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REVIEWS AND COMMENTARY

FROST REVISITED: THE MODERN EPIDEMIOLOGY OF TUBERCULOSIS

THE THIRD WADE HAMPTON FROST LECTURE[1, 2]

GEORGE W. COMSTOCK[3]

At the outset, I would like to express my pleasure and gratitude at the very great honor bestowed upon me by the Epidemiology Section of the American Public Health Association. And then, I wish to enter a quick disclaimer, for, to use a hackneyed phrase, no man is an island. During virtually all of my professional life, I have been blessed by challenging assignments, by reliable, capable assistants, and by colleagues and supervisors who were both tolerant and stimulating. One of the few unfortunate aspects of this occasion is the absence from this podium of the large team of diverse individuals to whom I am indebted.

Not the least of my good fortunes was the opportunity to work for and with Dr. Carroll E. Palmer, who was a student and colleague of both Reed and Frost. One of Carroll's stories about Frost that has come to mind more than once during recent years concerns student dissatisfaction with Frost's lectures in the basic course on epidemiology. Apparently Frost, in contrast to his gifts as a writer, was a poor lecturer. He was not dramatic, and tended to deliver his thoughts in a flat monotone. The students complained to Carroll Palmer, who as a young instructor may have been seen as only partially contaminated by the establishment. His response, as he often recalled, was, "Sure, he's no orator, *but listen to what the man is saying!*"

Fortunately, Carroll Palmer and many others did listen to what the man was saying. In part because of the benefits he derived from his years with Reed and Frost, and the secondary benefits that this experience brought to his employer, the US Public Health Service, Dr. Palmer urged his own subordinates to become associated with teaching institutions. In this way, my personal good fortune continued with an assignment that brought me into close contact with Frost's successors, Dr. Kenneth Maxcy and Dr. Philip Sartwell. The combination of academic and field experience not only helped me immeasurably as an epidemiologist, but I believe that in turn it has also been useful to my erstwhile employer, the Public Health Service. In any event, collaboration with

Abbreviations: BCG, bacillus of Calmette and Guerin; PPD, purified protein derivative of tuberculin-S (Standard), -B (Battey), -G (Gause); TU, tuberculin units.

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[2] Supported in part by Research Career Award HL 21,670 from the National Heart and Lung Institute.

[3] School of Hygiene and Public Health, Johns Hopkins University, 615 North Wolfe Street, Baltimore, MD 21205.

the Department of Epidemiology led to my present position, where my good fortune still continues in my association with the current recipient of Frost's mantle, Dr. Abraham Lilienfeld.

The wisdom of selecting Wade Hampton Frost as the inspiration for this series of lectures will become increasingly apparent as the years go by. Reviewing his work leads to the realization that his interest in the basic principles of epidemiology will make it possible for Frost lecturers to continue to relate his work to a wide variety of subjects. For my part, after much vacillation, I have elected to review some of the epidemiologic concepts of tuberculosis, how these have changed since Frost's time, and how these changes may have affected the outlook for control and eventual eradication of this disease. My cues for this topic come largely from the paper entitled, "How much control of tuberculosis?" (1). Frost gave this paper at the Annual Conference of State and Local Committees on Tuberculosis and Public Health of the State Charities Aid Association in May 1937. It was published only a few months later, in the August 1937 issue of the American Journal of Public Health.

On re-reading Frost's work, one is struck by how good his deductions and forecasts were in some respects and how poor they were in others. For the most part, it appears that his logic and reasoning were rarely at fault, but that in some basic bits of knowledge he was the victim of the inappropriate conceptualizations of his day. Unfortunately, many physicians and even a few epidemiologists still base their thinking about tuberculosis on the same faulty dogmas and inappropriate analogies with other infectious diseases. Tuberculosis was one of Frost's later interests, and there are suggestions in his writings that he was beginning to recognize these problems before his premature death. I suspect, but cannot prove, that his doubts may have been among the stimuli that prompted Carroll Palmer's monumental work on tuberculin sensitivity.

A major point made by Frost in his writings on tuberculosis was that for some time the biologic balance had been against the tubercle bacillus. As long as reported mortality and morbidity trends were approximately accurate and as long as these indices were decreasing, he pointed out that each infectious case of tuberculosis was giving rise to less than one new case. Continuation of the conditions producing this sequence would obviously lead some day to the eradication of the disease. Although such reasoning engenders long-range optimism for this country and many others, it will be generations at present rates, and in some instances many generations, before tuberculosis becomes a really rare disease.

How did Frost assess the outlook for the future of tuberculosis control? First, he doubted that specific public health procedures were the principal causes of the decline in tuberculosis. The rate of decline seemed to bear little relationship to the efforts expended in control, and, as others have noted, tuberculosis began to decrease before the germ theory was accepted by the medical profession (2). Frost also considered the possibility that the decline could be part of a long-term decline seen in a number of diseases, such as scarlet fever and diphtheria. We still have no solid information about possible prolonged cyclic changes in disease, but we need to keep in the back of our minds the humbling possibility that some of our progress may merely result from riding the downward limb of a cycle. In any event, it did not seem likely then, nor does it seem likely now, that changes in the nonspecific determinants of tuberculosis are likely to favor anything but a continued gradual decline.

Among specific preventive procedures, Frost gave first priority to isolation of infectious cases, an effort to which he felt more and more attention would be given as

the numbers of such cases diminished. This prediction has held true even though we now stress chemical isolation by chemotherapy rather than physical isolation in sanatoria. His second priority was preventive treatment for noninfectious cases, a procedure which has since been demonstrated to be highly effective though not yet universally applied. Third priority was given to early case-finding, based on the now moot concept that most tuberculosis develops insidiously. Finally, he advised special economic and nutritional protection for high-risk groups, a procedure desirable on humanitarian grounds but no longer medically necessary in many instances because of the effectiveness of isoniazid prophylaxis.

Frost also recognized that tuberculosis differed from most other communicable diseases in several important respects. For example, he pointed out that one of the factors operating against its survival was the proclivity of infecting tubercle bacilli to become buried within tissues. In most instances, body defenses were sufficient to prevent further spread. Only in the infrequent instances when pulmonary cavitation occurred did the bacilli become surface dwellers and thus available for widespread dissemination to others.

He also made it clear that the incubation period of tuberculosis was highly variable, often lasting for many years. This fact was noted in one of his last papers, the exposition of the cohort effect entitled, "The Age Selection of Mortality from Tuberculosis in Successive Decades" (3). Unfortunately, he did not live to point out the implications of this observation for the epidemiology of tuberculosis. However, he did infer from the data in this paper that reducing the risk of infection and thereby delaying the time of first infection to adult life was not demonstrably harmful, as analogies with other communicable diseases had once led him to fear.

The major factor that misled Frost and other epidemiologists of his day was the belief that the risk of infection with tubercle bacilli was so high that virtually everyone became infected before adult life. This belief was founded on a combination of observation and dogma. At that time, tuberculin testing was routinely a two-step process. First, a weak dose of tuberculin was given to identify the strongly positive reactors, and then a strong dose was given to the others. Numerous studies showed that 80 to 90 per cent of 15-year-old children were classified as reactors by this procedure (4). If infection was a nearly universal and unavoidable phenomenon, it could have little effect on variations in the prevalence and incidence of tuberculosis, and consequently factors related to the fact of infection per se were usually ignored in the interpretation of such data.

The dogma of invariant specificity of tuberculin reactions was not seriously challenged until the late 1930's when it ran head on into three obstacles: another cherished dogma, an iconoclast, and one of Frost's disciples. The other dogma held that pulmonary calcifications were also pathognomonic of tuberculous infection. The conflict arose when several studies at this time showed that children with pulmonary calcifications often did not react to tuberculin (5).

The iconoclast was Dr. L. L. Lumsden, a friend of Frost's and one of the Public Health Service's outstanding shoe-leather epidemiologists (6). Lumsden not only made the same observation about the nonconcordance of tuberculin reactions and pulmonary calcifications, but found that different tuberculin preparations, especially the stronger doses, gave discrepant results (7). He came to the conclusion that the tuberculin test was worthless and said so plainly.

A confidential conference was held in Hagerstown to consider these disturbing findings (5). The findings were confirmed but the conference came to no further

conclusions. After this conference, Carroll Palmer, a participant and a disciple of Frost, embarked on a long series of coordinated studies to show conclusively that both dogmas were wrong, as was the iconoclast (8, 9). Pulmonary calcifications resulted from histoplasmosis as well as from tuberculosis. Purified preparations of tuberculin were more likely to identify tuberculous infections than their source material, Old Tuberculin, which has been aptly called a witches' brew (10). Furthermore, strong tuberculin reactions, those resulting from small doses of test material, correlated well with other indices of tuberculosis. In contrast, weak tuberculin sensitivity, which required a large dose of tuberculin to elicit, bore little relationship to tuberculosis, varied markedly with geography, and was ultimately demonstrated to result principally from cross-reactions caused by infections with mycobacteria other than tubercle bacilli.

We can now look back at the results of some of the older tuberculin testing surveys and see how present-day interpretations might differ from those made at the time. Table 1 shows results from two areas where testing was done by careful observers using a tuberculin preparation reasonably similar to those in use today. The tests in Philadelphia were done by Hetherington and his co-workers from the Phipps Institute (11) and those in the rural South by

TABLE 1

*Prevalence and estimated prior annual incidence of tuberculous infection in two areas**

Age (years)	% positive (any induration) to 1.0 mg Old Tuberculin	
	Philadelphia	Rural South
5–9	54.2	39.8
10–14	76.6	61.6
15–19	83.0	70.9
Est. incidence in group 5–9	9.9	6.5

* Data from Hetherington et al. (11) and Aronson (12).

TABLE 2

*Prevalence and estimated prior annual incidence in tuberculous infection in two areas**

Age	Percentage positive (10 or more mm induration) to 0.01 mg Old Tuberculin	
	Philadelphia	Rural South
5–9	13.3	10.4
10–14	24.0	17.7
15–19	22.0	25.4
Est. incidence in group 5–9	1.9	1.5

* Data from Hetherington et al. (11) and Aronson (12).

Aronson from the same organization (12). A positive test was considered to be any reaction to either dose of tuberculin resulting in induration at least 5 mm in diameter. As can be seen, by this criterion, the great majority of the children were classified as infected by the age of 15. These frequencies correspond to average annual infection rates of 9.9 per cent per year for 5- to 9-year-olds in Philadelphia and 6.5 per cent per year in the rural South. However, the proportion reacting with 10 mm or more of induration to the first dose, and therefore the only ones probably infected with tubercle bacilli according to present-day evidence, was much lower in both areas (table 2). The annual infection rates for 5- to 9-year-olds would now be estimated as only 1.9 and 1.5 per cent per year, respectively, for Philadelphia and the South. It is now apparent, contrary to the dogma, that a child in the 1930's had a very good chance of reaching adult life without having been infected with tubercle bacilli.

There are two important lessons for epidemiologists to gain from past experience with the interpretation of the tuberculin test. The first is that conceptualization of disease processes, although a natural tendency and one often urged on us by our more theoretical brethren, can sometimes seriously interfere with the interpretation of facts. If workers in the 1930's had looked at reactions to the second strong

dose of tuberculin as a phenomenon possibly distinct from reactions to the first dose, the two would not always have been lumped together. Furthermore, it would have been more obvious that another entirely legitimate way to look at second dose reactions would be to study their frequency among nonreactors to the first dose: When this is done, as illustrated in table 3, it can be seen that while white and Negro children in the rural South differed markedly in the frequency of positive first-dose reactions, the proportion of second dose reactors among those at risk of having this characteristic demonstrated is remarkably similar. Because other indices of tuberculosis were much higher among Negroes than whites, the discordant results of this simple calculation should have suggested that second dose reactions were not reflecting exposure to tuberculosis.

TABLE 3

*Tuberculin sensitivity in the rural South**

Age	% positive to			
	0.01 mg Old Tuberculin		1.0 mg Old Tuberculin	
	White	Negro	White	Negro
5-9	7.3	17.2	29.5	29.4
10-14	11.6	26.2	51.3	45.1
15-19	16.5	33.2	57.1	52.7

* Data from Aronson (12).

The second lesson deals with the value of working with frequency distributions rather than the convenient but potentially misleading proportion positive (such as I have just done). A good illustration is afforded by two populations of school children examined by the Tuberculosis Research Office of the World Health Organization during the mass BCG (bacillus of Calmette and Guerin) campaigns of the early 1950's (13). One group of children was tested in England, the other in South India. As can be seen in figure 1, both groups had almost the same proportion of persons with induration of 10 mm or more in diameter, and both would therefore have the same proportion classified as positive. However, inspection of the frequency distributions

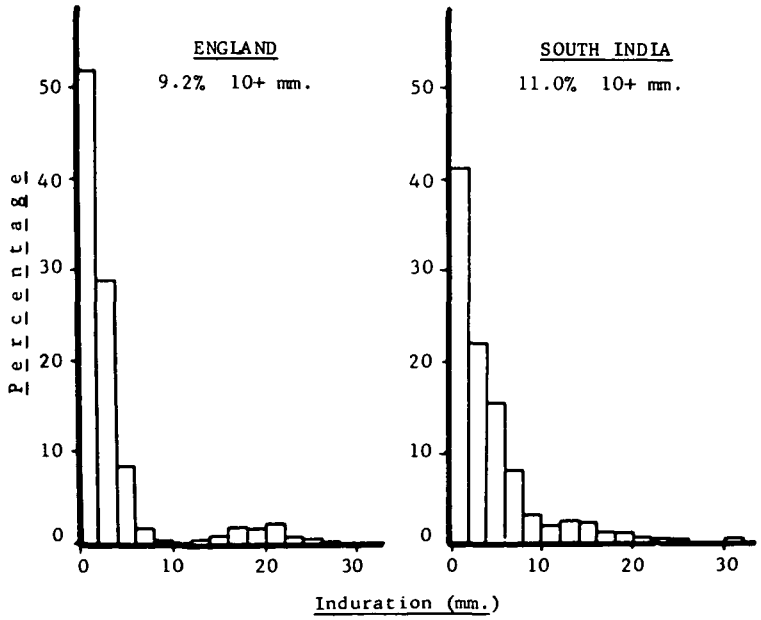

FIGURE 1. Percentage distributions of school children in two countries by size of reaction to 5 TU PPD. (Based on data given in WHO Tuberculosis Research Office: Further studies on naturally acquired tuberculin sensitivity. Bull WHO 12:73, 1955.)

shows marked differences between them. The positive reactions in the South Indian children seem to be largely the right hand tail of a distribution that is only suggestively bimodal. The distribution of English children, on the other hand, is obviously bimodal. It now seems clear to us that these particular English children were at greater risk of having been infected with tubercle bacilli than those in the South Indian sample. Although it seems elementary to emphasize the virtues of examining frequency distributions, it is disturbing to see how widely this basic precept is ignored.

One of Carroll Palmer's principal contributions came from his treatment of the tuberculin test as a quantitative rather than a qualitative procedure. His studies of frequency distributions led him to the vitally important step of differentiating homologous and heterologous reactions to tuberculin. In my opinion, this advance ranks with Koch's discovery of the tubercle bacillus in its implications for understanding the epidemiology of tuberculosis. We can now identify with considerable accuracy both stages of tuberculosis—the acquisition of infection is identified by an appropriate tuberculin test and the development of significant disease by bacteriologic studies.

It may not be immediately obvious why one should make such an issue of looking at the development of tuberculosis as a two-stage process. After all, the development of all communicable disease requires first that an infection become established, and second that infection progress to identifiable disease.

But tuberculosis differs from most other communicable diseases in a very important respect, namely, that the resistance which develops after successful recovery from the primary infection is often not sufficient to rid the body of invading organisms. As a consequence, an unknown but significant proportion of tuberculin reactors is at risk of reactivation for the rest of their lives. In epidemiologic terms, this means that the incubation period of tuberculosis is highly variable, ranging from a few weeks to a lifetime. For almost all other communicable diseases, the incubation period is fixed within a relatively short and discrete interval after infection. Once this interval is past, the individual has nothing to fear from that particular infection, and indeed is usually better off as a result of the immunity that follows, even though for some diseases this may be transient. Not so for the person infected with tuberculosis. Even those who pass through the highest risk period shortly after infection still have a lifetime risk which may actually exceed the initial risk because of the cumulative effect of a low risk operating over many years.

In addition to the fact that the acquisition of infection is often so far removed from the development of disease, it is useful to consider tuberculosis as a two-stage process because the known risk factors for infection are so different from the risk factors for the development of disease after infection. In spite of the voluminous literature on tuberculosis, very little of the work has been done in such a way that these two risks can be disentangled. Even in determining the frequency of infection, there are serious problems because of insufficient attention to the tuberculin used, to the technique of administration and measurement, and to the detailed reporting of results.

In reviewing what is known with reasonable certainty about the risks of becoming infected with tubercle bacilli, I shall take the traditional approach of time, place and person. Perhaps the most reliable study of time trends was conducted by Palmer and Edwards among Navy recruits, a study started in 1949 and finished in 1969 (14). The results are shown in figure 2. Although these men are not a representative sample of the United States, they probably com-

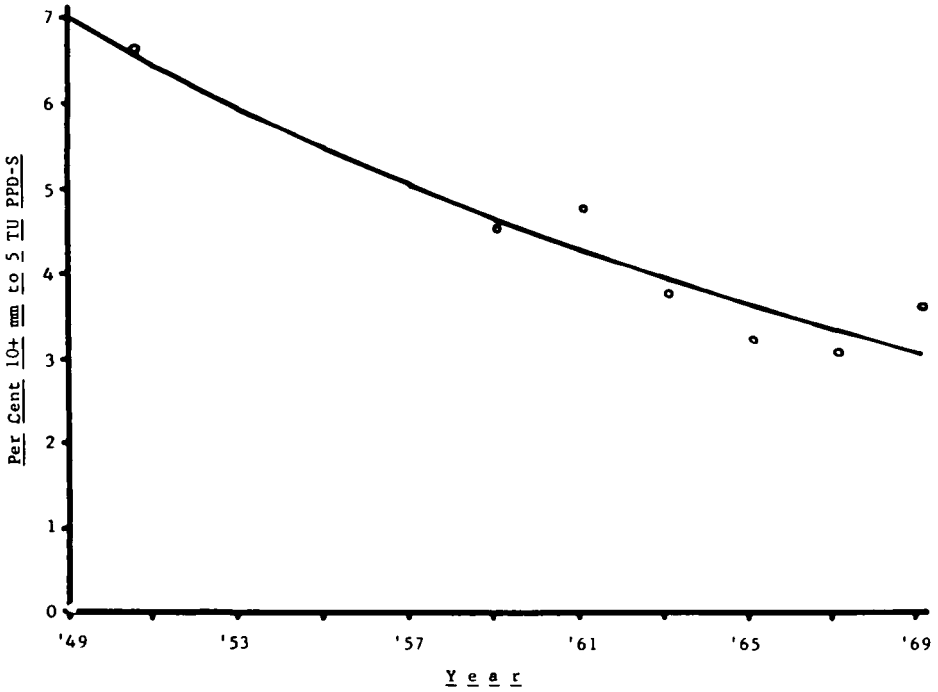

FIGURE 2. Percentage of positive reactions to 5 TU PPD-S among white Navy recruits, aged 17–21 years, 1949–1969. (From Comstock GW, Edwards LB, Livesay VT: Tuberculosis morbidity in the US Navy: its distribution and decline. Am Rev Resp Dis 110:574, 1974. Used by permission.)

prise the same kind of sample from year to year, and it seems reasonable to believe that the rate of change in tuberculin sensitivity among them mirrors the rate of change throughout the country as a whole. In 1950, nearly 7 per cent of the white Navy recruits aged 17 to 21 years were classified as positive tuberculin reactors. Testing was discontinued between 1951 and 1958, but the prevalence of reactors for the succeeding 12 years indicated a considerable and continuing decline in spite of some irregularities that appear to be the result of technical difficulties. If one assumes that there will be no tuberculin reactors after tuberculous infection has disappeared, the rate of decline is 4 per cent per year. But such an assumption is unrealistic. The frequency of cross-reactions to tuberculin in this population is sufficiently great that the prevalence of true tuberculous infections among white recruits may already be approaching zero. If this is so, the rate of decline in tuberculous infections has been closer to 10 per cent per year.

Less elegant data for assessing the risk of becoming infected in recent years come from tuberculin testing of first grade children in the tuberculosis program projects sponsored by the Center for Disease Control from 1959 through 1969 (15). Because there was a tendency to start these projects in areas with serious problems and to expand the program to areas where tuberculosis was less prevalent, the downward trend shown in table 4 may be somewhat illusory. But even when all the difficulties of interpreting such diversely obtained data are taken into account, it is again hard to escape the conclusion that many of these infrequent reactions are attributable to cross-reactions, and that the reactor rate in young children is also approaching the irreducible minimum, even in many of our less advantaged areas.

But these encouraging averages, like all

averages, hide some interesting extremes. To reveal the variations in tuberculous infection from place to place we need to call again on the Navy recruit studies by Palmer and Edwards (14). Their map of the United States (figure 3) shows that even 10 to 16 years ago there were vast areas, including a number of metropolitan centers, where the frequency of positive reactions in young white males was less than 4 per cent. In only 11 of the 506 State Economic Areas as defined by the Bureau of Census was the frequency above 10 per cent, and in none of them was the average annual infection rate derived from these frequencies as high as 1 per cent per year.

TABLE 4

*Results of tuberculin testing first grade children, tuberculosis project areas, USA**

Years	No. tested	% positive
1965–1966	476,073	0.5
1966–1967	1,415,345	0.5
1967–1968	2,949,665	0.4
1968–1969	2,334,550	0.3

* Data from Tuberculosis Branch, Center for Disease Control (15).

The areas with the highest risks of acquiring infection were concentrated north of the Mexican border, and along and west of the Appalachian mountains. But there is good evidence that cross-reactions accounted for the high ranking of at least some areas. The large section of northwestern Colorado owed its high reactor rate to cross-reactions produced by infections with *Mycobacterium balnei* acquired in a popular swimming pool (16). Cross-reactions are also thought to have accounted for the high frequency of reactors around the Chesapeake Bay (17). The dark area on the center of the Georgia-Alabama border was the aftermath of two trials of BCG vaccination in Muscogee and Russell Counties (18).

In estimating current infection rates in other areas, it is necessary to remember that the results represent the experience acquired over 18 years of life. The findings should thus be considered to reflect the situation in 1952, the approximate midpoint of the life experience of the tested group. More recent direct evidence is lacking, but reported case rates suggest that

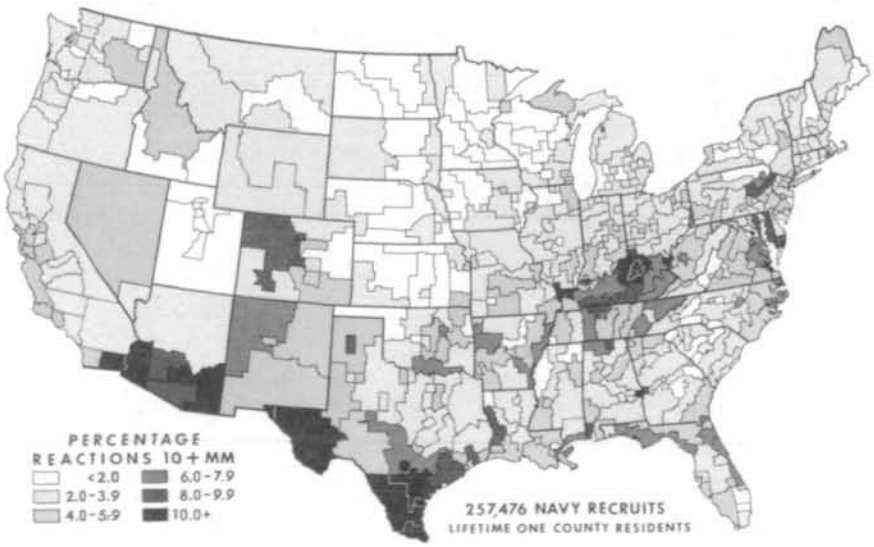

FIGURE 3. Percentage of Navy recruits with reactions of 10 or more mm induration to 5 TU PPD-S, by State Economic Area (white, ages 17–21, tested 1958–1964). (From Lowell AM, Edwards LB, Palmer CE: Tuberculosis. Cambridge, MA, Harvard University Press, 1969, p 142. Copyright 1969 by the President and Fellows of Harvard College. Used by permission.)

the relative ranking of most areas is essentially unchanged, although the current risks of becoming infected must now be much lower everywhere.

Residence abroad has also been suggested as a significant risk factor for acquiring tuberculous infection. Evidence on this point is shown in table 5. Among white Navy recruits, there were 6,817 who had been born in the United States but had lived abroad for at least 6 months. The frequency of positive reactions among them was only slightly greater than among lifetime residents of this country. The high reactor rate among the foreign-born recruits, most of whom were naturalized citizens, is believed to reflect both the high tuberculosis rates in their home countries after World War II and the subsequent widespread use of BCG vaccination. For native-born Americans living abroad, the findings summarized in table 5 indicate that the risk of tuberculous infection was low and not much different than that in many areas of the United States.

Information on the infection rate in older adults is scanty, and often limited to highly selected populations. What may still be among the best evidence comes from a community-wide testing program conducted in Muscogee County, Georgia, and Russell County, Alabama, in 1950, using 5 turberculin units (TU) of purified protein derivative (PPD) (19). As can be seen in figure 4, reactor rates among Negroes were much higher than among whites; males of each race had higher rates than females. More recent testing indicates that this pattern has persisted throughout the United States (14). The declining curves at older ages suggest that some old people have lost their sensitivity. At younger ages, the upward concavity of the curves is consistent either with a decreasing risk of infection with time, or with an increased risk in adolescence and early adult life. Neither possibility can be disproved, but current evidence favors the hypothesis that infection has been decreasing with time, so that younger persons had been exposed to lower rates of infection.

TABLE 5

Percentage of Navy recruits with reactions of 10 or more mm induration to 5 TU PPD-S by residence history (white US residents, ages 17–21, tested 1958–1964)

Residence	No. tested	% 10+ mm
Lifetime US	539,138	3.9
US-born, lived abroad	6,817	4.7
Foreign-born	6,599	19.9

* Data from LB Edwards and CE Palmer: Tuberculous infection. *In* Tuberculosis. By AM Lowell, LB Edwards, CE Palmer. Cambridge, MA. Harvard University Press, 1969, pp 123–202. Copyright 1969 by the President and Fellows of Harvard College.

One of the most imaginative and useful studies of personal factors related to the risk of infection is summarized in table 6. Chapman and Dyerly related a considerable number of personal and household characteristics to the probability that a contact would be infected, using a multiple regression method to isolate insofar as possible the effects of each individual characteristic (20). They found that infection in the contacts was most closely related to the extent of disease and sputum positivity of the source case, a finding previously noted by others (21). Crowding (measured as persons per room) and a subjective assessment of the intimacy of exposure, were also related to the probability of infection, but were not as important as the severity of disease in the source case. A most intriguing finding was that household income in and of itself was not important, while what household furnishings the family purchased with their income seemed to be a factor of considerable significance.

The infectiousness of tuberculosis patients appears to be rapidly reduced by adequate chemotherapy. The most convincing study, because it was strictly controlled, came from the very useful series of

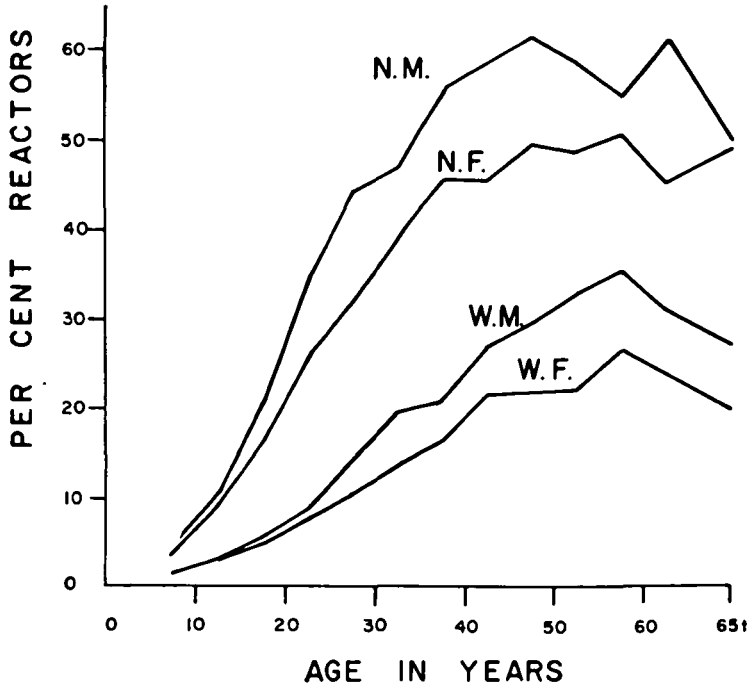

FIGURE 4. Percentage of tested population in Muscogee County, Georgia, and Russell County, Alabama, with reactions of 10 or more mm induration to 5 TU PPD, by race (N, Negro; W, white), sex and age. (From Sartwell PE (ed): Preventive Medicine and Public Health. New York, Appleton-Century-Croft, 1965, p 217. Copyright 1965 by Meredith Publishing Company. Used by permission.)

TABLE 6

Correlation of factors related to the source case and household with number of infected contacts

Factor	Correlation
Severity of source disease	.41
Crowding	.22
Intimacy of exposure	.19
Low family income	.12
Lack of household furnishings	.25
Age of child	.06

* Data from Chapman and Dyerly (20).

TABLE 7

*Active tuberculosis developing among contacts of patients treated at home and in the hospital, Madras, India**

	Place of treatment of case	
	Home	Hospital
No. of contacts	256	272
Total cases (%)	24 (9.4)	38 (14.0)
Cases in first year	12	20

* Data from Kamat et al. (22).

chemotherapy trials in Madras, India (22). Because there were too few hospital beds for all active cases of tuberculosis, cases that were not considered emergencies were randomly allocated to home and to hospital treatment. Both groups received the same chemotherapy. At the end of 5 years, there were actually fewer cases among contacts of patients treated at home than among contacts of those isolated in hospital (table 7). This result strongly suggests that chemotherapy was as effective as hospitalization in breaking contact.

The apparent marked decrease in infectiousness following the institution of adequate chemotherapy is remarkable in view of the fact that it takes eight weeks on the average for sputum to convert from positive to negative (23). One might reasonably expect infectiousness to persist until bacilli cannot be domonstrated in the sputum. A number of possible explanations for this

discrepancy have been put forth, including the increased concentration of chemotherapeutic agents on tubercle bacilli as droplet nuclei evaporate, and the diminution in cough frequency (24, 25).

Another factor that may play some role is that tuberculosis, with few exceptions, is really not highly communicable. Attack rates for three communicable diseases are contrasted with infection rates for tuberculosis among 5- to 9-year-old contacts in Table 8. For measles, mumps and pertussis, the secondary attack rates range from 81 to 86 per cent, and the infection rates are presumably even higher. But among household contacts of active tuberculosis cases, only one-half to two-thirds showed evidence of infection, and at least some of them must have been infected prior to the current exposure, making the true infection rate even lower. Furthermore, communicability of measles, mumps and pertussis is measured in days or weeks, while in tuberculosis the period of infectiousness is weeks, months, or even years. If we epidemiologists were to practice what we preach, and affix a time base to secondary attack rates, it would be clear that the infectiousness of tuberculosis per day of exposure is very low indeed. Thus it may be that the additional exposure to contacts during the time while chemotherapy is taking effect is usually of little consequence compared with the exposure prior to treatment. A further corollary of these observations is that there is very little basis for the alarm hospital personnel frequently experience when a case of tuberculosis is admitted or discovered.

TABLE 8

Comparison of apparent infectiousness of measles, mumps and pertussis with tuberculosis, among household contacts aged 5 to 9 years

	Secondary attack rates (%)
Measles (41)	81
Mumps (42)	86
Pertussis (43)	81
5+ mm to 5 TU PPD-S	
Tennessee, 1931–1955 (30)	67
USPHS contact study, 1958 (28)	48

In summary, the known risk factors for tuberculous infection appear to be extrinsic in nature, and are principally the probability of having prolonged close contact with an infectious source case and the degree of infectiousness of that case. In addition, there is evidence that something in a family's life-style is also related to the likelihood of becoming infected. Whether or not intrinsic factors, such as depth of respiration or efficiency of the tracheobronchial cilia are also important is completely speculative.

Once infection with tubercle bacilli has occurred, the probability of developing manifest tuberculous disease varies greatly, ranging from 600 per 100,000 per year in some Eskimo populations (26) to only one-twentieth of that value in nonmetropolitan Denmark (27). The reasons for this remarkable variation are obscure, because few studies have made an attempt to separate the risks of becoming infected and the subsequent risks of developing disease. For example, we know that older people have higher tuberculosis case rates than young people. Is this only because a higher proportion of old people have been infected, or does the risk of reactivation of latent foci change with age? Which component of risk is more important? Answers to these questions have important implications for the prospects of eliminating tuberculosis from our society.

However, some determinants of disease among infected persons are reasonably well established. First to be considered is time after infection, which can only be measured in sizeable numbers of people as time after exposure to an infectious case. Table 9 shows data from the large study of tuberculosis contacts conducted by the Public Health Service (28). During the first year after the source case was diagnosed, 1 per cent of the tuberculin-positive contacts developed tuberculosis. Eight to ten years

later, the case rate had fallen to 72 per 100,000 per year, not much higher than the rates among tuberculin-positive persons without a history of contact.

Age, sex and race are also related to the risk of disease following infection. The effect of age is shown in figure 5 by results from a long-term follow-up study of tuberculin reactors in Puerto Rico who were 1 to 18 years of age in 1950 (29). There is a high peak of incidence during infancy and early childhood, followed by a second peak in late adolescence and early adult life. The first peak is usually interpreted as being caused by decreased ability in the early years of life to control tuberculous infection, an opinion strengthened by the high frequency of hematogenous dissemination at this age. However, at the beginning of the life span, the effects of age and time after exposure can hardly be disentangled. If the points from table 9 were to be plotted on figure 5, they would fall only slightly below the line on the figure. Such a comparison suggests that much of the high risk observed among tuberculin-positive infants is attributable, not to infancy per se, but to the fact that any exposure during infancy must be recent by definition.

TABLE 9

*Tuberculosis case rates per 100,000 per year among tuberculin positive contacts, by year after contact**

Year after contact	Rate per 100,000 per year
1	1,044
2–4	291
5–7	195
8–10	72

* Data from Ferebee (28).

A number of studies have indicated that the risk of disease is greater among infected females than males, and that this excess is limited to young adults (27,30). Data from a study among Alaskan Eskimos are shown in figure 6 (26). Virtually all adults were infected at that time. The peak in the case rate in young adult life is more prolonged than it was among Puerto Ricans, and is clearly higher among females than males. Case rates among persons above 40 years of age in this population are essentially the same for both sexes.

There also appear to be differences be-

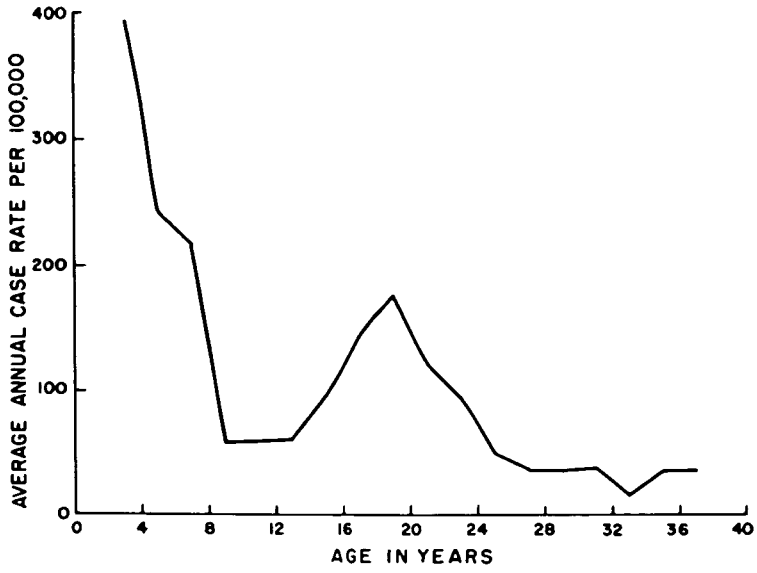

FIGURE 5. Incidence of tuberculosis among initial reactors to tuberculin by age when tuberculosis was first diagnosed. (From Comstock GW, Livesay VT, Woolpert SF: The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol 99:134, 1974. Used by permission.)

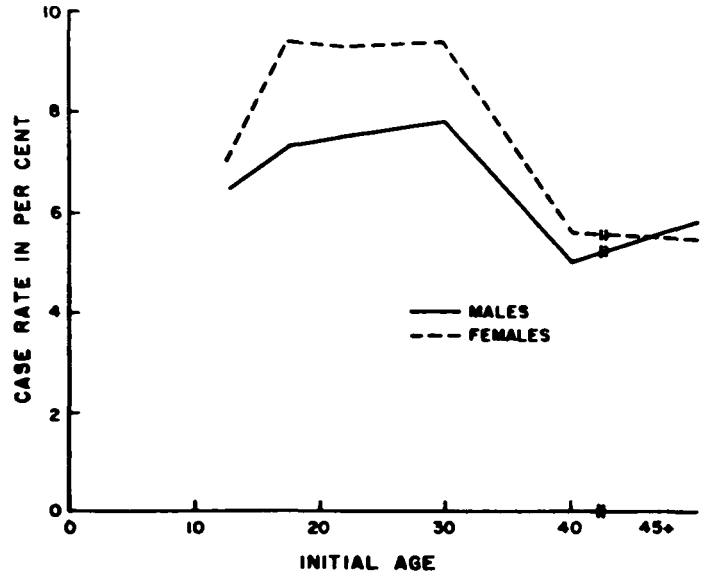

FIGURE 6. Tuberculosis case rates in per cent among Eskimos in the Bethel area of Alaska, by sex and age, 1958–1964. (From Comstock GW, Ferebee SH, Hammes LM: A controlled trial of community-wide isoniazid prophylaxis in Alaska. Am Rev Resp Dis 95:937, 1967. Used by permission.)

tween whites and Negroes during the young adult years of life. Table 10 shows the results of a 20-year study in Georgia and Alabama involving nearly 12,000 tuberculin reactors (31). In the youngest age group, almost all the participants were over 5 years of age. A significant difference was observed between the two races only for persons 20 to 39 years of age initially, and this difference is largely caused by the high rates among Negro females at this age.

Because the prevalence of tuberculous infections increases markedly with age, it is particularly important to know something about the likelihood that older tuberculin reactors will develop disease. Reported case rates in this country show a steady increase with age. The fact that prospective studies such as the one summarized in table 10 often show the highest rates among older persons has been interpreted to mean that an infected person's chance of developing tuberculosis also increases in old age. However, none of the prospective studies has had sufficient cases among older persons to look at the effects

TABLE 10

Tuberculosis case rates per 100,000 per year among persons with 10 or more mm of induration to 5 TU PPD, Muscogee and Russell Counties, 1950–1969, by race and age

Initial age	No of cases		Rate/100,000/year	
	White	Negro	White	Negro
0–19	2	7	30	43
20–39	10	44	32	82
≥40	34	33	104	89

of both age and time. It is thus possible that case rates may show a cohort effect similar to that demonstrated for mortality rates nearly 40 years ago by Frost (3).

To look for a possible cohort effect, it is necessary to have large numbers of cases, and therefore to use reported cases from a large population. Unfortunately, the tuberculin status of most general populations is not known. However, a number of studies have shown that the risk of becoming infected in the United States has been very low over the past 20 years and that as a consequence, a large majority of the tuberculosis cases occur among persons who were infected in the distant past (29, 31,

32). For this reason, it may be justifiable to assume that the pattern of development of tuberculosis in older people is largely dependent on the fate of the tuberculin reactors among them.

Data from reported case rates in the United States are shown in figure 7 by age for the years 1953, 1963, and 1972 (33, 34). The broken line at the bottom shows the age-specific case rate for 1972. There is a steady increase in the case rate with age. If the tops of the short diagonal lines were similarly connected, the resulting curve would represent the age specific case rate for 1953; it too increases with age. The short diagonal lines show rates for the specified cohorts, representing the experience for each cohort from 1953 to 1972 as they aged over that 19-year interval. In all instances, there is a very marked decrease as the cohort ages, so marked in fact that unless case reporting in 1972 has become much less complete than it was in 1953, it is difficult to escape the conclusion that as adult tuberculin reactors become older, their risk of developing tuberculosis decreases sharply. If this is so, time is doubly on our side, as long as we can hold the risk of becoming infected to its present low level. The passage of time not only removes a disproportionate number of reactors by death, but is also apparently associated

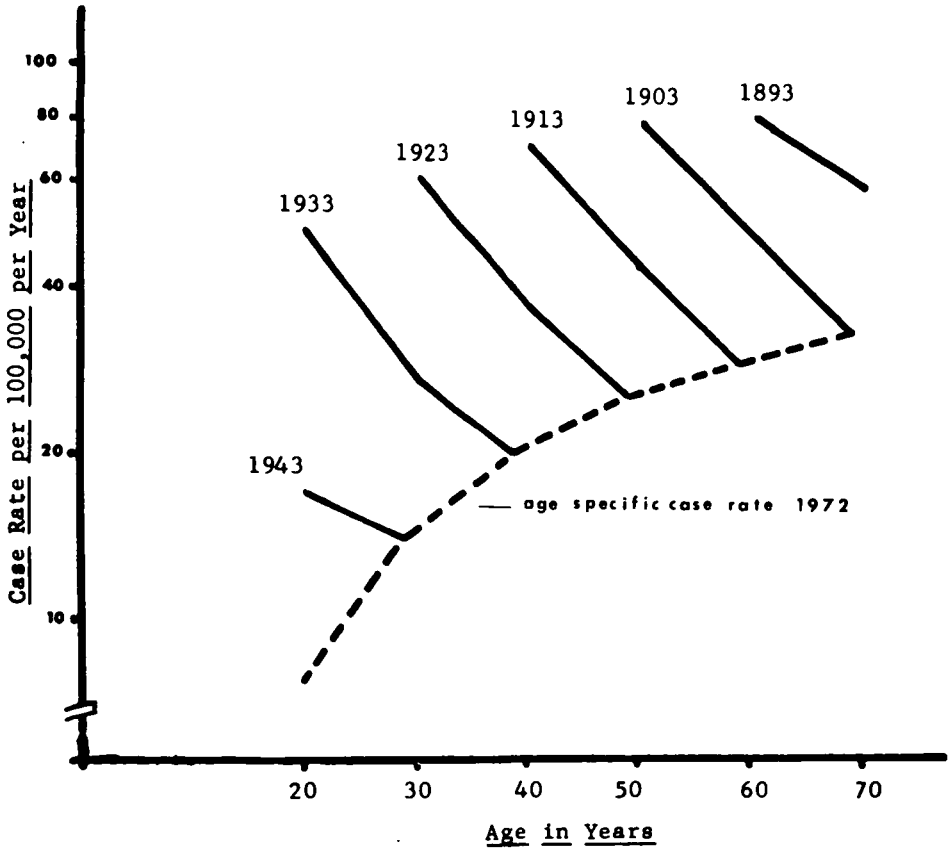

FIGURE 7. Reported tuberculosis case rates among US adults, by age and cohort, 1953–1972. (Based on data in Reported Tuberculosis Data 1967, Public Health Service Publication No 638, Washington DC, US Government Printing Office, 1969; and in Reported Tuberculosis Data 1972, DHEW Publication No (CDC) 74-8201. Atlanta, GA, Center for Disease Control, 1973. Used by permission.)

with a marked decline in the risk of disease as the reactors pass into middle and old age.

In discussing the risks of becoming infected, it was noted that several of the concomitants of poverty—notably severity of disease before diagnosis and crowding—were important risk factors for infection. Much less is known about the relationship of poverty to the risk of disease among reactors, although numerous studies have documented the association of socio-economic factors with tuberculosis, without trying to determine whether the association was related to the risks of becoming infected or to developing disease after infection. One study in Muscogee County, Georgia, assessed the effect of socio-economic status measured in terms of housing quality on the risk of developing disease, after adjustments for the frequency of infection (35). A total of 82 cases was known to have developed after 1950 among persons whose housing status was classified in 1946 (table 11). After adjusting for race and for tuberculin and BCG vaccination status, the expected distribution of cases did not differ significantly from the total observed distribution, as indicated by the ratio of observed to expected cases, thereby failing to show an association of housing with risk of reactivation.

Malnutrition is widely believed to favor reactivation of latent tuberculous foci. This may well be so, but there is only indirect evidence on this point. The association of relative weight to tuberculosis has been carefully studied among Navy personnel (36). As is shown in figure 8, the prevalence of infection was almost identical among the three relative weight classes. However, both among the recruits who were tuberculin reactors on entry into the Navy, and among those who subsequently became infected, tuberculosis case rates were 3 times greater among men at least 10 per cent underweight for their height than among those at least 10 per cent overweight.

Because overweight does not necessarily signify obesity, nor underweight leanness, it is useful to carry the Navy experience

TABLE 11

*Observed (O) and expected (E) cases of tuberculosis developing between 1950 and 1964 by housing score in 1946**

Housing Score in 1946	Tuberculosis cases		O/E Ratio
	Observed	Expected	
Total	82	82.0	1.00
Low	37	32.5	1.14
Medium	31	35.3	0.88
High	14	14.2	0.99

* Data from Comstock and Palmer (35).

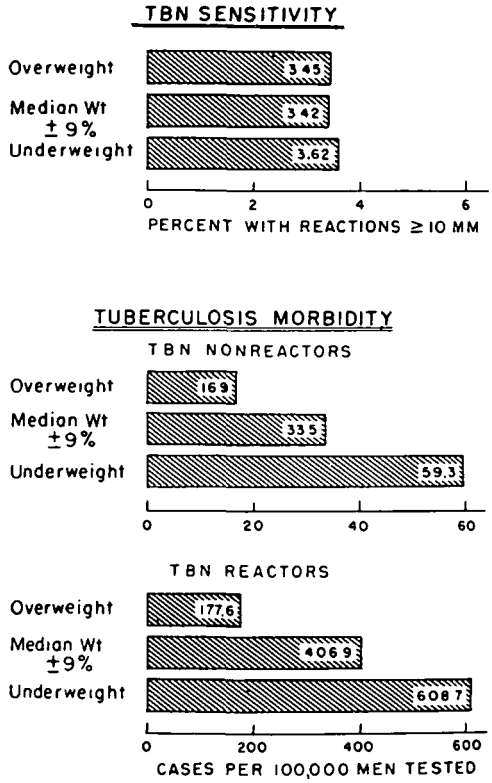

FIGURE 8. Tuberculin sensitivity and tuberculosis morbidity according to relative weight for height among US Navy recruits tested 1958 through 1967. (From Edwards LB, Livesay VT, Acquaviva FA, et al: Height, weight, tuberculous infection, and tuberculous disease. Arch Environ Health 22:111, January 1971. Copyright 1971, American Medical Association. Used by permission.)

one step further. In the Muscogee County Tuberculosis Study, 64 cases of tuberculosis developed after 1950 among persons whose subcutaneous fatness was measured in 1946 (35). After adjusting for race and for tuberculin and BCG vaccination status, it can be seen in table 12 that the total observed cases showed a markedly different distribution from what would have been expected if there were no association of leanness in 1946 with tuberculosis developing after 1950. An excess of cases was observed among the very thin and a deficit among the fat. This finding suggests that the pertinent component of excess weight in the Navy study was fat, and not muscle or bone.

The foregoing studies still do not conclusively answer the questions about diet and tuberculosis. Although it is entirely possible that undernutrition causes both leanness and susceptibility to tuberculosis, it is also possible that some other aspect of body build, such as a hormonal or genetic factor, is the underlying cause of both. Favoring the latter hypothesis is the impression that very few people in Muscogee County in 1946 could have been considered to be seriously undernourished, and the observation among Navy recruits that tuberculosis contacts weighed less than men who had not lived in the same house with a tuberculosis case (36).

To summarize, only a few risk factors have been demonstrated to play a part in the second stage of the pathogenesis of tuberculosis, i.e., the development of disease after infection. All of them—age, sex, race, and body build—are intrinsic or inherent characteristics, in marked contrast to the risk factors for acquiring infection, which are all extrinsic.

TABLE 12

*Observed (O) and expected (E) cases of tuberculosis developing between 1950 and 1964 by thickness of subcutaneous fat in 1946**

Thickness of subcutaneous fat (mm)	Tuberculosis cases		O/E Ratio
	Observed	Expected	
Total	64	64.0	1.00
0–4	31	23.9	1.30
5–9	25	26.4	0.95
≥10	8	13.8	0.58

* Data from Comstock and Palmer (35).

A final characteristic to be discussed does not fit the dichotomy of infection and disease, since it overlaps both areas. This characteristic is the degree of sensitivity to tuberculin. Several studies have shown that persons who are most sensitive to tuberculin are also most likely to develop tuberculosis later on (32, 35, 37). Fifty years ago, attention was focussed on whether allergy to tuberculo-protein was beneficial or harmful; now, at least in epidemiologic circles, principal interest lies in the ability of the degree of hypersensitivity to indicate whether a person has been infected with mycobacteria or not, and if so, whether the infecting organism was *Mycobacterium tuberculosis* or one of the usually benign nontuberculous mycobacteria.

Figure 9 illustrates the prognostic importance of degree of sensitivity to tuberculin. In 1950, nearly 200,000 Puerto Rican children were tuberculin tested (38). The first dose was 1 Tuberculin Unit. Those with reactions of less than 6 mm to this dose were then given 10 Tuberculin Units. And again, those with less than 6 mm to the 10 unit dose were tested with 100 Tuberculin Units. Part of this last group was also given BCG vaccination. Over the next 19 years, tuberculosis cases were identified in the study population, and case rates among study participants with various degrees of tuberculin sensitivity were calculated. It is clear that those with the highest level of sensitivity to tuberculin, that is, those with the largest reactions to the smallest dose, had by far the greatest risk of subsequent tuberculosis. It is also clear that the degree of sensitivity to the 100 Tuberculin Unit dose did not show any relationship to subsequent tuberculosis, a finding in keep-

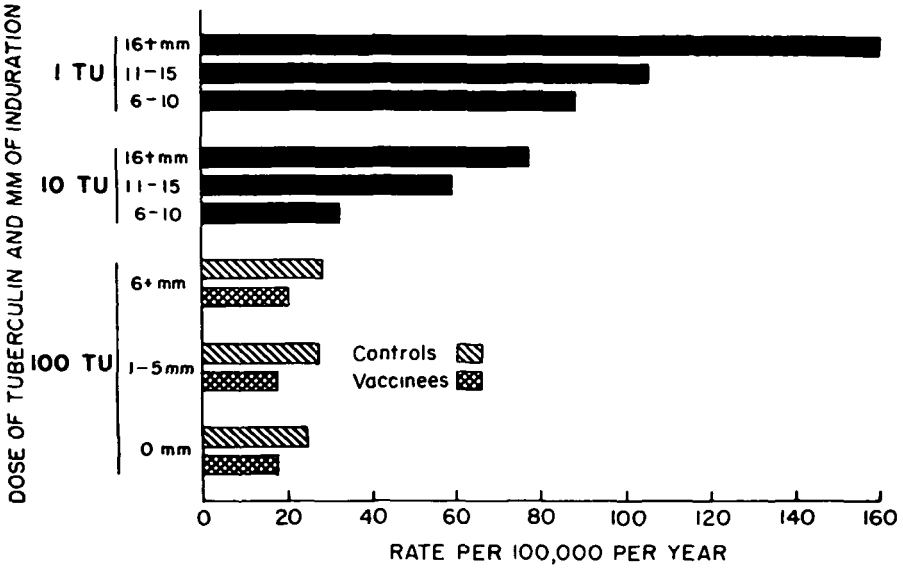

FIGURE 9. Incidence of tuberculosis among Puerto Rican children and adolescents, by initial tuberculin sensitivity and BCG vaccination status. (From Comstock GW, Livesay VT, Woolpert SF: Evaluation of BCG vaccination among Puerto Rican children. Am J Public Health 24:286, 1974. Used by permission.)

ing with the current belief that persons who react only to this large dose of tuberculin have almost always been infected with nontuberculous mycobacteria.

The results among the 1 and 10 Tuberculin Unit reactors in Puerto Rico are consistent both with the hypothesis that hypersensitivity is somehow harmful in and of itself, and also with the hypothesis that higher levels of sensitivity are more likely to be caused by infections with tubercle bacilli. The Navy recruit study is one of several that shed some light on this problem (32). On entry into the Navy, recruits routinely received a skin test with PPD-S (a tuberculin prepared from mammalian tubercle bacilli) and also with a PPD prepared from a nontuberculous mycobacterium, either the so-called Battey or Gause strain, these tests being indicated in Table 13 by S, B or G, respectively. Cases developing among these men during their first four years of Navy service were identified. Numbers of cases and case rates according to their reaction to 5 Tuberculin Units of PPD-S on entry are underlined.

TABLE 13

Tuberculosis morbidity according to results of dual tests in 1,124,883 white Navy recruits

Dual test reactions (mm)	Tuberculosis	
	No.	Rate/100,000
PPD-S, 0–5	384	36
PPD-S, 6–11	36	110
S < B/G - 1	5	29
S = B/G ± 1	10	127
S > B/G + 1	21	272
PPD-S, 12–17	80	382
S < B/G - 1	5	216
S = B/G ± 1	12	297
S > B/G + 1	63	432
PPD-S, ≥ 18	49	372

* Data from Edwards et al. (32).

Those with less than 6 mm on entry had a low rate of tuberculosis subsequently, those with intermediate reactions an intermediate rate, and those with reactions of 12 mm or more, a high rate.

Experimental and clinical evidence both indicate that reactions to a homologous antigen are usually larger than cross-reactions to a heterologous antigen. Thus, in

theory, the group of persons whose reactions to PPD-S are smaller than those to either PPD-B or PPD-G are not likely to have been infected with tubercle bacilli, and should therefore have a low risk of tuberculosis. Although the numbers are small in the two subgroups whose reactions to S are smaller than those to B or G, the theory seems to hold well for persons with intermediate reactions to PPD-S, but not so well for persons whose reactions to PPD-S measure 12 mm or more in diameter.

These findings are not as neat as one might wish, possibly because of the bewildering variety of mycobacterial infections and the inability to test for more than a few of them. Furthermore, no one knows how to test for multiple infections in the same individual. Nevertheless, these and similar findings support the current belief that the larger the reaction to a small or intermediate dose of tuberculin, the more likely it is that an individual has been infected with tubercle bacilli, and consequently the more likely that tuberculous disease will develop at some time in the future.

Identification and classification of risk factors usually have practical applications. This is fortunate, for the temper of the times tends to value only that knowledge which can be applied to some useful purpose. In reviewing the use of epidemiology in tuberculosis control, one should underscore our ability to document the virtual elimination of new tuberculous infections from nearly every segment of this country. Knowledge that this has occurred leads to three corollaries. First, except for persons with known contact with tuberculosis, repeating tuberculin tests at frequent intervals is not likely to be economical, because so few converters will be found. In fact, most adults need only a single tuberculin test to identify their lifetime status. Second, when the risk of becoming infected is almost zero, the need for the kind of protection that vaccination can give is likewise almost zero. And third, even though the biologic imbalance is now even more strongly against the tubercle bacillus than it was in Frost's day, maintenance of that imbalance will require continued effort. That effort, as I see it, has several components which can be supported by epidemiologic knowledge. These components are 1) readily accessible medical attention to provide early diagnosis, 2) a system for insuring continuous treatment of active cases until a cure is obtained, and 3) sufficient housing to prevent overcrowding.

In theory, tuberculosis could eventually be eliminated merely by keeping the infection rate at or close to zero. But because the incubation period of tuberculosis can be a lifetime, control measures would have to maintain this situation until virtually all reactors had died, a matter of at least three generations. Unless greater emphasis is placed on prevention of the second stage of tuberculosis—i.e., the development of disease among infected persons, tens of thousands will be needlessly afflicted.

Control of disease after infection, like control of many chronic diseases, requires much individualized motivation and education, both of subjects and their medical attendants, with all the difficulties that this approach entails. For example, many older physicians still do not realize that a positive tuberculin reaction is a risk factor to be treated. Another favorable factor is that knowledge from epidemiologic studies can help focus efforts where they are most needed. It is well documented that the tuberculin test, carefully administered, measured and interpreted as a quantitative test, can identify most of the persons at risk of reactivation. Another important determinant of risk is age. Because of the long incubation period of tuberculosis, the lifetime risk of disease is closely related to life expectancy, so that lifetime risk is much greater for a young reactor than it is for an old reactor. Another important risk

factor is abnormal leanness since the risk for a thin reactor is several times greater than it is for a fat reactor. Finally, extensive controlled trials have clearly demonstrated the feasibility and effectiveness of preventing tuberculosis among infected persons by the oral administration of isoniazid once a day for a period of 6 to 12 months (28, 39).

Epidemiologic information also helps to determine the costs of preventive treatment relative to its benefits. In medical terms, the principal cost of preventing tuberculous disease is the occasional case of hepatitis associated with the administration of isoniazid. Large scale epidemiologic studies have shown that age is a major risk factor for this side effect of treatment (40). Hepatitis is very rare in childhood and uncommon until about 35. Consequently, prior to this age, the benefits of preventive treatment clearly outweigh the costs.

Although the threat of hepatitis has greatly reduced preventive treatment of older reactors unless they have additional risk factors, this limitation may yet turn out to be advantageous, by forcing us to focus our attention on the groups at greatest risk. At current tuberculosis rates, a 30-year-old tuberculin reactor has about one chance in 25 of developing tuberculosis at some time in the future, and a 10-year-old reactor has almost twice that risk. These are not trifling threats to health, yet they can be markedly reduced by an essentially trivial procedure—one tablet of cheap medication each day for 6 to 12 months.

In keeping with the theme of this convention, I hope that present knowledge of the epidemiology of tuberculosis will be applied to the provision of health care for nonwhite and poor Americans in a way that will accelerate the downward trend of tuberculosis among the groups who for decades have had the highest incidence of the disease. With proper community support and planning, the biologic imbalance that Frost identified 35 years ago can be brought to fruition within the next generation.

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