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Infectious Disease Epidemiology in the 21st Century: Will It Be Eradicated or Will It Reemerge?

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Although there are several notable examples of early epidemiologic investigations of noninfectious diseases (e.g., the work of Pott (1) on scrotal cancer, Baker (2) on lead poisoning, Ramazzini (3) on occupational illnesses, and Goldberger on pellagra (4)), most of the early development of the field of epidemiology revolved around studies of infectious diseases. Although we have a broader and more encompassing definition of epidemiology now, the word literally means "the study of epidemics," which at the time the word was created were epidemics of infectious diseases. Every student of epidemiology knows of John Snow's brilliant and groundbreaking work on cholera in London in 1854 (5), and many are familiar with Panum's outstanding studies of measles in the Faroe Islands (6), Budd's work on typhoid fever (7), Ross's work on malaria (8), Reed et al.'s work on yellow fever (9), and Frost's work on tuberculosis (10), to name but a handful of the early pioneers of epidemiology.

By the 1960s and early 1970s, however, a combination of improved sanitation, childhood immunizations, and an ever-increasing number of antibiotics had led to substantial reductions in infectious disease-related morbidity and mortality (at least in rich countries like the United States). This "epidemiologic transition" left many in the scientific and medical community believing that infectious diseases were (or soon would be) a problem of the past and that we were free to concentrate our future research and prevention efforts on "chronic diseases" such as cancer, diabetes mellitus, stroke, and cardiovascular disease. This point of view was aptly, if somewhat prematurely, illustrated in a cartoon (11) on the front page of the *Buffalo Evening News* in 1955, at the time of the successful Salk polio vaccine field trial (see figure 1).

During this same time period, a dramatic expansion of the field of epidemiology began, with substantial increases in the number of epidemiologists being trained and in the funding available for epidemiologic studies. Given that "chronic diseases" accounted for the lion's share of the mortality, morbidity, and disability being experienced by the population of the United States at that time, it is neither surprising nor inappropriate that academic and other research organizations and their funders (e.g., National Institutes of Health) expanded the portfolio of "chronic disease" epidemiologic research and the number of "chronic disease" epidemiologists being trained. Epidemiology departments at schools of public health, medical schools, and freestanding research organizations increasingly focused their training and research efforts on "chronic diseases." Even the Centers for Disease Control and Prevention and the US military, bastions of strength in infectious disease research, began devoting a growing share of their resources and energies to "chronic diseases."

What of infectious disease epidemiology and epidemiologists—what happened to them during this same time period, as infectious diseases increasingly disappeared from the lists of major causes of morbidity and mortality in the United States and "chronic disease" epidemiology expanded? Was there a concomitant reduction in funding for infectious disease epidemiologic research and in the number of infectious disease epidemiologists? Data to answer this question are not readily available, but a quick perusal of the programs of epidemiology meetings, the contents of epidemiology journals, and the examples used in leading textbooks of epidemiologic methods provides convincing evidence that infectious disease epidemiology shrank dramatically as a proportion of the overall field of epidemiology. For example, at the annual meeting of the American Epidemiological Society, the proportion of papers dealing with an infectious disease topic began declining steadily in the early 1950s (figure 2), while the proportion of papers published in the *American Journal*

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Abbreviation: AIDS, acquired immunodeficiency syndrome.

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FIGURE 1. Illustration of the optimism about the control of infectious diseases at the time of the release of the results of the Salk vaccine field trial. (Reproduced from the *Buffalo Evening News*, Special Edition, April 13, 1955:1).

of Epidemiology and its forerunner (the *American Journal of Hygiene*) dealing with an infectious disease topic began declining in the late 1960s (figure 2). Other meetings and journals devoted exclusively to epidemiology have come into existence too recently to permit a similar examination of temporal trends, but recent programs from the Society for Epidemiologic Research and the American College of Epidemiology, as well as recent issues of the *Annals of Epidemiology*, the *Journal of Clinical Epidemiology*, *Epidemiology*, and the *International Journal of Epidemiology*, reinforce the impression that only a very small proportion of the epidemiologic research currently being performed concerns infectious diseases, although like all epidemiologists, those working on infectious diseases also present and publish their findings elsewhere.

Similarly, of the examples used in two leading textbooks of epidemiologic methods published in the 1980s, one of 26 and zero of 28, respectively, used data concerning an infectious disease rather than a "chronic disease" (12, 13), reflecting the fact that most authors of such textbooks (and many, if not most teachers of epidemiologic methods in academic departments) are "chronic disease" epidemiologists. Thus, it seems clear that, by the mid- to late 1970s, the epidemiologic transition had been accompanied by a transition in epidemiology. Infectious disease epidemiology had, at the very least, lost the prominence it had enjoyed a generation or two earlier.

Over the ensuing years, however, while mortality from the classic infectious diseases continued to decline in the United States, not only did infectious diseases not disappear, but new infectious diseases and infectious agents kept being discovered. Thus, the late 1970s saw the discovery of Legionnaires' disease, Lyme disease, and hemorrhagic fevers such as Lassa and Ebola, and

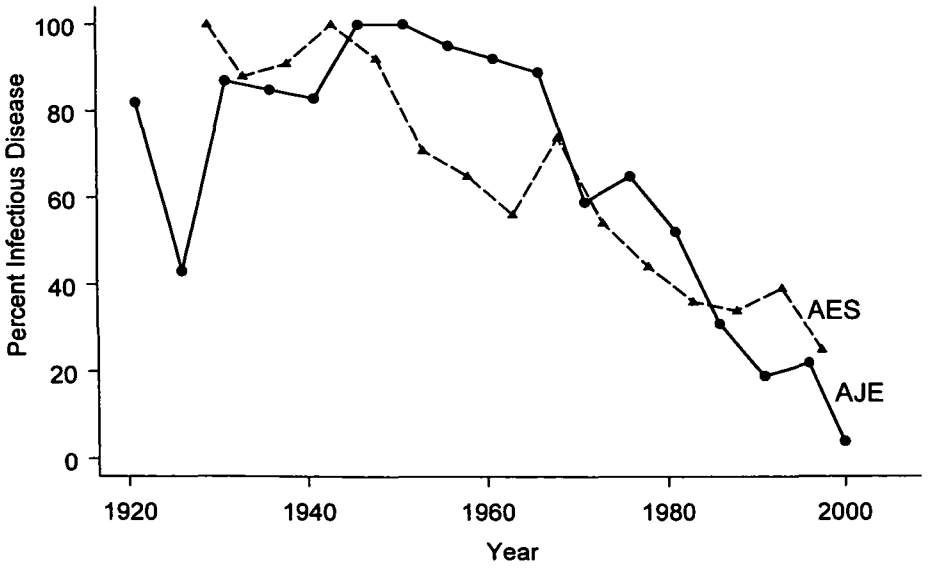

FIGURE 2. Percentage of papers presented at the American Epidemiological Society (AES) and proportion of original research contributions and commentaries published in the *American Journal of Hygiene/American Journal of Epidemiology* (AJE) that concerned an infectious disease topic, 1928–1999 (AES) and 1921–2000 (AJE). For the American Epidemiological Society, programs of all meetings were examined and percentages were calculated for 5-year blocks (1931–1935, 1936–1940, etc.), except for a 3-year block at the beginning (1928–1930) and a 4-year block at the end (1996–1999). For the *American Journal of Hygiene/American Journal of Epidemiology*, the first two issues published every fifth year (1921 (volume 1), 1926 (volume 6), 1931 (volume 13), 1936 (volume 23), etc.) were examined, through the first two issues of 2000 (volume 151).

the 1980s brought us toxic shock syndrome, hepatitis C, and most dramatically, acquired immunodeficiency syndrome (AIDS), to name but a few prominent examples. In 1994, a report from the Institute of Medicine made the case that such "emerging and re-emerging infectious diseases" demonstrated that the war against infectious diseases was not over; that numerous factors contributed to the emergence and reemergence of infectious diseases; and that we were not adequately prepared to deal with such problems (14). Together with the AIDS epidemic, accompanying media hype and the concurrent appearance of numerous movies and both fiction and nonfiction books about infectious diseases intended for the general public, not to mention more recent concern about bioterrorism, have led to an infusion of substantial new interest in and resources into the field of infectious diseases research.

If infectious diseases have not disappeared and if there will be an ongoing need for infectious disease epidemiology and epidemiologists well into the 21st century, what will their role be and how can they be better prepared to meet the challenges that await them? One thing seems certain: Emerging new infectious diseases, while providing a fresh infusion of research funds at present, are unlikely to sustain the careers of many infectious disease epidemiologists in the long run. Most infectious disease epidemiologists and students interested in entering the field cannot sit and wait for a truly new infectious disease to emerge.

Where then lies the future for infectious disease epidemiology and epidemiologists? First, it is clear that infectious disease epidemiologists must be as well-trained and as sophisticated in their knowledge of epidemiologic and biostatistical methods as their colleagues who work on noninfectious diseases. Many of the methodological developments in biostatistics and data analysis of the past 25 years are highly relevant to the study of infectious diseases, particularly those that are chronic in nature or that induce sequelae years to decades following infection (see below). The rich panoply of biostatistical and epidemiologic methods used, even developed, to study human immunodeficiency virus (HIV) infection and AIDS have demonstrated clearly that sophistication in such methods was both needed and readily achieved by infectious disease epidemiologists.

At the same time, infectious disease epidemiologists need to have a basic understanding of mathematical modeling and the ways in which it can be helpful, even if they lack the mathematical skills or the interest to construct and manipulate their own models. Under varying sets of assumptions, mathematical models can help infectious disease epidemiologists predict the relative impacts of various intervention strategies. More importantly, attempts to construct such models invariably point to gaps in the available empirical data and often suggest fruitful areas for future research.

However, most important in the preparation of the next generation of infectious disease epidemiologists is rigorous, state-of-the-art training in the biologic and social sciences relevant to the study of human disease. The concept that disease results from the complex interplay of host, agent, and environment has been one of the pillars of epidemiology for a number of decades, almost invariably appearing in one of the first chapters of many introductory textbooks, often depicted as a triangle (see figure 3). This simple model of how three distinct sets of factors interact to produce disease (or, conversely, health) is even more relevant today, as our tools for dissecting and characterizing the agent, the human host susceptibility and response, and the environment gain increasing sophistication. Any well-trained infectious disease epidemiologist of the future will need to have at his or her command a high level of competence in the biologic and social sciences that have produced sometimes startling new levels of understanding of the three corners of this triangle.

To illustrate how the advances in these fields can contribute to the study of infectious diseases, it is instructive to go back to the cartoon from the *Buffalo Evening News*. In the cartoon, medical history, in the form of a bearded old man, is busy crossing off classic "infectious diseases" from the list of ailments afflicting humankind, leaving future generations of scientists and doctors to deal with "chronic diseases," such as cancer and heart disease. As we enter the 21st century, however, there remains much for infectious disease epidemiologists to do regarding diseases listed on both pages of medical history's book.

In retrospect, medical history was somewhat premature in crossing off classic "infectious diseases" from its list. Although concerns about its use as an agent of bioterrorism now seem destined to keep us from destroying the last remaining vials of the virus itself, smallpox has now been eradicated (but only some 20 years after the cartoon was published), and there is reason to be optimistic that polio will be eradicated early in the 21st century (15, 16). However, diphtheria has "reemerged" in a number of countries recently because of a failure to maintain high levels of immunity through routine vaccination (17). Pneumonia, which is caused by *Streptococcus pneumoniae* (the pneumococcus), influenza virus, and a panoply of other etiologic agents, has never gone away and has consistently been one of the leading causes of mortality around the world, as has tuberculosis, which is, in essence, a form of pneumonia (i.e., an infection of the lungs).

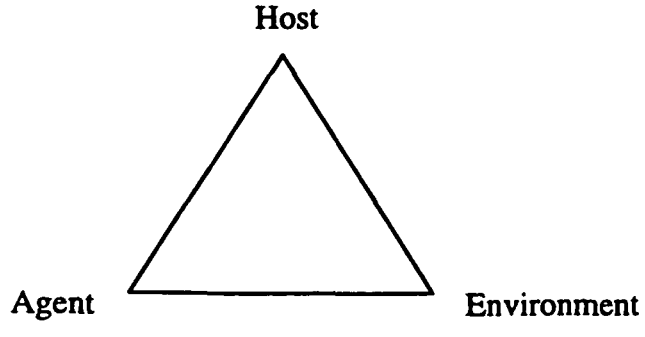

FIGURE 3. Illustration of the conceptual interplay of host, agent, and environment in the study of disease by epidemiologists.

Thus, many of the classic "infectious diseases" have not disappeared, and there is still much that can be learned about them. However, future advances in our understanding and prevention of diseases such as pneumococcal pneumonia, tuberculosis, and influenza will require multidisciplinary approaches that incorporate the modern methods of molecular microbiology, human genetics and immunology, and social and behavioral sciences. For example, methods for characterizing and studying the pathogenic mechanisms of the microbial agents that cause the classic infectious diseases grow increasingly more sophisticated every year. Such methods are at the heart of modern day studies examining how these agents spread; evolve over time; develop resistance to antimicrobial agents; and cause disease, as well as being instrumental in the development of new diagnostic tests, antimicrobial agents, and vaccines. Recent studies of tuberculosis that combine epidemiologic data and information about the molecular basis for the enhanced pathogenicity of certain strains of *M. tuberculosis* illustrate the insights that can result from the thoughtful application of these methods (18, 19).

At the same time, our ability to characterize biologically the human host susceptibility and response to infection with a given microbial agent is growing at a phenomenal rate. Until recently, studies of the genetic basis of human susceptibility or resistance to infection have been limited to an assessment of the relation between susceptibility and a relatively small number of genes (e.g., genes in the human lymphocyte antigens' (HLA) regions and genes controlling red blood cell antigens). However, with the expected availability in the next few years of the sequence of the entire human genome, it will become possible to tease apart the genetic contribution to human susceptibility to various infectious agents at a level of detail not previously imaginable. Similar advances in the techniques available to study the human immune response to infection and the basis for immunity from or susceptibility to infection may have profound implications for the development of new vaccines and other prevention or treatment modalities. Finally, in the important area of human behavior, a key attribute of host susceptibility

to infectious diseases, particularly those transmitted sexually, there have been substantial increases in the sophistication of our approaches to assessing human behavior and its determinants.

The third corner or side of this triangle, the environment, has also received increasing attention. In the context of emerging or reemerging infections, there has been an explosion of interest in joint epidemiologic-ecologic studies examining the impact of environmental factors on microbial populations; the factors that influence the likelihood of human exposure to microbial agents; and the response to such exposure, particularly for vectorborne infections, zoonotic infections, and food- and water-borne infections. At the same time, there has been a renewed appreciation of the importance of the social environment and community (rather than individual) level factors such as crowding on the spread of infectious agents like *M. tuberculosis*.

While the "classic" infectious diseases, represented in the cartoon by those listed on the left-hand page of medical history's book, will continue to provide infectious disease epidemiologists with many challenges, it is, perhaps, the "chronic diseases" represented in the cartoon by those listed on the right-hand page (e.g., cancer and heart disease) that represent the greatest challenges and opportunities for infectious disease epidemiologists. We now know, with a fair degree of certainty, that the rigid distinction between "infectious diseases" and "chronic diseases," which is clearly displayed in the cartoon and which dominated the thinking of generations of epidemiologists, is at best simplistic and misleading.

Elegant epidemiologic studies that required little or nothing in the way of sophisticated laboratory methods demonstrated a number of years ago that infectious agents were intimately involved in the pathogenesis of cervical cancer and hepatocellular carcinoma, two of the leading causes of cancer morbidity and mortality in the world. In fact, there was compelling evidence that a sexually transmitted agent was involved in the pathogenesis of cervical cancer long before advances in virology and molecular biology permitted the elucidation of the role of selected types of human papilloma virus in this "chronic" disease (20). While the earliest studies demonstrating that the risk of hepatocellular carcinoma was intimately linked with hepatitis B virus infection (particularly when acquired at birth) obviously required the availability of laboratory markers of infection with the virus, the laboratory methods required for these studies were rather unsophisticated compared with those developed since that time (21).

Over the last 10–15 years, it has become clear that a number of other "chronic diseases" may need to be moved from the right-hand page to the left-hand page of medical history. There is now strong evidence that *Helicobacter pylori* infection plays an important role in the pathogenesis of peptic ulcer disease and gastric carcinoma (22, 23). There is also growing evidence that chronic infection with hepatitis C virus, like chronic infection with hepatitis B virus, is associated with an increased risk of hepatocellular carcinoma and cirrhosis (24). Intriguing, but still conflicting results suggest that infection with *Chlamydia pneumoniae* and/or other infectious agents is involved in the pathogenesis of ischemic heart disease, perhaps the quintessential "chronic disease" (25, 26). Moreover, various epidemiologic and laboratory observations provide tantalizing suggestions that infectious agents may be involved in the pathogenesis of diverse other "chronic diseases," including juvenile onset diabetes mellitus, schizophrenia, multiple sclerosis, selected types of arthritis, inflammatory bowel disease, and sarcoidosis, among others (27–36) (table 1).

Will infectious agents prove to be involved in the pathogenesis of all these "chronic diseases"? Probably not. If in the future a link between infection and a "chronic disease" such as ischemic heart disease is established beyond a reasonable doubt, will we be able to substitute a weekly dose of an antimicrobial agent for abstinence from smoking, a prudent diet, exercise, and control of hypertension? Perhaps, but alas, probably not. The evidence linking various "lifestyle" risk factors and ischemic heart disease is consistent and strong, and the role, if any, of one or more infectious agents in what is clearly a multifactoral process is almost certain to be only a contributory one.

Even in those "chronic diseases" in which a role for an infectious agent is most clear cut, infection does not invariably lead to disease. While the risk of hepatocellular carcinoma in those infected at or near birth with hepatitis B virus is over 100 times that of uninfected individuals, most hepatitis B virus-infected individuals do not develop hepatocellular carcinoma. Similarly, most women infected with human papilloma virus, even those infected with the types that are most closely associated with cervical dysplasia (e.g., types 16 and 18), do not develop invasive cervical cancer. In addition, only a tiny proportion of those infected with *H. pylori* develop gastric cancer. Thus, it is clear that, in the pathogenesis of "chronic diseases" in which infectious agents play a role, just as in the pathogenesis of the classic acute infectious diseases, human host characteristics and environmental factors are key in determining which infected individuals will develop disease. Genetically determined differences in response to infection, as well as the presence or absence of other relevant exposures, undoubtedly influence this process.

TABLE 1. Selected examples of "chronic diseases" in which a role for one or more infectious agents has been demonstrated or suspected

Disease	Suspected infectious agent	Reference no.
Cervical cancer	Human papilloma virus	20
Hepatocellular carcinoma	Hepatitis B virus	21
	Hepatitis C virus	24
Peptic ulcer disease	*Helicobacter plyori*	22
Gastric carcinoma	*H. pylori*	23
Ischemic heart disease	*Chlamydia pneumoniae*	25, 26
Juvenile onset diabetes mellitus	Enteroviruses	27
Rheumatoid arthritis	Mycoplasmas or another agent susceptible to tetracycline	28
Crohn's disease	*Mycobacterium paratuberculosis*	29
Sarcoidosis	Human herpes virus 9	30
Renal stones	Nanobacteria	31
Schizophrenia	Borna disease virus	32
Major depression	Borna disease virus	32
Kaposi's sarcoma	Human herpes virus 8	33
Childhood medulloblastoma	JC virus	34
Multiple sclerosis	Human herpes virus 6	35
Polycystic kidney disease	Fungi	36

For example, the presence at the cervix of one or more carcinogenic substances from tobacco smoke may well interact in some way with the effects of human papilloma virus infection to produce dysplasia or carcinoma. Or, *H. pylori* infection may only lead to gastric cancer in the presence of one or more chemical carcinogens in the diet, and only in individuals with a given genetically determined susceptibility.

Further elucidation of the role of infectious agents in what formerly were considered "chronic" (i.e., noninfectious) diseases presents a wide array of opportunities and challenges for infectious disease epidemiologists to tackle over the next decade or more. New methods for identifying novel infectious agents and detecting them in biologic samples, such as representational difference analysis, used to pinpoint the role of human herpes virus 8 in Kaposi's sarcoma (37), and broad-range polymerase chain reaction testing for bacterial 16S rDNA, used to identify *T. whippelii* as the cause of Whipple's disease (38), will be at the heart of such efforts (39). As is the case for the "classic" infectious diseases, furthering our understanding of the relative contributions of the microbial agent, the human host, and other factors/the environment in the complex pathogenesis of such diseases will depend heavily on combining sophisticated epidemiologic and biostatistical methods with state-of-the-art methods from other fields. Progress is likely to be made most rapidly if infectious disease epidemiologists join with chronic disease epidemiologists to conduct joint studies of the role of "our" agents in "their" diseases. Such studies will, like future studies of the "classic" infectious diseases, require epidemiologists with excellent training in the relevant biologic and social sciences, working together with scientists from these other fields.

Thus, it would appear that infectious diseases and the epidemiologists who study them are not likely to be eradicated in the foreseeable future. Even if other new infectious diseases don't emerge, there is much for infectious disease epidemiology and infectious disease epidemiologists to do in the decades ahead.

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