Young
Epidemiology
Scholars
Competition

Epidemiology as a Liberal Art

by David W. Fraser
The New England Journal of Medicine

Reproduced by permission

Abstract

Epidemiology has features that resemble those of the traditional liberal arts. This makes it fit both for inclusion in an undergraduate curriculum and as an example in medical school of the continuing value of a liberal education. As a "low-technology" science, epidemiology is readily accessible to nonspecialists. Because it is useful for taking a first look at a new problem, it is applicable to a broad range of interesting phenomena. Furthermore, it emphasizes method rather than arcane knowledge and illustrates the approaches to problems and the kinds of thinking that a liberal education should cultivate: the scientific method, analogic thinking, deductive reasoning, problem solving within constraints, and concern for aesthetic values. (N Engl J Med 1987; 316:309-14).

Text:

The sharp distinction between undergraduate and medical education has been a peculiar and useful characteristic of the educational system in the United States. Because physicians-to-be are expected to finish four years of college before medical school, they are encouraged to acquire a broad understanding of the liberal arts. Recently, the importance of this breadth has been emphasized, especially in the humanities (Ref. 1). The distinction, however, may have obscured the fact that a medical discipline need not be confiningly narrow and may in fact contain many of the elements of the liberal arts that make them suitable for an undergraduate curriculum.

In judging the suitability of a discipline for undergraduate study, one should look for the essential characteristics of the liberal arts, which I take to be the fields that help free students from the limitations of prior beliefs and experiences and that teach important modes of thinking so as to prepare them to ask and answer new questions. Five approaches to problems or modes of thinking stand out as particularly important, and although not all may be used in a particular discipline, students should seek to become competent in each during the course of liberal arts study. The five, in no particular order, are the scientific method, analogic thinking, deductive reasoning, problem solving within constraints, and concern for aesthetic values.

In this paper, I propose epidemiology as an example of a discipline that, although rarely included in undergraduate liberal arts education, (Ref. 2,3) might well be. This essay is not intended particularly as a brief for epidemiology or to explain why an epidemiologist (myself) might head a liberal arts college (Swarthmore). It is meant more as an exploration, using a concrete example, of the characteristics of a discipline that fit it for inclusion in a liberal arts curriculum and a demonstration that, at least for some disciplines, an emphasis on teaching rather than content distinguishes liberal from purely professional learning.

Although it is often assumed to be limited to the investigation of epidemics, epidemiology is more properly considered either the study of patterns of disease occurrence in human populations or, even more broadly, the comparison of rates of occurrence of phenomena in various populations so as to increase understanding of the human situation. Epidemiology is commonly considered one of the subdisciplines of medicine, which -- like other professional disciplines -- is often seen as antithetical to the liberal arts. In some ways that characterization of the professions is fair. Certainly, the arcane nature of the professions, with their heavy emphasis on detailed information, the repetitive application of knowledge to solve common problems, and the narrowness of the scope of inquiry suggest that professional studies are inappropriate for an undergraduate liberal arts education. But epidemiology as a professional discipline is anomalous. The heavy emphasis on the method of inquiry, rather than specialized information, is distinctive. Its usefulness as a technique for taking a first pass at a new problem makes it applicable to a wide range of interesting phenomena. And the fact that it is a "low-technology" science makes it accessible to many who are more interested in clear thinking than in complicated laboratory experimentation.

A series of examples may illustrate best the ways epidemiology draws on various modes of thinking.

Scientific Method

Central to the scientific method are the framing of a hypothesis based on a particular conception of causality in a given situation and the carrying out of an experiment to test that hypothesis. If the data turn out to be inconsistent with the hypothesis, the hypothesis is rejected, and alternatives are sought that can in turn be tested. If the data are consistent with the hypothesis, it is retained, and further ways are sought to test its validity. In laboratory science, that experiment is planned and executed prospectively. In epidemiology, the "experiment" is often carried out by the collection of information retrospectively, after events have already occurred. The information is analyzed in much the same way as that from prospective experiments, although -- because the investigator does not control the conduct of the "experiment" -- additional care must be taken to find convincing evidence that the hypothesized chain of causation, and not some confounding alternative, led to the observed pattern of events.

In April 1973, reports of eight instances of a severe grippe-like illness of uncertain cause in employees of Strong Memorial Hospital and the University of Rochester School of Medicine prompted an epidemiologic investigation (Ref. 4). One of the first steps in such an investigation is to define, at least tentatively, what constitutes a case of the illness. In the first few days of this investigation, before the infectious agent was discovered, a case was defined as occurring in an employee of or a visitor to the medical center who had an episode of fever and muscle aches after January 1, 1971. Once the agent was shown to be lymphocytic choriomeningitis virus, a virus that infects rodents and that may be excreted in their urine for years, another requirement was added: serum antibody to lymphocytic choriomeningitis virus had to be demonstrated by indirect immunofluorescence at a serum dilution of 1:12. That revised definition was used in reporting the results here, although the preliminary definition led to the same conclusions.

A total of 23 cases were found by interviewing employees and reviewing records. Four cases had occurred sporadically before October 1972, but cases had occurred every month thereafter, reaching a maximum of seven in April 1973. Eighteen cases were in people who worked in the radiation departments, and three were in people who worked in the vivarium, the medical center's animal-holding facility.

Testing of serum from various groups of employees confirmed that the radiation therapy department was the focus of infection. Thirty-one of 80 radiation workers (39 percent) had demonstrable antibody to lymphocytic choriomeningitis virus, as compared with 12 of 60 vivarium employees (20 percent) and 5 of 25 others (20 percent). The presence of antibody correlated particularly well with reports of grippe-like illness in the radiation departments, providing further evidence that the recent outbreak was centered there: in the radiation departments, 17 of 31 ill workers (55 percent) had demonstrable antibody, as compared with 14 of 49 workers who were well (29 percent); in other departments, 4 of 20 ill workers (20 percent) had antibody, as compared with 13 of 65 workers who were well (20 percent).

The fact that lymphocytic choriomeningitis virus causes persistent infections in some animals suggested that animal contact might account for the outbreak among the radiation workers. In fact, animals were kept in the radiation department for experiments on the effect of x-rays on implanted tumors. As predicted, the presence of serum antibody in the radiation employees was associated with direct contact with animals in the animal-holding room. Fourteen of 20 persons who had such direct contact (70 percent) were seropositive, as compared with 17 of 60 (28 percent) with no direct contact. However, more than half of the seropositive radiation workers (17 of 31) reported no such contact with animals, so the mechanism of their infections remained unexplained.

It happened, however, that limitations of space in the radiation department had led to creative combinations of functions in the available rooms. One of these involved placing the departmental Xerox machine on the back wall of the animal-holding room. To get to the machine, employees had to pass through a narrow passage flanked by rabbit and hamster cages.

This suggested the hypothesis that the risk of acquiring infection with lymphocytic choriomeningitis virus might be related to the frequency with which one used the Xerox machine. Among those with no direct animal contact, this was indeed the case. Eight of the 14 who entered the holding room daily had antibodies to lymphocytic choriomeningitis virus, whereas 6 of 14 with a weekly exposure of once to four times, 2 of 10 with an exposure of less than once a week, and 1 of 22 with no exposure were seropositive. As for the employees in the vivarium, the pattern of seropositivity confirmed the hypothesis that infection was particularly associated with direct contact with hamsters or rabbits. That left only the illnesses of two other people to explain. One was a plumber, who worked throughout the medical center and was likely to have had considerable contact with rodent urine. The other was the Xerox repairman, who had last serviced the machine in the animal-holding room on March 16 and who became ill on April 4.

This investigation demonstrated that lymphocytic choriomeningitis virus could spread not only by direct contact with infected animals but also indirectly -- probably through the inhalation of infected urine droplets or droplet nuclei. Subsequent testing of the animals and their implanted tumors showed that the hamsters, not the rabbits, were infected and that the source of the infection had been the tumors themselves, which were already infected when the medical center received them several years earlier. Destroying the infected tumor lines and killing the hamsters stopped the outbreak. Nine months later, a nationwide outbreak of lymphocytic choriomeningitis in persons with pet hamsters was traced to a part-time breeder whose regular job was with the firm that had propagated and distributed the tumor lines that the University of Rochester had received contaminated with lymphocytic choriomeningitis virus (Ref. 5). Although it was never proved, an attractive theory is that the breeder had started his colony with infected hamsters he had brought home from work.

Analogic Thinking

Insight into many complex situations, in human experience generally and in scientific exploration specifically, comes from analogy with situations that seem roughly comparable. Much of the value of history and literature derives from the analogies with other times and places, factual or otherwise, that illuminate our lives. In many instances, the wise selection of a hypothesis to be tested by the scientific method comes from insightful analogic thinking.

In September 1972, a Peace Corps physician working in the eastern province of Sierra Leone reported several cases of a severe febrile illness that he thought might be Lassa fever (Ref. 6). The high fatality rate and lack of responsiveness to therapy for malaria and typhoid fever were typical of that disease -- a viral infection that had been discovered in 1969 and recognized in Nigeria and Liberia. However, the Sierra Leone cases were scattered over at least two towns, whereas all earlier outbreaks had occurred in hospitals and had shown clustering typical of person-to-person spread.

When testing of serum specimens from the patients in Sierra Leone confirmed the diagnosis of Lassa fever, an investigation was organized to determine how the disease was spreading and -- if it was not from one person to another -- what the ultimate source might be. Because Lassa virus under the electron microscope resembles lymphocytic choriomeningitis virus and other arenaviruses (which also cause chronic infections in particular rodents), the investigators reasoned, by analogy with the spread of the lymphocytic choriomeningitis virus, that some West African rodent may be susceptible to Lassa virus infection and may infect humans through contaminated urine.

The epidemiologic investigation identified 63 cases in the two years ending October 1, 1972. Fourteen (4.4 per 1000 population) were in Panguma and 18 (1.6 per 1000) were in Tongo; both towns are in the center of the diamond-mining area in the eastern province. The rest were scattered through other villages and towns in that province. Twenty-four patients had died (38 percent). Only 6 of the 63 were known to have had contact with a patient with Lassa fever in the month before they became ill -- 5 members of the Panguma Hospital staff and 1 household contact of a case.

A survey of the households of cases and a random sample of the households of controls in Panguma and Tongo showed that Lassa virus infection clustered in certain households. Excluding the known cases, antibody to Lassa virus was found in 13 percent of the people in case households (27 of 206) but only 6 percent of those in control households (16 of 255). Trapping and testing of a wide variety of animals yielded one -- Mastomys natalensis, known as the multimammate rat -- that was infected with Lassa virus (Ref. 7). That virus was recovered from 14 of 82 mastomys (16 percent) and none of 371 representatives of other species. Of the mastomys trapped in and around the household compounds of two persons with fresh cases of Lassa fever, more than 80 percent were positive for the virus. Mastomys is a feral rat that competes with Rattus rattus for location in human residences in much of sub-Saharan Africa. Social upheaval in the diamond-mining area may have tipped conditions in some way to favor mastomys, which -- once present in a typical West African village household -- would have ample opportunity to contaminate food supplies and surfaces with urine containing virus. Research in Sierra Leone since 1972 has focused on seeking drugs to treat Lassa fever, instituting barrier nursing to prevent person-to-person spread in hospitals, and identifying ecologic factors that might discourage mastomys from occupying houses (Ref. 8).

Deductive Reasoning

Given a set of assumptions, deductive reasoning can lead to conclusions that are particularly firm because of the logical structure in which they are imbedded. Of course, the truth of the assumptions may be challenged, but in some cases that can be tested empirically. A stiffer limitation is often the need to restrict consideration to relatively simple problems, for the solving of which logical reasoning can be made clear and convincing.

Deductive reasoning has proved useful in estimating the efficacy of pneumococcal vaccine in the United States (Ref. 9). Efforts to develop a vaccine against pneumococcal disease began more than 40 years ago because of the importance of the pneumococcus as a cause of pneumonia, meningitis, and other life-threatening infections in adults and children. It has been estimated that some 10 percent of the approximately 3 million cases of pneumonia that occur in the United States each year are caused by the pneumococcus, making it the most common cause of bacterial pneumonia. Early studies showed that antibody to the polysaccharide capsule of some types of pneumococcus could protect against infection, so a vaccine composed of those polysaccharides seemed the most promising candidate. Unfortunately, 83 capsular types of pneumococci have been identified, and the prospect of making 83 different vaccines was daunting. However, the 14 most common types caused about 80 percent of all pneumococcal disease, and several other types had capsular polysaccharides chemically related to the 14, so vaccine development focused on these most common capsular types. Placebo-controlled, randomized prospective trials of vaccines against multiple pneumococcal capsular serotypes were conducted in South Africa among healthy young gold miners, who have a particularly high rate of pneumococcal disease. Estimates of vaccine efficacy in that population against serotypes included in the vaccine ranged from 76 to 100 percent. Subsequent prospective trials in this country in nursing-home residents and alcoholics -- two groups at relatively high risk of pneumococcal disease here -- showed no convincing evidence of efficacy, but the small size of the trials may have obscured efficacy.

In 1977, a pneumococcal vaccine designed to be effective against 14 capsular types was licensed for use in the United States. Continuing questions about the efficacy of the vaccine in groups at high risk of pneumococcal disease in the United States limited its use. The fact that the vaccine was licensed, however, made it unfeasible and probably unethical -- because the control group would be denied the vaccine -- to conduct further randomized clinical trials to determine whether the vaccine was effective in the groups for which it was recommended in this country. This quandary called for a method other than a vaccine trial -- one that would permit a vaccine's efficacy to be estimated after licensure.

The creation of such a method by deduction took advantage of the fact that more pneumococcal serotypes existed than were in the vaccine. Let us call the ratio of vaccine-type to nonvaccine-type pneumococcal cases in the vaccinated group a/b and that in the unvaccinated group c/d. If the vaccine were ineffective in preventing nonvaccine-type cases, then the ratio of vaccine type to nonvaccine-type cases in the vaccinated group (a/b) would be equal to c(1 - E)/d, where E is the best estimate of the efficacy of the vaccine against vaccine-type cases. This implies that E = 1 - ad/bc. The validity of the assumption that the vaccine is ineffective against nonvaccine types was confirmed by comparing the risk of pneumococcal disease caused by nonvaccine types in vaccinated and unvaccinated people enrolled in three pneumococcal vaccine trials. Little difference was seen in two trials, (Ref. 10,11) and in the third the difference was not statistically significant (Ref. 12).

To estimate the vaccine's efficacy against types in the vaccine, the serotypes of pneumococcal isolates from vaccinated persons all over the United States were compared with those of unvaccinated persons from specially selected sentinel hospitals in various locations throughout the United States. From vaccinated persons, 92 isolates were vaccine types and 58 were nonvaccine types, whereas from unvaccinated persons, 974 were vaccine types and 229 were nonvaccine types (Ref. 13). This gives an overall estimate of efficacy of 63 percent against vaccine types. This demonstration by deduction of the reasonably good efficacy of pneumococcal vaccine in groups at high risk in this country has encouraged the U.S. Public Health Service Advisory Committee on Immunization Practices to strengthen its recommendations for the use of the vaccine. At the same time, the vaccine has been reformulated to improve its efficacy against problematic types as well as to increase (to 23) the number of types it includes.

Solving Problems within Constraints

Engineering has not generally been considered one of the liberal arts, but at Swarthmore College, where it has been taught for more than 100 years, it fits in quite well. Recently, other colleges have begun to emphasize technologic thinking as a valid part of a liberal arts education (Ref. 14). The emphasis is not on the mastery of the technical details of machinery, systems, and materials, but rather on the principles under which they operate and their use to solve problems within a given set of constraints.

In the hands of the public health physician, epidemiology has traditionally been used as a tool to reduce the incidence of disease. The investigation of the outbreak of lymphocytic choriomeningitis described above illustrates one way in which epidemiology can help solve the problem of an epidemic within the constraints imposed by the institution in which it occurred and the limits of scientific knowledge about the agent and its hosts.

Increasingly, setters of public health policy use the methods of epidemiology (and economics) to determine how to minimize disease within the constraints of a budget. A new technique like the use of pneumococcal vaccine requires careful assessment, because not only are there limits on its effectiveness, but also, with its many components, it is fairly expensive.

The Office of Technology Assessment of the U.S. Congress has looked at pneumococcal vaccine to determine at what cost life of good quality could be prolonged by its use, and how that cost varies according to the age of the person to be vaccinated (Ref. 15). The total cost was taken to be the sum of the costs of vaccination, vaccine side effects, and future illnesses not prevented by vaccination among persons whose lives are prolonged by vaccination, minus the cost of treating episodes of pneumococcal pneumonia prevented by vaccination.

The total effects were measured in "healthy years of life," by a system according to which a year of full functioning counted as 1, one of disability but not confinement to bed counted as 0.6, and one of confinement to bed counted as 0.4. The total effect was taken to be the number of healthy years gained by vaccination, either through the prolongation of life or the prevention of morbidity, reduced by the morbidity and mortality resulting from vaccine side effects and the morbidity from future illness not prevented by vaccination among persons whose lives are prolonged by vaccination.

Assuming that vaccination costs $11.37, that it is 80 percent effective against the 14 vaccine types for eight years after it is given, and that 75 percent of the cases of pneumococcal disease are caused by those 14 types, the analysis suggested that an additional healthy year of life would cost on the average $4,800. That cost would vary greatly with age, from $77,200 for children 2 to 4 years old down to $5,700 for people 45 to 64 years old and $1,000 for those 65 and older.

In setting the recommendations of the U.S. Public Health Service for the use of pneumococcal vaccine, the Advisory Committee on Immunization Practices has suggested that it be used routinely for those over 65, as well as for younger people who have medical conditions that predispose them to pneumococcal infection (Ref. 16).

Aesthetic Values

All good work is sound. Some is elegant. The four methods of thinking described above may permit the student to tell the sound from the flimsy, but a liberal arts education should go further, to give the student a sense of beauty.

Since 1966, the Centers for Disease Control (CDC) has awarded the Alexander D. Langmuir Prize to the epidemiology trainee who has written the best paper summarizing an epidemic investigation or study. The award honors the founder of CDC's Epidemic Intelligence Service, a two-year training program in epidemiology that was initiated in the early 1950s as a defense against the threat of biologic warfare and that has produced more than 1000 persons trained in shoe-leather epidemiology.

As practical as training in the Epidemic Intelligence Service has been, the Langmuir award is traditionally given not to the most important paper or the most publicized outbreak, but to the work that shows the greatest elegance in design and execution. It is, quite clearly, an award for artistic merit, and since it is the only award specifically for Epidemic Intelligence Service officers, it sets a fine standard for all epidemiologists to live up to.

The award was given in 1980 for a study of the effectiveness of various actions taken to avoid injury during a tornado (Ref. 17). By interviewing those who were injured in the Wichita Falls tornado of 1979 and a sample of those who were not, the winner disproved the mythic advantage of driving in a direction perpendicular to the path of a tornado and showed the danger of staying inside a mobile home. In 1981, the award was given for a study that demonstrated that toxic shock syndrome was particularly common in women who used tampons (Ref. 18). Although the study was highly publicized, what was striking about it for the purposes of the award was that, once 54 cases of toxic shock syndrome had been reported to the CDC, the study was designed and carried out entirely by telephone, and the data were analyzed, in less than a week. The investigators called women with toxic shock syndrome, asked each for the name of a female friend, and interviewed both sets of women about a range of experiences and behavior in the weeks before the onset of the illness in the case. The use of tampons stood out as the one activity clearly associated with risk.

My favorite, however, was the Langmuir award winner in 1984, which involved the investigation of a curious cluster of unexplained deaths in a Toronto children's hospital (Ref. 19). One nurse had been arrested briefly on suspicion of murder. The epidemiologic study showed that the unexpected deaths clustered during the night shift, especially on nights when a particular nurse -- not the one who had been arrested -- was on duty. Strong evidence was collected that suggested that she had given the infants fatal doses of digoxin intravenously. Such selections may suggest that the aesthetic sense is acquired, and such is no doubt the case. But so it is with each of the methods of thinking that we try to help our students master.

Summary

If an unlikely discipline such as epidemiology is found to have elements that qualify it for inclusion in a liberal arts curriculum, one must conclude that the previous boundaries of that curriculum have been at least partly artificial. This deduction is supported by the experience of the past 20 years, as newly heard voices -- of women and minorities, for example -- have brought new insights to traditional disciplines, and as newly recognized disciplines -- such as computing science and neurobiology -- have been found to fit in well beside their older siblings among the liberal arts.

Perhaps there is no subject that cannot be fit material for liberal arts study. But surely that does not mean that selection is unimportant in designing an undergraduate program. The perspective from which the discipline is taught is important. A skilled teacher not only introduces students to the content and methods of a discipline, but also fosters in those students an inclination to use those methods to go further. Under a good teacher, students progress from simply taking in knowledge to questioning assumptions and arguments (their own or others').

Another crucial consideration is how to assemble a course of study out of a wide variety of curricular offerings. Here, the principles of breadth and depth have great importance. The course of study should be sufficiently broad to expose students to good writing about the issues most important to our species and to give them some experience in the major forms of clear thinking. But once this is accomplished, a student should study deeply enough in one area to develop real competence. Such depth gives a student an important sense of the construction of human knowledge and how to add to it. It opens to students the possibility of intellectual leadership.

Whether or not epidemiology is included as a liberal art is probably unimportant. If it is included, however, it should be done with the clarity and rigor that have set a good liberal arts education apart as uniquely exciting and empowering. When epidemiology is taught in medical school, emphasis would be well placed on the methods of thinking that help us understand the unknown. Such an emphasis would highlight the intersection of the liberal arts and professional disciplines.

Cited References

1. Warren KS. The humanities in medical education. Ann Intern Med 1984; 101:697-701.

2. Lilienfeld AM, Garagliano F, Lilienfeld DE. Epidemiology 101: the new frontier. Int J Epidemiol 1978; 7:377-80.

3. Lilienfeld DE. Epidemiology 101. II. An undergraduate prospectus. Int J Epidemiol 1979; 8:181-3.

4. Hinman AR, Fraser DW, Douglas RG, et al. Outbreak of lymphocytic choriomeningitis virus infections in medical center personnel. Am J Epidemiol 1975; 101:103-10.

5. Biggar RJ, Woodall JP, Walter PD, Haughie GE. Lymphocytic choriomeningitis outbreak associated with pet hamsters: fifty-seven cases from New York State. JAMA 1975; 232:494-500.

6. Fraser DW, Campbell CC, Monath TP, Goff PA, Gregg MB. Lassa fever in the Eastern Province of Sierra Leone, 1970-1972. I. Epidemiologic studies. Am J Trop Med Hyg 1974; 23:1131-9.

7. Monath TP, Newhouse VF, Kemp GE, Setzer HW, Cacciapuoti A. Lassa virus isolation from Mastomys natalensis rodents during an epidemic in Sierra Leone. Science 1974; 185:263-5.

8. McCormick JB, King IJ, Webb PA, et al. Lassa fever: effective therapy with ribavirin. N Engl J Med 1986; 314:20-6.

9. Broome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination: an alternative method to estimate the efficacy of pneumococcal vaccine. N Engl J Med 1980; 303:549-52.

10. Ekwurzel GM, Simmons JS, Dublin LI, Felton LD. Studies on immunizing substances in pneumococci. VII. Report on field tests to determine the prophylactic value of a pneumococcus antigen. Public Health Rep 1938; 53:1877-93.

11. MacLeod CM, Hodges RG, Heidelberger M, Bernhard WG. Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. J Exp Med 1945; 82:445-65.

12. Austrian R. Vaccines of pneumococcal capsular polysaccharides and the prevention of pneumococcal pneumonia. In: Beers RF Jr, Bassett EG, eds. The role of immunological factors in infectious, allergic, and autoimmune processes. New York: Raven Press, 1976:79-89.

13. Bolan G, Broome CV, Facklam RR, Plikaytis BD, Fraser DW, Schlech WF III. Pneumococcal vaccine efficacy in selected populations in the United States. Ann Intern Med 1986; 104:1-6.

14. Koerner JD, ed. New liberal arts: an exchange of views. New York: Alfred P Sloan Foundation, 1977:1-77.

15. Willems JS, Sanders CR, Riddiough MA, Bell JC. Cost effectiveness of vaccination against pneumococcal pneumonia. N Engl J Med 1980; 303:553-9.

16. Centers for Disease Control. Update: pneumococcal polysaccharide vaccine usage -- United States: recommendations of the Immunization Practices Advisory Committee. Ann Intern Med 1984; 101:348-50.

17. Glass RI, Craven RB, Bregman DJ, et al. Injuries from the Wichita Falls tornado: implications for prevention. Science 1980; 207:734-8.

18. Shands KN, Schmid GP, Dan BB, et al. Toxic-shock syndrome in menstruating women: association with tampon use and Staphylococcus aureus and clinical features in 52 cases. N Engl J Med 1980; 303:1436-42.

19. Buehler JW, Smith LF, Wallace EM, Heath CW Jr, Kusiak R, Herndon JL. Unexplained deaths in a children's hospital: an epidemiologic assessment. N Engl J Med 1985; 313:211-6.

February 5, 1987 ; 316 (6), pp 309-314