Advances Toward the Conquest of Tuberculosis

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The eventual conquest of tuberculosis has been predicted for a long while. In the 1930s Wade Hampton Frost made a cautious prediction. He wrote, "The evidence indicates that in this country the balance is already against the survival of the tubercle bacillus; and we may reasonably expect that the disease will eventually be eradicated. There can be no certainty of this result, but it is an expectation sufficiently well grounded to justify shaping our tuberculosis control program toward this definite end."

Somewhat later, a more dramatic and optimistic prediction was offered in a book on tuberculosis control, as follows: "The bells that ring in the year 2000 may sound the death knell of the tubercle bacillus . . . The ultimate surrender of the tubercle bacillus, therefore, is at least two generations away unless new developments in treatment come to our aid."

And they did! Chemotherapy and chemoprophylaxis began to be used soon after the second prediction was made. Nevertheless, it now seems unlikely that the prediction will prove correct. Epidemiologists know well the hazards of extrapolation of trends. But it is striking that the prediction was made at a time when no drugs effective against tuberculosis were in use. The decline has continued, the disease has become more focal in distribution, and knowledge about it has grown, but the goal is still at a distance. Which of the new developments give the greatest hope, and will the predictions ultimately prove correct?

Dr. George W. Comstock discusses these developments. Dr. Comstock is professor of epidemiology at the Johns Hopkins School of Hygiene and Public Health and editor-in-chief of the American Journal of Epidemiology. Most of his earlier career was spent with the Public Health Service in tuberculosis control. He has worked extensively on BCG vaccination, chemoprophylaxis, mass chest radiography, and the use of the tuberculin test, and still maintains a very active interest in these topics.—PHILIP SARTWELL, MD

ANY CHOICE OF LANDMARKS is susceptible to selection bias, for judgments and the effects of past experiences can never be completely disentangled. To minimize this bias, the following criteria were used. A landmark in epidemiology had to make a fundamental contribution

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to our knowledge of the distribution of tuberculosis and its natural determinants or to epidemiology in general. This meant that important contributions to pathogenesis, therapy, and prevention of tuberculosis were omitted unless they also contributed directly to epidemiologic knowledge. Furthermore, I did not always pick the first study in a given field. This decision is based on a geographic analogy: the Mississippi River is clearly a landmark for much of its length but its sources, while essential to the river's existence, would scarcely be looked upon as landmarks.

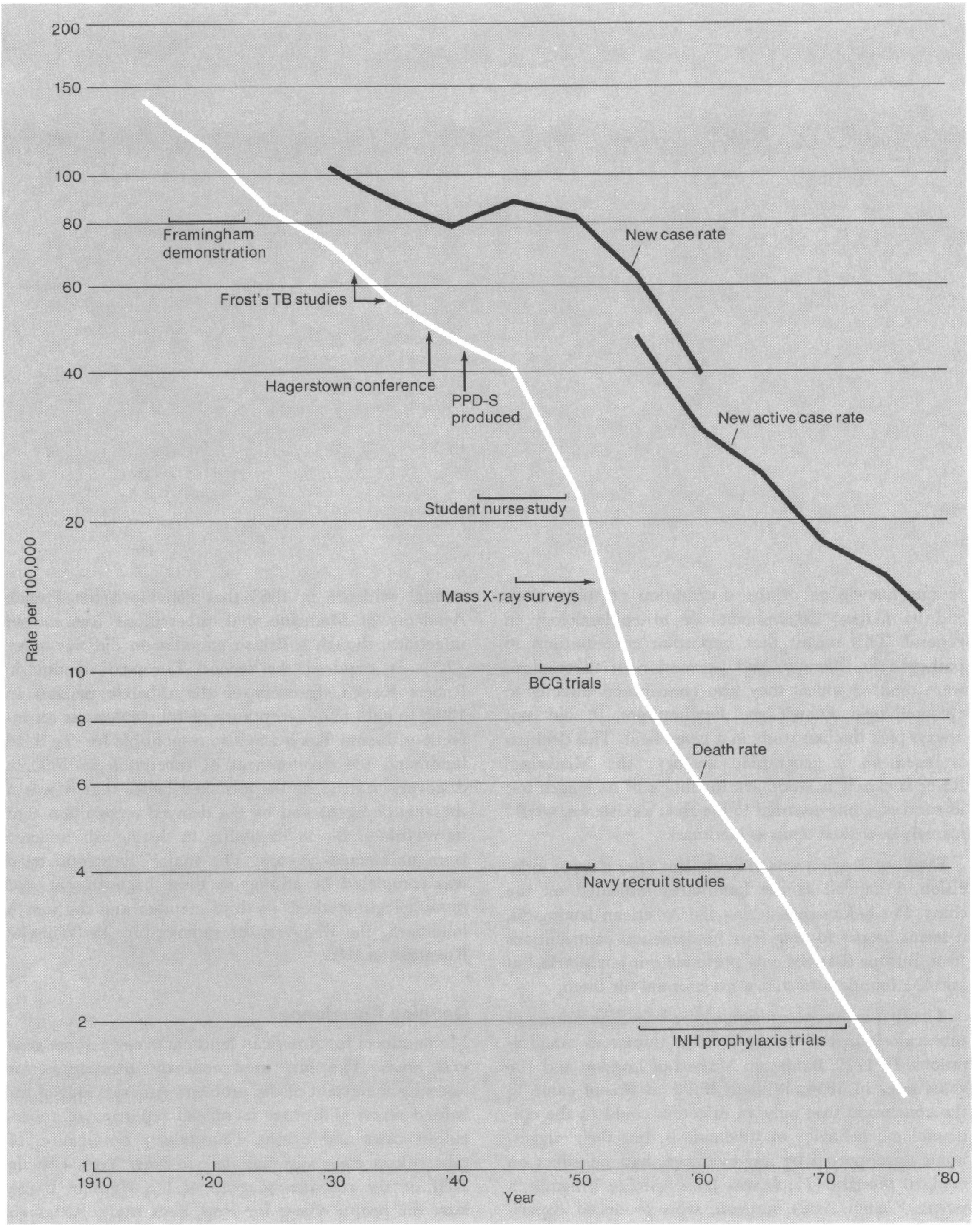
Even so, decision was difficult. But after days of indecision, I arrived at the landmarks indicated on the chart. But before considering the American landmarks, it seems proper to note four fundamental contributions from Europe that not only preceded our landmarks but laid the foundations that were essential for them.

The first is the recognition of the infectious nature of tuberculosis and of the unity of its numerous manifestations. In 1720, Benjamin Marten of London and 136 years later in 1856, William Budd of Bristol came to the conclusion that only an infection could fit the epidemiologic behavior of tuberculosis, but their suggestions, unsupported by any evidence, had no effect on medical thought (*1*). It was Jean Antoine Villemin, a young French Army surgeon, who produced experimental evidence in 1865 that convinced the French Academy of Medicine that tuberculosis was indeed infectious, though a British commission did not agree (*2,3*). It required the second European landmark, Robert Koch's discovery of the tubercle bacillus in 1882, to gain final acceptance of tuberculosis as an infectious disease. Koch was also responsible for the third landmark, the development of tuberculin in 1890, a discovery marred by his mistaken belief that it was a therapeutic agent and by the delayed recognition that its usefulness lay in its ability to distinguish infected from uninfected persons. The major diagnostic triad was completed by adding to these bacteriologic and immunologic methods its third member and the fourth landmark, the discovery of radiography by Wilhelm Roentgen in 1895.

Gauging Prevalence

My nominees for American landmarks cover three general areas. The first area concerns procedures for assessing the extent of the problem. America lagged far behind much of Europe in official reporting of tuberculosis cases and deaths. Compulsory notification of tuberculosis cases was initiated in New York City in 1897 on the recommendations of Dr. Herman Biggs, later the health officer for New York State. Although

Trends in the death rate from tuberculosis, the new case rate, and the new active case rate for the death registration area of the United States, 1910–1976, and selected landmarks in the epidemiology of tuberculosis.



tuberculosis subsequently became legally reportable in all States, information on newly reported cases did not become available for the entire country until 1930 (*4*). And only in 1952 did the case rate become truly meaningful by limiting it to newly reported active cases.

Universal death reporting in the United States showed a similar lag. In the middle of the last century, death statistics were available for only a few cities. In 1897, Charles V. Chapin of Providence, R. I., an active promoter of accuracy in death certification, joined Cressy L. Wilbur of Michigan and John S. Fulton of Maryland on the American Public Health Association's Committee on Demography and Vital Statistics, a group that was one of the principal proponents of registration (*5*). In 1900, the annual collection of mortality statistics for the national death-registration area began, but this area did not include all 48 contiguous States until 1933 (*6*).

Although reported cases and deaths gave important clues to the distribution of tuberculosis by time, place, and person, neither was satisfactory as a measure of prevalence. There was good reason to believe that new case reports represented only part of the tuberculosis problem because of inadequacies both in diagnosis and reporting. Notifications of tuberculosis deaths, on the other hand, appeared to be much more nearly complete, but gave a drastic under-estimate of the problem. The demonstration in Framingham, Mass., supported by the Metropolitan Life Insurance Company, helped remedy this defect (*7*). After a careful review of the morbidity and mortality records for Framingham and seven similar control towns, an ambitious program of health education, casefinding, and treatment was instituted in Framingham in 1917. Six years later, the tuberculosis case rate in Framingham had fallen by 68 percent compared to 32 percent for the control towns. In the demonstration it was found that for every annual death from tuberculosis, there were nine active cases prevalent in the community. Although it was recognized that this ratio of 9 to 1 undoubtedly varied from community to community, it remained a useful guideline for health planners for the next 20 years (*8*).

The mass X-ray surveys during the years following World War II, even though dependent on voluntary participation, gave a much better picture of prevalence of disease. Millions of persons were examined, and rates of demonstrable disease became available by age, sex, and race (*9,10*). Many whose ideas of the distribution of tuberculosis had come from mortality and morbidity statistics were surprised that the prevalence of disease was higher among whites than among blacks, and that bacteriologically positive tuberculosis was more frequent among old than young adults (*10*). The epidemiologic tragedy of the survey years is that we did not follow the example of Cochrane and his colleagues in the Rhondda Fach of Wales and measure the effect of removing chronic spreaders on the rate of transmission of tuberculous infection (*11,12*).

Contributions to Epidemiologic Methodology

The second general area covers the contributions of tuberculosis studies to general epidemiologic methodology. In considerable measure, these contributions resulted from the abilities of Wade Hampton Frost as a synthesizer and teacher. In the 1930s, he became interested in the problems of analyzing data on chronic diseases. Because tuberculosis seemed an appropriate model for the transition from acute infectious diseases, he worked with findings that developed from his relationships with studies in Kingsport and Williamson County, Tenn.; Cattaraugus County, N. Y.; and the Harriet Lane Clinic and the Eastern Health District in Baltimore (*13*).

The usefulness of the secondary attack rate in measuring risks in acute infectious diseases had already been clearly demonstrated. In tuberculosis, however, it was often impossible to identify who had the primary case, but rates comparable to secondary attack rates could be developed by treating the first case to be recognized in a family—the index case—similarly to the primary case of an acute disease. To obtain appropriate denominators for his rates, Frost recognized the usefulness of applying actuarial life table methods to disease outcomes, an approach developed by Pope at the Trudeau Sanatorium to study survivorship of tuberculosis patients after treatment (*14*). Frost's work and that of his students played a major role in popularizing the life table method for handling variable periods of observation, a procedure that has now become commonplace.

At one point, Frost was concerned that the success of tuberculosis control activities might merely postpone tuberculosis infection from childhood to adult life and, as was known to occur in many childhood diseases, that postponement might lead to increased severity. In his study of tuberculosis mortality rates in Massachusetts, this fear at first appeared to be confirmed. In each successive decade, the peak of mortality was shifting to older and older ages. But by rearranging the usual presentation of such tables to show the experience of successive birth cohorts as they passed simultaneously through time and life, he was able to demonstrate that the peak risks for every generation came in infancy and in early adult life (*15*). Not only is his description of this work one of the clearest expositions of cohort analysis, but his interpretation of the findings led to a

very early recognition of the importance of long-delayed reactivation of dormant lesions in the development of tuberculous disease.

The third and last general area concerns the identification of risk factors. The risk of developing any infectious disease depends on two sets of risks—the risk of becoming infected and the risk of developing disease after infection. For most acute infections, this separation into two stages is inconsequential. Their incubation periods are fixed within short, discrete intervals after infection. Once this interval is past, there is usually no further danger of becoming ill, and the infected person may actually be better off as the result of having developed immunity. This is not so for tuberculosis. Even though the highest risk of disease is likely to come shortly after infection, the subsequent lifetime risk will still be great because of the net effect of a low risk operating over a very long time.

Unfortunately, most of the tuberculosis literature does not distinguish between these two risks. For example, there is a plethora of evidence that tuberculous disease is more common among persons of low socioeconomic status. Is this because they are more likely to have been infected? More likely to develop disease after infection? A combination of these factors? As will be mentioned later, the scanty evidence that is available indicates that in the United States the controlling factor associated with poverty is the increased risk of becoming infected, not the subsequent risk of disease.

Risk of Infection

The tool for assessing the existence of past or present infection is the tuberculin test. For many years, any reaction to any dose of tuberculin was considered to be pathognomonic of infection with tubercle bacilli. Evidence of pulmonary calcification was also believed to be pathognomonic. When several groups of competent workers found widespread evidence of disagreement between these two indicators, a period of doubt about our ability to diagnose tuberculous infection ensued. That there was a real basis for these doubts was confirmed by a conference in Hagerstown in 1938 (*16*). But the major benefit of that conference was its effect on a young investigator named Carroll Palmer, who came away with the notion that the most likely explanation of the discrepant findings was that neither tuberculin sensitivity nor pulmonary calcification was pathognomonic. Most of his subsequent professional life was spent in demonstrating just what tuberculin sensitivity signified. His work was based on very large numbers of subjects; his animal and human studies were thoughtfully integrated, designed with attention to statistical and epidemiologic principles, and conducted with special attention to accurate and unbiased measurements. In addition, his studies of human beings were carried out within the framework of public health practice, thereby making long-term observations possible at minimal cost. Had he worked in a more dramatic field, less removed from the mainstream of medicine than tuberculosis, I have no doubt that he would be acclaimed as America's greatest practicing epidemiologist.

A necessity for all studies of the risk of acquiring tuberculous infection was an adequate test material. For a half century after its discovery, tuberculin was prepared in small batches which varied widely in composition and potency. The need for a uniform test material was finally met by the preparation of a tuberculin, PPD–S, by Florence Seibert. PPD–S was accepted as the U.S. standard in 1941 and later as the international standard (*17*). It is intriguing to note that no one has yet been able to produce a more sensitive and specific test material. Even more important than the development of this test material was the foresight of Dr. Seibert in preparing a single, very large batch so that numerous large studies could all use the same material, thereby removing a major potential variable.

One of the first large-scale uses of the new standard tuberculin was a study of student nurses, conducted in the late 1940s by the Public Health Service, which involved 25,000 young women from all parts of the country (*18*). Every 6 months during their training, they were examined by skin tests and chest X-rays. Several important points quickly became apparent as a result of conducting similar examinations on large numbers of comparable subjects living in different areas. First, pulmonary calcifications were much more likely to be associated with sensitivity to histoplasmin than to tuberculin. Second, sensitivity to a low dose of tuberculin exhibited a dramatically different pattern from sensitivity to a high dose. Low-dose sensitivity was closely associated with a history of close contact with tuberculosis and showed little geographic variation. High-dose sensitivity, on the other hand, was unrelated to tuberculosis exposure and showed remarkable variation in frequency according to place of residence.

These conclusions were confirmed and amplified by skin tests of more than a million Navy recruits (*19*). These young men were routinely tested wtih PPD–S and histoplasmin. In addition, they received two other skin tests, usually with antigens from other mycobacteria that had been carefully standardized in guinea pigs, but occasionally with duplicate tests or diluent as controls on the test readings. Sensitivity to several nontuberculous mycobacterial antigens was remarkably widespread, reaching frequencies of more than 90 percent for some antigens among men from certain areas.

This was further evidence of the high frequency of nontuberculous mycobacterial infections in the southeastern United States and the problems they cause in interpreting reactions to tuberculin. An added bonus was that the administration of a standardized test over a period of years to the same kind of a sample allowed an estimate of changes in the risk of infection with time as well as with place and person. In this country the average risk of becoming infected must now be close to 1 per 10,000 per year.

A landmark not indicated on the chart is the study of tuberculous infection among household contacts by Chapman and Dyerly (*20*). This investigation appears to have been the first to have examined personal risk factors for infection in a way that allows an estimate of the relative effects of each risk, independent of the effects of the others. Particularly intriguing was the finding that household income was only slightly associated with the risk of infection: what the family had to show for their income in the way of household furnishings was much more important.

Risk of Disease After Infection

Risks of developing tuberculous disease after infection were established by the BCG vaccine trials in Puerto Rico, Georgia, and Alabama (*21*); the Navy recruit studies (*22*); and the isoniazid prophylaxis trials (*23*). These studies all involved very large numbers of individuals with periods of observation ranging from 4 years for the Navy recruits to more than 20 years for the BCG trial participants. All subjects had their infection status established initially by careful examinations. Long-term followup was possible at low cost by utilizing data that were being routinely collected for other purposes.

Prior to these studies, it was widely believed that almost all tuberculosis cases arose as the result of a recent infection (*24*). This belief was responsible for an investigation in Muscogee County, Ga., of all contacts of persons with newly developed disease. That the tuberculosis among those with the index cases was recent was established by demonstrating that the person's previous chest X-ray was normal on review. Current thinking led us to expect that the source of infection for these cases would be easy to discover, thereby making it possible to study factors related to disease transmission. More than 1,300 contacts of all sorts were identified for the first 56 newly developed cases, and nearly all of these contacts were examined. To our surprise, only one possible source case was discovered. This single possibility was a dramatic indication that most cases of tuberculosis in the United States were not coming from new infections but from old ones, a fact now solidly established by the long-term followup of persons in the Navy study and in the BCG and isoniazid trials.

This conclusion had a profound effect on tuberculosis control in the United States. With a very low risk of becoming infected, and most disease arising among persons who had been infected years ago, there was little need to vaccinate uninfected persons, even if it were possible to identify a potent vaccine. Rather, the need is for a means of identifying those who are harboring tubercle bacilli, and an effective, safe method of treating their dormant infections. These needs are only partially and inadequately met by the current tuberculin tests and preventive treatment with isoniazid.

The demonstration that BCG had little potential usefulness in this country and the administrative decisions not to use it as a general prophylactic procedure have given American epidemiologists a tremendous advantage over their colleagues in other countries where tuberculin reactions from vaccination cannot be distinguished from those from natural infections. Here, without vaccination, it is possible to study both stages in the pathogenesis of tuberculosis. For example, we have been able to obtain evidence bearing on the observation that the poor have more tuberculosis than the rich. The risk of becoming infected is clearly greater among the poor (*25*) while the risk of developing disease after infection is not (*26*). The association of body weight with tuberculosis, on the other hand, shows a reversal of the importance of the two stages. Underweight and overweight persons are equally likely to be infected, but infection in the underweight individual is more likely to lead to subsequent tuberculosis disease (*27*).

To reduce the risk associated with poverty requires actions that reduce the risk of infection, such as early diagnosis and adequate treatment of cases by improving access to medical care and further decreasing the likelihood of transmission by improvements in hygiene, housing, and ventilation. To reduce the risk associated with being underweight, on the other hand, requires some way of altering the complex factors involved in resistance so that they weigh against the tubercle bacillus and in favor of the host.

The ability to distinguish risk factors for infection from those for subsequent disease can be simply summarized as follows. The known risk factors for becoming infected are exogenous: the probability of coming in contact with a person who has an infectious case, and factors related to the likelihood of airborne transmission of organisms such as intimacy and duration of contact, adequacy of ventilation, and the presence of ultraviolet irradiation. The known risk factors for de-

veloping disease after infection are all endogenous, namely, age, sex, body build, and immune status.

The brevity of the foregoing summary is indicative of how little we know about the epidemiology of tuberculosis. Despite this, the balance in developed countries has long been tipped against the tubercle bacillus, and the United States has demonstrated that a massive application of present-day control activities can bring one of the world's worst tuberculosis epidemics close to eradication (*28*). But such encouraging reports must not lead to optimism. Massive applications of control activities are unrealistic for all but a handful of the world's population. Tuberculosis is not declining in many areas and, where it is, there is often a tendency to eradicate the control program before the disease.

It seems unlikely that tuberculosis can be brought and kept under control throughout the world without landmark progress in several scientific fields. Perhaps the most needed is some way to identify the relatively small minority of infected persons who under ordinary circumstances will contribute greatly to the tuberculosis problems of developed and developing countries alike. Second only to this need is a medication that will safely and significantly reduce the mycobacterial burden of these infected persons. While the initial steps in meeting these needs must come from the laboratory, epidemiologic studies will be necessary to assess the applicability of the proposed solutions. Only when we have passed these two future epidemiologic landmarks will we be reasonably safe in talking about our conquest of tuberculosis.

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