Wade Hampton Frost, who was a Professor of Epidemiology at Johns Hopkins University from 1919 to 1938, spurred the development of epidemiologic methods. His 6 publications in the American Journal of Hygiene, which later became the American Journal of Epidemiology, comprise a 1928 Cutter lecture on a theory of epidemics, a survey-based study of tonsillectomy and immunity to Corynebacterium diphtheriae (1931), 2 papers from a longitudinal study of the incidence of minor respiratory diseases (1933 and 1935), an attack rate ratio analysis of the decline of diphtheria in Baltimore (1936), and a 1936 lecture on the age, time, and cohort analysis of tuberculosis mortality. These 6 American Journal of Hygiene/American Journal of Epidemiology papers attest that Frost's personal evolution mirrored that of the emerging “early” epidemiology: The scope of epidemiology extended beyond the study of epidemics of acute infectious diseases, and rigorous comparative study designs and their associated quantitative methods came to light.

The Virginian Wade Hampton Frost, commonly known as Jack, was born in 1880 and received a doctor of medicine degree in 1903. His professional life comprised 4 distinct periods: 1) From 1905 to 1908, he was an assistant surgeon in the Public Health and Marine Hospital Service (now the Public Health Service). 2) From 1908 to 1913, he worked at the Hygienic Laboratory (the forerunner of the National Institutes of Health) in Washington, DC. 3) From 1913 to 1918, while still working for the Public Health Service, he began to oversee Cincinnati’s water quality. 4) For the historically most distinct period of his life, from 1919 until his death in 1938 (from esophageal cancer; he was a chain smoker but did not seem to have suspected the association), he moved to the Johns Hopkins School of Hygiene and Public Health to be the first chair of the newly created Department of Epidemiology and eventually the Dean (1931–1934). Until 1929, he remained on the Public Health Service payroll, officially as expert in water quality.

The magnitude and diversity of Frost’s contribution to the evolution of epidemiology is reflected in articles about him by colleagues at Johns Hopkins (1–6), epidemiologists (7, 8), and historians (9) and in a biography (10). The present article focuses only on some aspects of Frost’s published scientific work, specifically his publications in the American Journal of Hygiene/American Journal of Epidemiology, because the “Snippets From the Past” articles are about the history of
epidemiology viewed from the vantage point of this journal.

FROST’S PUBLICATIONS

Table 1 shows some characteristics of Frost’s 63 publications (including 2 that were printed posthumously). Approximately 75% were single-authored, and almost half (29 of 63; 46%) appeared in the Public Health Reports and Public Health Bulletin (journals of the US Public Health Service) and in the Hygienic Laboratory Bulletin (forerunner of the NIH Bulletin); polio was the most common topic in his papers written mostly before he joined the Johns Hopkins School of Hygiene and Public Health.

Frost authored 6 papers in American Journal of Hygiene/American Journal of Epidemiology, including 2 that were published posthumously (11–16). The gist of these papers is summarized below in chronological order of conception.

The agent, host, and environment triad (1928)

On February 3, 1928 at Harvard University, Frost presented a Cutter Lecture, named after a 19th-century medical doctor who allocated half of his estate’s net income to the founding of an annual lecture on preventive medicine (17). Frost’s lecture, published in 1976, sketches a theory of epidemics that was founded on a postulated equilibrium between the agent, the host, and the environment. Admittedly, the now famous concept of the “epidemiologic triad” was already in the air in the 19th century, but this was the first instance to my knowledge that it was explicitly laid out. “The factors concerned in keeping up this equilibrium and in bringing about the changes from one level of prevalence to another are: 1) A specific microorganism capable of producing the infection and the disease . . . . 2) A host population (man being usually the host to which we refer) containing susceptible individuals in sufficient numbers to keep up the infection. 3) Such conditions of environment as are necessary for bringing the specific microorganism into potentially effective contact with infectible hosts” (13, pp. 143–144).

Frost explained how changes in the equilibrium govern the course of an epidemic. The editor of the American Journal of Epidemiology represented the theory in a figure that did not belong to Frost’s paper (Figure 1). In a 100% susceptible population, incidence grows rapidly when susceptible persons abound, ebbs when susceptible persons die off, and then progressively dies out completely. As the 22% of remaining susceptible persons at the end of the epidemic in Figure 1 illustrates, “to check an epidemic and bring the rate of prevalence temporarily below the level of equilibrium it is by no means necessary that all the susceptible persons in the population must have been infected. They need only be reduced below a certain critical ratio” (13, p. 148).

Frost had discussed this theory of epidemics with Lowell J. Reed, who was then head of the Department of Biometry and Vital Statistics of the Johns Hopkins School of Hygiene and Public Health and who had developed its mathematical aspects. Neither Reed nor Frost ever wrote about their eponymous Reed-Frost epidemic theory.
Does tonsillectomy confer a protection against diphtheria? This clinical belief developed out of surveys conducted in Baltimore (by a student of Frost, James A. Doull) (20) and Hagerstown (21), Maryland. It was unclear whether tonsillectomy disenfranchised the diphtheria bacillus from its favorite invasion tissues or whether it stimulated immunity. Since 1910, immunity was able to be assessed using the Schick test, an intradermal injection of diphtheria toxin that caused an erythematous edema. The age distribution of the excess cases. They assumed that respiratory diseases of different etiology would have different age distributions. Table 2 compares the weekly incidence of febrile and nonfebrile cases of acute minor respiratory diseases by age. The new difference in attack rate was 24% (73 cases out of 308 subjects) rather than the 11% observed in the full sample of families. The higher incidence of cases with fever that occurred throughout 1928–1929 fully accounted for this difference. The age distributions of all the 2-way combinations of febrile and nonfebrile illnesses were compared using the conventional Chi-square test for goodness of fit with 6 degrees of freedom, indicating that "the frequency (P) with which an equal or greater difference may be expected to occur in random samples of the same numbers drawn from the same universe" (14, pp. 661–662). Only the comparisons between febrile and nonfebrile illnesses within a given year were statistically significant (Table 3). Moreover, trends in febrile diseases in the sample correlated well with the overall deaths.
from influenza and pneumonia in Baltimore (see Figure 1 of Frost and Van Volkenburgh (14)).

The paper fell short of a consequentialist conclusion about the role of febrile respiratory illnesses in the surveillance of influenza, but it stressed that, of febrile and nonfebrile diseases, the former was more frequent in times of severe influenza. “This naturally raises the question of the etiological relationship between the disease which was so widely epidemic in 1928–29, and the more or less similar disease or group of diseases which occurs endemically. Any useful discussion of this question must, however, take into consideration a much broader range of facts than is here presented, and such a review is far beyond the scope of this paper” (14, p. 663).

Factorizing the decline of diphtheria in Baltimore (1936)

Why did the rates of mortality and morbidity from diphtheria, shown in Figure 2, fall abruptly after 1928? The comparison of 2 surveys of white school children from East Baltimore who were 5 to 14 years of age in 1921–1922 and 1933–1934 provided the basis for Frost et al. to address this question (15). The paper stemmed from the dissertation that the last author, Morton Levin, defended in 1934 (10).

With active immunization of the source population having begun in 1925, the proportions of immunized children in the 2 surveys were 0% and approximately 55%. No age adjustment was needed for the comparison of the 2 surveys. In approximately 12 years, the attack rate of diphtheria (i.e., the probability of developing diphtheria within 1 year) had declined by a factor 0.10, from 683 to 66 per 100,000 per year. However, the prevalence of Schick-negative immune children had only declined by a factor 0.65, from 49.4% to 32.3%. Immunization did not therefore tell the whole story.

Frost et al. proposed the following factorization of the attack rate ratio:

\[ \text{if:} \]
\[ p = \text{the probability of being Schick-positive;} \]
\[ p' = \text{the probability of being infected with virulent } \text{Corynebacterium} \text{ diphtheriae within 1 year;} \]
\[ r = \text{the proportion of infected Schick-positives who develop diphtheria}; \]
\[ P = \text{the probability of developing diphtheria within 1 year}, \]
\[ P = p \times p' \times r. \]

Using the subscripts 1 and 2 to denote, respectively, the periods 1921-24 and 1933-36, conditions in the two periods are related as follows:
\[
\frac{(1933-36) \, P_2}{(1921-24) \, P_1} = \frac{p_2 \times p'_2 \times r_2}{p_1 \times p'_1 \times r_1}.
\]

Thus, \( P_2/P_1 = 0.10 \) and \( p_2/p_1 = 0.65 \). Frost et al. then estimated, using the decline of the proportion of immune carriers of \( \text{Corynebacterium diphtheriae} \) from 2.44\% to 1.08\%, that \( p_2/p_1' = 0.44 \). Jointly, more immunization and less infection could explain a decline in the mortality rate by a factor \( 0.65 \times 0.44 = 0.286 \). An additional element must have reduced the risk of nonimmune Schick-positive children contracting diphtheria by a factor of \( r_2/r_1 = 0.10/0.286 = 0.35 \). Besides immunization and reduced infection, concluded the paper, “human resistance and bacterial quality” must have changed too and reduced the “proportion of infected Schick-positives who develop diphtheria” (15, p. 583).

The age, time, and cohort analysis (1936)

Does the rate of death from tuberculosis increase with age? In 1936, Frost discussed before the Southern Branch of the American Public Health Association a source of concern in the vital statistics for tuberculosis (16). Between 1880 and 1930, mortality rates had continuously declined in all age groups, suggesting a tapering exposure to \( \text{Mycobacterium tuberculosis} \). Nonetheless, in 1930, the greatest risks of death from tuberculosis seemed to occur between the ages of 50 and 60 years.

For some years, Frost had thought of the high mortality rate experienced in later life as a “postponement of maximum risk to a later period” (p. 96) resulting from having “escaped” (p. 91) excessive mortality in earlier adult life (16). He drew an analogy to nontuberculosis pneumonia, which is fatal chiefly in the extremes of life, to explain his reasoning.

However, when Frost took mortality rates from tuberculosis in Massachusetts, compiled by the late Edgar Sydenstricker (1881–1936), and arranged them in cohorts of people born during the same decade, tuberculosis mortality rates consistently decreased after 30 years of age. Frost understood that the age-specific mortality rates for any single year incorporated the rates from multiple cohorts and that “the present high rates in old age were the residuals of higher rates in earlier life” (16, p. 96). In Figure 3, consider how the middle curve, corresponding to the cohort of people born between 1880 and 1889 (“cohort of 1880”) merges with the 2 other curves. The cohort makes up for the people aged 1–9 years in 1880–1889, (“year 1880,” upper curve) and for the people aged 50–59 years in 1830–1839 (“year 1900,” lower curve).

Thus, Frost’s cohort analysis rebutted his own fear that the declining trends in tuberculosis hid a postponement of infections with \( \text{Mycobacterium tuberculosis} \). Even though this paper is one of his most enduring contributions, Frost did not try to publish it during the 2 additional years he lived.

The manuscript was found in his desk drawer and published posthumously in 1939 (4).

CONCLUSIONS

The 6 publications Frost had in the American Journal of Hygiene/American Journal of Epidemiology are spread throughout the last decade of his life, while he was the Chair of Epidemiology at Johns Hopkins University. There is a clear progression in the papers. Frost’s personal evolution closely tracked the traits of the emerging phase of early epidemiology: The scope of epidemiology extended beyond the study of epidemics of acute infectious diseases, and rigorous comparative study designs and their associated quantitative methods came to light (23).

As shown by Frost’s evolving definition of epidemiology (24), he began his chairmanship with a concept of epidemiology confined to the natural history of the infectious diseases. Unsurprisingly, he chose to elaborate on a theory of why epidemics recur periodically as one of the topics for his 1928 Cutter lectures. The theory was relevant for diseases such as typhoid fever, diarrheal diseases of infants, pneumonia, measles, scarlet fever, and yellow fever. Why didn’t Frost publish the text of the lecture? Between 1928 and his death in 1938, he would have had the opportunity to refine and publish the theory of epidemics he had conceived with Reed. Could it be that his interest in the topic was waning? As a matter of fact, Frost progressively enlarged the definition of epidemiology to incorporate the study of tuberculosis and
scurvy, and finally of all diseases and disabilities. In this process, the center of gravity of his expertise switched from content (e.g., water quality and epidemic outbreaks) to methods of comparative studies.

The primacy of group comparisons was already present in the 1931 paper about diphtheria and tonsillectomy (11), despite the fact that it was based on 2 surveys. The design served as a substitute for what would today be approached using a cohort study of rates of immunity acquisition among students who had and had not undergone tonsillectomy or a case-control study of Schick-positive and Schick-negative students.

However, a qualitative change occurs in the influenza/respiratory disease papers of 1933 and 1936 (12, 14). The longitudinal study assessed real-time incident cases in a large number of families. By then, the brunt of Frost’s thinking was being applied to longitudinal designs. In a project conducted in Tennessee, he had contrived a way to avoid the long-term follow-up of families by reconstructing cohorts of persons exposed and unexposed to tuberculosis on the basis of family histories, computing and comparing morbidity and mortality rates of tuberculosis with person-time as the denominators (25).

Further methodological forays occurred when in 1935, Frost and his collaborators analyzed the decline of diphtheria morbidity. They used a novel effect measure that is now an integral part of comparative designs: the rate ratio. They computed an attack rate ratio of diphtheria and decomposed it into 3 probability ratios because to fall sick with diphtheria (P), the child had to be Schick-positive (nonimmune) (p), infected by C. diphtheriae (p′), and liable for developing a clinical disease for reasons that were at the time still elusive (r).

The age, time, and cohort analysis of the mortality rates from tuberculosis is one of the more lauded contributions by Frost (16). This neat work reflects the growing awareness of the limitations of the traditional vital statistics–based cross-sectional perspective and of the need to enrich it with a longitudinal one. George Comstock defended Frost’s cohort analysis as a genuine discovery (4).

This selected sample of Frost’s publications, spanning over his last 10 years, suggests that his methodological creativity was taking momentum at the time of his premature death. It also makes one dream of a Frost-written textbook. The long review paper entitled “Epidemiology” (26) published in 1927 reads like the nucleus of a potential textbook, but it was written before the work on tuberculosis had transformed Frost’s vision of epidemiology and probably the way he taught it.

A final note is that reviewing the publications by Frost’s students in the American Journal of Hygiene can give a more complete representation of Frost’s scientific contribution. Frost was notoriously reluctant to co-author papers, even when he had substantially contributed as mentor or advisor. The fact that 75% of his publications were single-authored speaks of his tendency to restrict his signature to papers he had written alone. However, there is also this testimony of one of Frost’s students that can serve as a conclusion to this snippet, while shedding light on Frost as a man and on limitation of the present review. “I’d have my tables and what I had drafted as a paper, and he would go over it carefully, and he’d look for those jokers [confounders and biases] with you. Oh, he devoted an awful lot of time to his students . . . A number of papers that I wrote should have had his name on [them], because he did just as much as I did, but he wouldn’t . . . I would have been so proud to have his name on a paper with mine, but he said, no, you did this research. I’m just reviewing it with you” (10, pp. 165–166).

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REFERENCES


