INTRODUCTION

Both authors were introduced to infectious disease epidemiology by Alexander D. Langmuir, and he taught us the principles of this field by example. We came to the Communicable Disease Center (now the Centers for Disease Control and Prevention (CDC)) directly out of clinical training with absolutely no formal training in public health or epidemiology. Perhaps this was a fortunate happenstance; in any event, it is clear that we knew little and carried few preconceptions. Our training was truly in the classic mode of an apprenticeship. The Epidemiology Branch was confronted with problems and challenges, and we were put to work assisting Langmuir in dealing with them. We learned on the job, with little time spent on formal didactic training. Whatever was neglected in the way of formal training was more than compensated for by the drama of dealing with public health problems at a local and national level. Imbued with the excitement of investigating an outbreak, the power of the discipline became apparent.

It was sufficient to absorb the methods as the investigation unfolded and to defer systematic schooling to a later time.

Since this is a memoir, we will illustrate from our personal experiences and then draw a few generalizations at the end.

THE CUTTER INCIDENT: EPIDEMIOLOGY DEALS WITH A NATIONAL EMERGENCY

In the spring of 1955, I (N. N.) was a resident in internal medicine at the University of Chicago Clinics, planning to take further clinical training in neurology. I was abruptly diverted from this course when I received a notice from my local draft board informing me that I would be inducted into the army in 60 days unless I arranged a commission in one of the services. In a panic, I consulted Tom Grayston, a recent alumnus of the Epidemic Intelligence Service (EIS) and chief resident in medicine at the University of Chicago. He arranged an appointment for me as an EIS officer at CDC, Atlanta, Georgia, beginning on April 1, 1955. Due to my unseasonal appearance at CDC (EIS officers routinely are activated on July 1st of each year), it was not clear where I should be assigned, and I was given a desk to use while Langmuir decided how to deploy me.

Later that month, on April 12th, the anniversary of the death of Franklin Delano Roosevelt, the results of the field trial of inactivated poliovirus vaccine (Salk vaccine) were announced by its director, Thomas Francis, with the conclusion that the new vaccine was 60-90 percent effective in preventing paralytic poliomyelitis. During the previous winter, the National Foundation for Infantile Paralysis, which had commissioned the 1954 field trial, had contracted with five pharmaceutical firms to produce a modest supply of inactivated poliovirus vaccine, which would be available for use, assuming that the results of the field trial were successful. A series of decisions were made very rapidly by the Bureau of Biologics, the federal agency responsible for the licensure and release of vaccines. In consultation with several committees of experts, the Bureau developed guidelines for the production and safety testing of inactivated poliovirus vaccine and cleared the vaccine lots made during the previous winter, and on April 17, the first children were given their initial dose of vaccine. Truly, this was an unbelievably rapid response to a national opportunity to protect at least part of the population against a dread disease.

On the morning of April 25th, the Public Health Service received a report from the Chicago Board of Health of a case of paralytic poliomyelitis that had occurred in a child who had recently received inactivated poliovirus vaccine; several more cases were reported in the next 48 hours. Since these cases occurred at a time of year when natural poliomyelitis was
very infrequent, even a few cases were cause for concern. Langmuir, as Branch Chief, was called upon for an instant investigation of these cases. As one of two unassigned EIS officers (the other was E. Russell Alexander), I was available. By such small happen­stances are careers determined.

Between emergency trips and telephone calls to Washington, DC, Langmuir founded the “Poliomyelitis Surveillance Unit,” which issued its first report on May 1, 1955 (1). The unit was charged with the collection, collation, and analysis of information reported by state epidemiologists, often assisted by EIS officers in the field. Each case report was entered onto a standard form devised for the purpose, and the information was abstracted as a single line listing. All of this was organized in 10 days! How it happened I don’t quite understand, but I do remember that I worked harder during the month of May 1955 than I had during my internship!

The Poliomyelitis Surveillance Unit issued daily reports for about 5 weeks, and then weekly reports for many months thereafter. From the simple line listings, certain basic facts emerged very clearly. There were several salient characteristics of what came to be called “vaccine-associated” cases. Recipient cases were tightly grouped in the interval 3–25 days after first vaccine dose and often showed initial paralysis in the arm or leg in which the vaccine was injected. In addition, vaccine-associated cases showed an unexpected geographic distribution, concentrating in a few states, particularly Idaho and California.

Most crucial, the cases appeared to be associated with vaccine manufactured by a single company, Cutter Laboratories, in Berkeley, California. This analysis was complicated because the vaccine produced by different manufacturers was distributed to different states, and it was necessary to determine the amount of vaccine administered for each lot of product produced by each manufacturer. Ultimately, Langmuir devised an estimate of vaccine administration based on the manufacturers’ records of distribution, less returns, with a correction based on clinic records of total vaccine administered. Inevitably, the data contained inaccuracies and omissions, but Langmuir was accustomed to dealing with “dirty” data and maintained great confidence in the analysis in spite of the flaws in information.

In fact, when the tabulations were run, a picture of amazing clarity emerged. On the basis of past history of poliomyelitis by county and by week, it was possible to construct an expectancy, week by week, for the populations that received vaccines. Almost all cases of poliomyelitis, occurring in excess of expectancy, were associated with Cutter vaccine and with only two lots made by this manufacturer. This finding had great consequences. First, it strongly indicated that the major problem resided in the process used by a specific manufacturer rather than in the general method of inactivation. Second, it was recognized that there were a number of ways in which the production process could be improved to reduce the possibility that any infectious virus remained after inactivation and filtration. Finally, the methods of safety testing were altered to increase their ability to detect any residual infectious virus in the final product.

During the initial panic, Surgeon General Leonard Scheele had requested that Cutter Laboratories recall their vaccine (on April 27th) and had declared a moratorium on the entire vaccine program beginning on May 8th. As a result, public confidence in the inactivated poliovirus vaccine was seriously eroded. However, as a result of the very persuasive epidemiologic investigation, the Bureau of Biologics concluded that it would be acceptable to re-clear vaccine produced by the other four manufacturers, which was accomplished between May 13th and June 1st. Effectively, Langmuir had persuaded the public health authorities that the problem was with a single manufacturer and not with the vaccine itself; from this it followed that the vaccine of the other four manufacturers should be rereleased promptly. As a result of this decisive action, public confidence in inactivated poliovirus vaccine was restored before it was completely destroyed.

SURVEILLANCE: A SYSTEMATIC APPROACH TO THE EPIDEMIOLOGY OF INFECTIOUS DISEASES

Shortly after the urgency of the moment had necessitated the initiation of a poliomyelitis surveillance unit, Langmuir asked if I (E. R. A.) would head a surveillance section that would develop a series of national surveillance activities. Along with Neal Nathanson, I had joined EIS in midyear. The initiation of a surveillance unit was clearly a move that Langmuir had been planning for years, and this was the ideal time to initiate it, as everyone had readily welcomed the concept of surveillance for poliomyelitis. Langmuir’s underlying concept was that if there was an established need, we should assemble the best information that we could find for an established population base and share it with those who needed to know. From the onset, Langmuir insisted that surveillance activities would be initiated only when such an activity would result in a clear-cut intervention. Furthermore, although the Organization of State Epidemiologists was in its infancy and he did not submit his plans formally to that body, he did insist that we have the support of some, if not all, of the state epidemiologists in each effort.
My first surveillance assignment was unusual, arthropod-borne diseases (2). Although this was not the most important disease problem facing the United States, there was a body of information that was being collected by entomologists and sanitarians who had been working in disease control and prevention. Remember that the CDC developed from a program known as Malaria Control in War Areas, centered in the southeastern United States, where malaria was a problem. That was why we were in Atlanta. There was a rudimentary surveillance system already in existence regarding both human disease and the prevalence of infection in arthropods and their reservoirs. There was a most receptive audience who wanted that information and, in the instance of malaria, had looked to the CDC to provide it. We started with what was already available from the entomologists and added whatever we could. Arthropod-borne encephalitis (3) was another area where there was a dearth of information, although there was quite a lot available if you dug for it.

Since those early days, surveillance has developed methodologically (4–6). I remember discussing this with Langmuir a few years before his death. While he appreciated that there were general methods that could be drawn from the individual experiences, he believed that each application should be approached individually and that, above all, you better have a very good reason to be doing it.

EMERGING INFECTIONS—LANGMUIR STYLE

In the summer of 1956, Langmuir received a call from Reimert Ravenholt (EIS, 1952), who was now epidemiologist for Seattle-King County, Washington. Langmuir admired Ravenholt, but felt that he sometimes exaggerated issues. Ravenholt called to report that he was dealing with what he thought was the most important public health communicable disease problem in the United States at the time—staphylococcal disease in hospitals (7). Langmuir told Ravenholt in no uncertain terms that he thought Ravenholt was crazy. It had never been brought to the CDC as an issue. Ravenholt told him that many infants in his city were contracting the infection after birth and that there was a significant morbidity and mortality. Langmuir listed all of the other public health issues that we were dealing with, starting with poliomyelitis, and dismissed staphylococcal disease as an issue.

However, his bombastic verbal response did not fully reflect his openness to new ideas. As soon as he put down the telephone, he called me (E. R. A.) into his office and asked me (a pediatrician) what I knew about this issue. I told him I knew little, but that I had read a recent report on a case series of infected infants. He then assigned me the task of going to the library and coming back to him as soon as possible with all I could learn about staphylococcal disease.

I was able to do this in a couple of days. It was a little slower without computers, but I was able to review the world literature in short order. There were only about 30 references, most of them from the United Kingdom, Australia, and Canada. There were a couple of papers from the Bone and Joint Hospital in New York, New York, that described a bacteriophage-typing method that had been developed as a marker system for staphylococci. I reported this to Langmuir, and he sent me to work with the streptococcal disease laboratory unit to interest them in getting the bacteriophages from New York and getting prepared to use them in epidemiologic studies. For the next 3 weeks, I joined Elaine Updyke, a streptococcus expert in the laboratory, as she learned this method herself.

Three weeks later, Langmuir got a second call from Ravenholt asking for help. There had been two maternal deaths in a small military hospital in Seattle (8). The mothers, whose infants had developed impetigo, both died of septicemia after their own breast abscesses. This time, Langmuir did not try to argue with Ravenholt. He sent Elaine Updyke and me out on the next available plane to Seattle. (He asked us to have a bag packed and ready to go—the same day if we could).

Our first task was to assist the Health Department in assessing the immediate problem. The military hospital, like many hospitals in that era, had very poor infection control procedures, and we were able to correct these. However, what we had to report back to Langmuir was that there was no simple answer to what was a widespread, endemic hospital infection. There was no single rogue strain that could be attacked (Langmuir’s dream, which he knew was probably unrealistic), but there was a major issue of how to deal with hospital infections. His immediate solution was to assign an EIS officer to Seattle to work with the combined public health and academic team that was interested in this issue, and, in fact, it was the start of what would later become the CDC Hospital Infections Program. Over the years, this program expanded in size, scope, and level of responsibility, initially inspired and supported by Langmuir. It has assumed a national leadership role, piloting many innovations.

This story is recounted as an example of one of Langmuir’s most important traits. He might talk conservatively, but, in fact, he was always receptive to new concepts and ready to face new disease problems. However, he wanted to do this from the best knowledge base he could find and with cutting-edge tools. He had a problem understanding laboratory technol-
ogy and was often impatient in demanding more than the technology could yield. Some of those around him developed skills in negotiating with the technologists, for, if it were left to Langmuir, his impatience dissuaded some of his laboratory collaborators. It was clear, however, that he wanted to be on that cutting edge. A review of his bibliography will show that he was.

SWINE INFLUENZA VACCINE (9): EPIDEMIOLOGY GOES TO COURT

Twenty-five years later, beginning in 1980, I (N. N.) had another encounter with Langmuir when he reached out to me as a collaborator in a restudy of the swine influenza episode of 1976. At the time, I was the Chairman of the Department of Microbiology at the University of Pennsylvania, and Langmuir, having retired from CDC, was an Adjunct Professor at the Harvard School of Public Health. This exercise was a fine example of the "maestro" at work and brought out his "mature style," refined from his vast experience with epidemic investigations.

In the spring of 1976, there was a brief, but notable, outbreak of influenza among military personnel in Fort Dix, New Jersey. Surprisingly, the virus isolated from this outbreak was not the prevalent strain of human influenza virus but a virus enzootic in swine, generally known as the swine influenza virus. Since this virus had a hemagglutinin (the immunologically dominant virus protein) that was different from that in the prevalent human influenza virus, the human population had little or no prior immunity. Furthermore, there was circumstantial evidence that this newly appearing virus was similar to the strain of influenza responsible for the global pandemic of 1918-1919. This raised the specter of a major outbreak of influenza on a worldwide basis. After considerable debate, the CDC and the Public Health Service made a decision to initiate a crash program for the manufacture of an influenza vaccine from the recently isolated swine virus, with the intent to use this vaccine in a mass immunization campaign in the fall of 1976, prior to the winter peak of influenza. The vaccine was produced by pharmaceutical manufacturers, who insisted that the federal government assume liability for any unforeseen complications. Shortly after the vaccine program was initiated on October 1st, a surveillance program coordinated at the CDC by Larry Schonberger detected what appeared to be an excess of cases of Guillain-Barré syndrome in recent vaccinees. As a result, on December 16th, the program was temporarily and then permanently stopped when it appeared that Guillain-Barré syndrome was associated with vaccine produced by all manufacturers. At the time of termination, December 16, 1976, about 45 million persons had received one dose of vaccine (10).

Since the federal government had assumed liability, the Department of Justice was mandated to deal with all claims of injury resulting from prior use. Through 1984, a total of over 4,000 claims for an aggregate of more than 4 billion dollars had been submitted for potential litigation. In 1982, the Department of Justice decided to commission a study by a "blue ribbon" panel to advise them on the parameters that could be used to determine which cases of illness were associated with the vaccine and should be deemed eligible for compensation. The five-member panel was chaired by Langmuir, and I was asked to serve on it.

Langmuir decided that nothing less than a total reanalysis of swine influenza vaccine-associated Guillain-Barré syndrome would suffice. Therefore, with the help of Dennis Bregman, a member of the panel and CDC statistician, line listings of all of the cases were given a scrupulous, item-by-item review to authenticate their accuracy, correct any errors that could be ascertained, and complete any omissions wherever possible. Langmuir’s attention to detail was amazing and exhaustive. Since the diagnosis of Guillain-Barré syndrome is based primarily on expert clinical opinion and since there is no definitive objective clinical or laboratory test, the cases represented a spectrum from indisputable to questionable. Langmuir insisted that the panel, which included Maurice Victor, a senior neurologist from Case Western Reserve University, develop categories of definite ("extensive") and possible ("limited" and "insufficient data") Guillain-Barré syndrome into which all cases could be placed. He believed that the most credible analysis should be based on the best defined cases, although he retained the possible cases as another category carried throughout the analysis.

The central question was which cases were truly vaccine associated. The analysis was complicated by the fact that there is a background of "spontaneous" Guillain-Barré syndrome that occurs in all populations and was clinically indistinguishable from the vaccine-associated cases. The only way to identify vaccine-associated cases was an epidemiologic analysis based on the number of cases occurring per person week among the vaccinated population. Such an analysis indicated that the attack rate in vaccinees followed a lognormal curve peaking at weeks 2 and 3 postvaccine and declining thereafter to a plateau. The plateau level, reached at 6-8 weeks after vaccine, represented the level of spontaneous Guillain-Barré syndrome occurring in the population unrelated to prior use of swine influenza vaccine. To determine the shape of the curve, it was necessary to estimate the number of
persons vaccinated each week and to then devise a cumulative at-risk population for each week postvaccination. Needless to say, an enormous effort was made by Langmuir and Dennis Bregman to compute the denominators required for the analysis.

After this effort and in spite of the inevitable limitations of the data, the curve that emerged was surprisingly clean; it indicated that the rate dropped to a plateau by 6 weeks after vaccination (9). Furthermore, the plateau rate fell within the limits that had been previously reported for spontaneous Guillain-Barré syndrome in the United States. It was therefore possible to advise the Department of Justice that they might reasonably clean; it indicated that the rate dropped to a plateau by 6 weeks after vaccination (9). Furthermore, airport records showed that there was a strong wind blowing toward the south-southeast on April 2, 1979, 2–3 days before the onset of the first cases. The conclusion appears inescapable—that this was a common-source epidemic caused by the release of anthrax spores from the military microbiology facility on April 2, 1979. Langmuir would have been proud of this publication (11), appearing almost 1 year after his death, since it exemplifies the precepts that he taught for over 40 years.

REPRISE: WHAT LANGMUIR TAUGHT US ABOUT EPIDEMIOLOGY

Langmuir taught us many things, and this is but an incomplete list.

He had great faith in the powers of purely descriptive epidemiology from which important conclusions could be drawn. To use descriptive epidemiology, it was essential to collect the raw data with scrupulous care for both numerator and denominator, and no effort was too great to get the details right. In investigations of outbreaks, the data are always less than optimal. Nevertheless, one can often use the information if scrupulous care is paid to optimizing both numerator and denominator.

Often, very simple displays will yield key conclusions. We have given many examples above, but it seems appropriate to cite one more example, which was published (11) just as we were preparing this article. This is the report on cases of inhalation anthrax occurring in Sverdlovsk (now Yekaterinburg), Russia, in 1979. A simple map of the cases, based on meticulous case review, indicated that when the cases were plotted by residence or worksite, they were all grouped in a narrow band extending from the center of the city (where there was a military microbiology facility) to the south-southeast (compass bearings 135°-180°). Furthermore, airport records showed that there was a strong wind blowing toward the south-southeast on April 2, 1979, 2–3 days before the onset of the first cases. The conclusion appears inescapable—that this was a common-source epidemic caused by the release of anthrax spores from the military microbiology facility on April 2, 1979. Langmuir would have been proud of this publication (11), appearing almost 1 year after his death, since it exemplifies the precepts that he taught for over 40 years.

REFERENCES