
Sacramento, Calif	1. 133	31	25	5. 0	6	57
Salt Lake City, Utah	1. 147	28	22	4. 5	8	46
St. Louis, Mo	1. 266	83	140	15. 1	48	86

[1] Expressed in micromicrocuries per liter (a curie is a measure of radioactivity equivalent to that produced by 1 gram of radium, and a micromicrocurie is 1 millionth of a millionth of a curie).
[2] In grams per liter.

NOTE: The figures in parentheses are the maximum permissible limits for lifetime exposure of population groups to the specific radioisotopes in water, derived from the current recommendations of the National Committee on Radiation Protection and Measurements.