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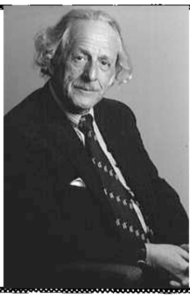

Current Comments®

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Mapping the World of Epidemiology. Part 1. The Disease Detectives

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Epidemiologists agree on the need for a more precise definition of and limits for epidemiology. "Modern" epidemiology encompasses all diseases—infectious and noninfectious—as well as occupation- and environment-related hazards, injuries, and even psychosocial problems. Epidemiologists investigate the causes, prevalences, controls, and prevention of all of these. Part 1 provides a brief history of epidemiology, highlights the major influences on this field, and identifies the most-active areas of current research.

For years ISI® has used its databases to analyze the literature of diverse research specialties. Citation and other studies help to pinpoint highly active areas of work and show how they are interrelated. In our discussions of research fronts, we refer to the multidimensional scaling drawings of their co-citation relationships as "maps," conjuring up the image of ISI as the "geographer" of science. (Indeed, Henry Small and I discussed the "geography of science" at length in a 1985 article published in the *Journal of Information Science*.[1])

The geographic metaphor, however, connotes a somewhat static model of science. In actuality, the world of science is in constant change. To portray the dynamics of moving research fronts, William Goffman, former dean, School of Library Science, Case Western Reserve University, Cleveland, Ohio, compared the spread of ideas within the scientific community to the spread of an infectious disease.[2,3] In 1972 he collaborated with Kenneth S. Warren of the Rockefeller Foundation, New York.[4]

Characterizing the epidemic process as one of "transition from one state (susceptible) to another (infective), where the transition is caused by exposure to some phenomenon (infectious material)," Goffman and Vaun A. Newill, also of Case Western Reserve, created a mathematical model that links the theory of epidemics to the transmission of ideas. "People are susceptible to certain ideas and resistant to others. Once an individual is infected with an idea, he may in turn, after some period of time, transmit it to others. Such a process can result in an intellectual 'epidemic.' "[2] In this sense, then, we at ISI could be called, on the one hand, students and vectors of research and, on the other hand, the "epidemiologists of science."

The Many Faces of Modern Epidemiology

The use of the word "epidemiology" in this context, however, may cause chagrin among many of the workers in this field, since it adds yet another application of a specialty that is already replete with definitions. Indeed, defining precisely what is encompassed by the discipline of epidemiology is one of the many obstacles to be overcome by modern practitioners of this multidisciplinary science.

As noted by David E. Lilienfeld, Division of Environmental and Occupational Medicine, Mt. Sinai School of Medicine, New York, although epidemiology is today regarded as an independent scientific discipline, "most...epidemiologists have yet to agree on what, exactly, is the scope of their discipline."[5] The word "epidemiology" dates back to the 1840s and is derived, of course, from "epidemic," which, in Greek, literally means "upon the people." As such, epidemiology can be taken to mean the branch of medical science concerned with epidemic outbreaks. But, as Milton Terris, formerly (1960-1964) head of the Chronic Disease Unit, Division of Epidemiology, Public Health Research Institute of the City of New York, and presently editor, *Journal of Public Health Policy*, pointed out, although epidemiologists traditionally were concerned with the causes, incidence, and prevalence of infectious disease, occupation-related and other noninfectious diseases have also gradually found a place in the field.[6] Indeed, epidemiology encompasses *all* diseases, and in addition to trying to identify the causes of illnesses, epidemiologists are also involved with finding ways to prevent them. Bernard Dixon, European editor of the *THE SCIENTIST*®, adds that "epidemiologists are also interested in tracing the spread of transmissible diseases and in explaining the uneven distribution of others, such as the comparative incidence of different types of cancer in different countries."[7]

As stated by Roger I. Glass, Center for Infectious Diseases, Centers for Disease Control (CDC), Atlanta, modern epidemiology can be defined as the study of the distribution and determinants of health and disease in human population groups or communities, with an emphasis on prevention. Epidemiology's scope is somewhat different than that of clinical medicine, which is mainly concerned with disease in the individual rather than in large groups.[8] This is not to say, however, that clinicians seeing individual patients are not concerned with the prevention of diseases. As Haroutune K. Armenian, Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health, Baltimore, points out, and I'm sure all would agree, "There is a lot that epidemiology has learned and will learn from a study of individual cases, in particular, cases that are epidemiologically unusual."[9]

Part 1 of this essay outlines a brief history of the field of epidemiology, highlights some of the leaders in the field, and identifies active areas of current research. Part 2 will focus on the nuts and bolts of epidemiology, such as its techniques of statistical analysis, and some of the technological advances that have enabled epidemiologists to broaden their scope. We will also list some of the institutes and organizations around the world that are involved with epidemiology, as well as the journals that publish epidemiological research.

The Roots of Epidemiology

It is pertinent to briefly review the history of epidemiology, since the modern science still draws on its roots as an ancient art. What follows is by no means a complete or exhaustive account of epidemiology's evolution. Such an undertaking would require inordinate time and space. Presented here instead are accounts of the major influences that have shaped the field of epidemiology as we know it, or are trying to know it, today.

Among many others, Lilienfeld and his father, Abraham M. Lilienfeld (1920-1984), Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health, noted that "the general concept that environment influences disease occurrence had its origin in antiquity, and so did a more specific idea that many diseases are contagious."[10] The first recorded reference to the importance of environmental influence on disease is contained in *On Airs, Waters, and Places*,[11] and was written by Hippocrates (ca. 460-ca. 377 BC), the father of medicine. He warned that the seasons of the year, the winds and waters of a locale, and the lifestyle of the inhabitants all contribute to disease.

The idea that disease could be caused by a living agent occurred surprisingly early: one of Caesar's physicians, Marcus Terentius Varro (116-27 BC), theorized that "small creatures, invisible to the eye, fill the atmosphere, and breathed through the nose cause dangerous diseases." Even so, little was actually known concerning microorganisms and their relationship to infectious disease until the Renaissance.[12] Indeed, proof that infectious disease is caused by a living agent of contagion (a *contagion vivum*) necessarily awaited the invention of the microscope and the development of the concept that diseases were different from one another, each with its own unique cause and natural history.[10]

The Theory of Contagion and the Germ Theory

It wasn't until 1546, when Italian physician and poet Girolamo Fracastoro (1483-1553) published *De Contagione*,[13] his theory of contagion, that a formalized idea of airborne contamination surfaced. Fracastoro believed that contagion was due to the transmission of minute particles, capable of self-replication, from diseased individuals to the healthy.[12] His conjectures were validated when bacteria were detected through the use of the microscope, developed in 1683 by the Dutch draper, microscopist, and naturalist Antonie van Leeuwenhoek (1632-1723).

Nevertheless, it was not until the great French chemist and microbiologist Louis Pasteur (1822-1895) disproved the Aristotelian ideas of spontaneous generation and showed that fermentation, souring, putrefaction, and infection are all caused by the growth of preexisting microbes that the validity of a germ theory of disease was established. Pasteur not only incriminated microbes, but also proved that specific organisms caused specific infections. He isolated the germ that caused cholera in chickens and the bacillus of anthrax.[14]

The germ theory was not accepted overnight, however. Competing with it was an alternative explanation of infectious disease, the "miasma theory." Based on a belief that air of "bad quality" could cause persons breathing it to become ill, the discredited theory still survives in the name of the disease malaria—a name that literally means "bad air."[10] Edward H. Kass, Channing Laboratory, Harvard Medical School, and Brigham and Women's Hospital, Boston, Massachusetts, notes that "the controversy between the contagionists and the noncontagionists of the 1820-1860 period is one of the most productive in medical history and certainly set the stage for the microbial discoveries, as did the invention of the achromatic microscope and the changing doctrines of the specificity of febrile disease, the latter spearheaded by the emerging discipline of pathologic anatomy."[15]

The Rise of Epidemiology

As scientists searched for the causes of infectious disease, they also strove to understand the mechanics of disease transmission and to express those mechanics mathematically in a law (or laws) of epidemics.[10] Original attempts at formulating such laws were limited largely to counting the dead and the dying. But in 1662 John Graunt (1620-1674), one of the earliest giants of epidemiology, became the first to apply numerical methods to the study of vital statistics.[16] In the early 1800s French physician Pierre Charles Alexandre Louis (1787-1872), one of the first "modern" epidemiologists, emphasized the importance of statistics in epidemiological studies and in medicine in general, although he was not the first to use them. However, it was not until the mid-1800s that British statistician William Farr (1807-1883) delineated many of the concepts vital to the handling of these data, such as life-table analysis, standardized mortality rates, dose-response relationships, and the interrelation of incidence and prevalence.[8]

It is John Snow (1813-1858), however, who is considered the father of modern epidemiology.[8] In 1855, while studying the transmission of cholera in England, he described new methods for studying epidemics.[17] Snow successfully tested hypotheses to establish how the disease was spread and identified a link with patients who had contracted cholera. These methods led to the correct hypothesis that cholera was caused by water contaminated with feces from infected humans. Snow clearly exemplified the goal of any epidemiologic investigator: to gather population-based data and compare disease rates between different groups with various exposures. Snow's methods are still used today when epidemiologists search for the cause and prevention of a disease for which the etiologic agent is unknown.[8]

A recent issue of *THE SCIENTIST*[18] included an interview of Nobel laureate Baruch S. Blumberg, Institute for Cancer Research, Fox Chase Cancer Center, Philadelphia. In 1976 Blumberg shared the Nobel Prize in physiology or medicine for his identification of the association of Australian antigen in human blood with serum hepatitis.

Blumberg was recently the narrator-host of a public-television program entitled "Plagues."[19] In the program, Blumberg described scientists' efforts to understand infectious diseases, including malaria and Legionnaires' disease, and Snow's landmark investigations into the 1849 cholera outbreak. A plaque at the John Snow Tavern in London still memorializes this discovery.

The Epidemiology of Noninfectious Diseases

The threat of contagious diseases and resulting mortality in industrialized nations was declining, mainly as a result of socioeconomic improvements such as clean water and better food, housing, and hygiene. In a brief history of American infectious-disease epidemiology, Kass, mentioned earlier, points out that socioeconomic improvements led to the thinking that "medical care accounted for improving health, a view that few physicians wished to dispel, and that most believed, in accordance with the concepts of therapy of the time."[20] Chronic noninfectious diseases, however, still remained a major problem. Thus, epidemiologists also undertook the study of noninfectious disease.

In 1747 British physician James Lind (1716-1794) discovered that scurvy could be prevented or cured by drinking the juices of limes and lemons. (Lind and his work were discussed in our essay on nutrition research.[21]) By the first half of the 1800s, a number of significant achievements had already occurred in the epidemiology of noninfectious disease: including Lind's studies, there was also George Baker's (1722-1809) investigations of lead colic in Devonshire, UK, as well as the reports by Percival Pott (1714-1788) on the increased incidence of cancer of the scrotum in chimney sweeps.[6]

By the latter half of the nineteenth century, as noted by Ian A. McGregor, Liverpool School of Tropical Medicine, UK, the microbiological era of epidemiology was emerging.[22] In France Pasteur was beginning to formulate his ideas on the role of microorganisms in the development of disease. In Egypt the German physician and bacteriologist Robert Koch (1843-1910) discovered the microorganism responsible for cholera, 29 years after Snow's hypothesis; he also discovered that repeated exposure to malaria induced effective immunity to the disease.[22] In 1905 he was awarded the Nobel Prize in physiology or medicine for his work involving the isolation of the tubercle bacillus.

During the latter half of this century, the field of epidemiology has continued to change and broaden in scope. The change in orientation was dramatically signaled in 1943 when physician John A. Ryle, originally of the University of Cambridge, UK, resigned to become a professor of social medicine at the University of Oxford, UK, where he led the British movement toward social medicine.[6] Social medicine is concerned with all diseases, infectious as well as noninfectious, and includes such disparate maladies as cardiovascular disease, cancer, psychoneuroses, and accidental injuries—all of which have epidemiologies and must be considered preventable, according to the writings of Ryle.[23] Although Ryle was not an epidemiologist in the sense of understanding the field's tools and methods, he was a remarkable humanitarian and an important force in the British establishment.[15]

By 1960 the focus of epidemiology had shifted from the study of vital statistics and major epidemics to the etiological factors in the distribution of human health and disease, as well as the prevention of disease. Although some may claim there are "two epidemiologies"—one for infectious disease and one for noninfectious disease—the Lilienfelds pointed out that the methods generally used and the inferences derived in both types of disease are the same.[10]

As stated by Kass, "Epidemiologic techniques, moving from their roots in infectious disease, have become necessary for the most efficient and acceptable solutions to major problems in chronic disease, health care, hospital management, and innumerable other problems.... These methods, refined and sharpened as they inevitably will be, are certain to be essential...for the advancement of public health."[20]

The Epidemiologist's Role in the Control and Prevention of Disease

According to Alfred S. Evans, Yale University School of Medicine, New Haven, Connecticut, and Philip S. Brachman, CDC, researchers involved with infectious diseases are faced with the challenge of determining why, after exposure to a pathogen, some people develop a clinical illness, others develop subclinical infections, and still others are unaffected. To control infections it is necessary to control clinical illness, with its associated morbidity, disability, and mortality; reduce or eliminate contact with the infectious agent itself; and eliminate transmission of the agent. One may only have to break the chain in one place to achieve control. When any of the three control measures are implemented, that disease can be eradicated.[24]

To help devise effective means of prevention and control, surveillance programs are vital in gathering data concerning disease occurrence. The mode of transmission can be inferred, for example, by finding foci of AIDS in gay men and blood recipients, even when essential cofactors are still murky. Information used to describe the natural history of an unknown illness may make it possible to initiate control and preventive measures before the actual pathogenic agent is identified. This is, in fact, what happened in the public-health response to Legionnaires' disease, toxic shock syndrome, and AIDS.[24] Alexander D. Langmuir, Department of Preventive and Social Medicine, Harvard Medical School, in an article in the *International Journal of Epidemiology*, considers Farr, mentioned earlier, to be the founder of modern concepts of surveillance. Farr viewed his role as one of collecting, assembling, and evaluating relevant facts and reporting them to health authorities and the general public. His ultimate goal was to improve the control of disease.[25]

Current Research

Table 1 lists selected 1987 research fronts on epidemiology. In compiling this table, we limited our search to those fronts that included the word "epidemiology" in their titles. However, since there are many fronts relevant to epidemiological aspects of specific diseases and conditions that do not contain the word "epidemiology," this list is by no means exhaustive. If we had used the epidemiology subfile of the National Library of Medicine's online database, TOXLINE, we would have no doubt retrieved numerous other papers. Even so, the titles in Table 1 illustrate not only some of the ways in which epidemiology is linked to other sciences, but also its emphasis on controlling and preventing disease.

The largest front in Table 1 concerns Legionnaires' disease. Entitled "Outbreak of Legionnaires' disease and community-acquired pneumonia" (#87-1745), it was associated with 270 papers published in 1987. Among the 34 cited core works for this front is a now-classic paper by David W. Fraser and colleagues, Bacterial Disease Division, Center for Infectious Diseases, CDC.[26] Cited more than 400 times since its publication in 1977, the paper reports the discovery of a previously unrecognized bacterium responsible for the 1976 outbreak of Legionnaires' disease in Philadelphia. In his *Citation Classic®* commentary on the paper, Fraser, now president, Swarthmore College, Pennsylvania, said that,

> while large, the epidemiological investigation followed some well-developed patterns. An initial step was to identify cases and confirm that there was indeed an epidemic.... Surveys showed that Legionnaires' disease tended to affect older men who were cigarette smokers.... The pattern of illness suggested airborne spread that was particularly intense in the hotel lobby and on the adjacent sidewalk.... It was hard to determine who should be listed as an author of this paper, for literally hundreds of people made contributions.[27]

Incidentally, Fraser was recently awarded the John Scott Award from the city of Philadelphia.

A related research front, entitled "Regional and community epidemiology" (#87-3945), is included among the cluster of C1 research fronts that make up the C2-level front entitled "Epidemiology, health care, and epidemiological research methodologies" (#87-0654). The map in Figure 1 illustrates the co-citation relationships between seven relevant research fronts. Only one of these (#87-3945), however, is mentioned in Table 1. Indeed, the number of C2 research fronts involved indicates the pervasive nature of the role of epidemiology in modern research.

Table 1: The 1987 *SCI®/SSCI®* C1-level research fronts on epidemiology. A = number of core papers. B = number of citing papers. C = 1987 C2-level research-front number that includes this C1 front. A dash indicates that the C1 is not included in a C2-level cluster and remains an "isolate."

Number	Name	A	B	C
87-0008	Time-related epidemiologic data, carcinogenic exposure, and quantitative risk assessment	15	152	87-0003
87-0518	Epidemiology of *Acinetobacter calcoaceticus* and nosocomial infections	3	18	87-0259
87-0903	Measles immunity, virus persistence, and epidemiological models	2	22	87-0379
87-1745	Outbreak of Legionnaires' disease and community-acquired pneumonia	34	270	87-0185
87-2689	Mortality in psychiatric patients, major affective disorders, and epidemiology of suicide	3	31	—
87-3945	Regional and community epidemiology	2	26	87-0654
87-4138	Pap smear screening, epidemiology of cervical cancer, and cytology laboratories	2	18	—
87-4373	AIDS epidemic, acquired immunodeficiency syndrome, and human T-cell lymphotropic virus type III infection	5	42	—
87-4777	Hepatitis delta virus infection and possible epidemiologic model for endemic areas	11	93	87-0239
87-5305	Genetic epidemiology, complex segregation analysis, Utah pedigrees, and lipoprotein cholesterol levels	10	98	—
87-5366	Environmental epidemiology, mortality trends, chemical workers, phenoxy herbicides, and military service in Vietnam	4	41	87-0973
87-5511	Clinical neuroepidemiology and conventional prognostic factors in predicting short-term survival	3	43	—
87-6250	Epidemiologic programs, mortality of young children, and respiratory cancer	3	80	87-0434
87-6764	Genetic epidemiology, binary pedigree data, and robust inference for variance components models	2	15	—

Other Infectious Diseases

Besides the front already mentioned (#87-1745), four other fronts in Table 1 are concerned with infectious diseases. The largest of them, named "Hepatitis delta virus infection and possible epidemiologic model for endemic areas" (#87-4777), is identified by 93 published papers. Of its 11 core works, 6 are by M. Rizzetto and colleagues, Department of Gastroenterology, Ospedale Mauriziano Umberto, Turin, Italy.[28-33] The earliest, a 1977 article published in *Gut*, describes a new antigen-antibody system associated with hepatitis B virus and the discovery of the delta antigen.[28] It has been cited nearly 200 times and set the stage for Rizzetto's later works involving hepatitis B and the delta antigen. Our data also show that Rizzetto and colleagues coauthored nine of the front's 1987 citing papers.

The other infectious-disease fronts concern "Measles immunity, virus persistence, and epidemiological models" (#87-0903), "Epidemiology of *Acinetobacter calcoaceticus* and nosocomial infections" (#87-0518), and, of course, AIDS: "AIDS epidemic, acquired immunodeficiency syndrome, and human T-cell lymphotropic virus type III infection" (#87-4373). The first contains two core articles, both written by R.M. Anderson, Imperial College of Science and Technology, University of London, UK, and R.M. May, formerly of Princeton University, New Jersey, and presently at the University of Oxford.[34,35]

In their first paper, Anderson and May used mathematical models to examine the impact that different vaccination policies may have on the age-specific incidence of rubella and measles. They wanted to show that "simple mathematical models for disease dynamics can be useful tools in the design of public health policy, provided that they are used sensibly."[34] The other core paper showed how "mathematical models provide broad biological understanding of the factors controlling disease and recurrent epidemic behavior."[35] More recently, Anderson and May have published reports of mathematical models of the transmission dynamics of infectious diseases and the human immunodeficiency virus in AIDS.[36,37] Anderson is also listed as the author of 3 of the 22 current citing documents that identify cluster #87-0903.

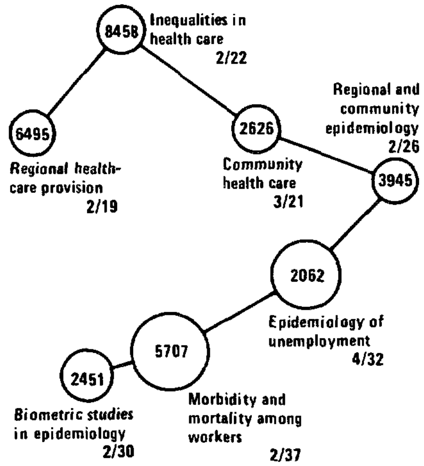
Two of the fronts deal with genetic epidemiology, a subject that will be more fully discussed in Part 2. One of these, "Genetic epidemiology, complex segregation analysis, Utah pedigrees, and lipoprotein cholesterol levels" (#87-5305), concerns some of the risk factors for coronary heart disease. Epidemiologists have shown that, among other factors, high blood levels of serum lipids, especially the components cholesterol and low-density lipoproteins, greatly increase the likelihood of developing cardiac disease, the leading killer in the US since 1950.[38]

Cancer

Four of the fronts in Table 1 deal with cancer, indicating the level of interest epidemiologists have in this subject. Cancer epidemiologists have made innumerable contributions to knowledge of cancer for over 300 years, according to Nicholas L. Petrakis, Department of Epidemiology and International Health, University of California, San Francisco.[39] For instance, it was epidemiological investigations that linked cigarette smoking to cancers of the lung, larynx, pharynx, and mouth; epidemiologists also related alcohol consumption to various cancers, including liver cancer, and implicated X rays in other forms of carcinoma. Screening methods for breast and cervical cancers have also been developed through epidemiological studies.[40] And in fact, one of the fronts on cancer deals with one of these very subjects. One of the two core documents for the front "Pap smear screening, epidemiology of cervical cancer, and cytology laboratories" (#87-4138), by E. Aileen Clarke, Division of Epidemiology and Statistics, Ontario Cancer Treatment and Research Foundation, Toronto, and Terrence W. Anderson, Department of Preventive Medicine and Biostatistics, University of Toronto, Ontario, Canada, assesses the effectiveness of the Pap test for detecting cervical cancer.[41]

Over 150 papers were published in 1987 on the topic of "Time-related epidemiologic data, carcinogenic exposure, and quantitative risk assessment" (#87-0008). Among its core works is a landmark paper by Sir Richard Doll and Richard Peto, Radcliffe Infirmary, University of Oxford;[42] this 20-year prospective study on the relationship between smoking habits and lung cancer mortality will be more fully discussed in Part 2.

Figure 1: A multidimensional scaling map for C2-level research front #87-0654 on epidemiological research methodologies and health care. Numbers of core/citing documents in each front are given after the research-front name.



Another Doll paper, coauthored with M.P. Vessey, also of the Radcliffe Infirmary, linked the use of oral contraceptives with an increased risk of thromboembolic disorders;[43] cited almost 350 times since 1968, it was the subject of a *Citation Classic* commentary by Vessey in 1986.[44] Of the study, Vessey wrote that the paper has been frequently cited because "it was the first to provide clear evidence that thromboembolism is a hazard of oral contraceptive use." Vessey also felt that the paper must be "methodologically interesting," since it is "a favourite amongst teachers of epidemiology."[44]

Environmental Epidemiology

In determining the health effects of low-level exposures to toxic substances in the environment, epidemiologists identify hazards and estimate their significance, relate hazards to disease and impairment, quantify such relationships, and summarize them in the form of dose-response curves, explains Ian T.T. Higgins, University of Michigan School of Public Health, Ann Arbor.[45] (The techniques of epidemiology will be more fully explored in Part 2.)

The research front on "Environmental epidemiology, mortality trends, chemical workers, phenoxy herbicides, and military service in Vietnam" (#87-5366) deals with the effects of exposure to the toxic components of herbicides and fungicides. Two of its four core papers were authored by L. Hardell and colleagues, Center of Oncology, University Hospital, Umeå, Sweden.[46,47] They show that exposure to phenoxyacetic acids (found in herbicides) and chlorophenols (found in fungicides) increased sixfold the risk of developing soft-tissue sarcoma.

"To Further the Understanding of Disease..."

As this essay has shown, the scope of epidemiology has broadened considerably. The early focus on infection has expanded to include occupation- and environment-related diseases, injuries, and psychosocial problems. Epidemiologists are also dealing with subclinical and early disease. They can now define people at risk by their genes or through sensitive biochemical indicators before disease even occurs.[48] Epidemiologists are concerned with the investigation of the causes, prevalences, controls, and prevention of all of these. As a result, epidemiologists are being called into other areas to work with laboratory investigators, clinicians, and public-health administrators.

As Glass sums it up, "In the largest sense, epidemiologists are concerned with determining the principal causes of death and disability in an entire population and in identifying interventions to improve the health of all.... The focus of all efforts is to further our understanding of disease causality and the prevention of premature morbidity and mortality."[8]

Part 2 will focus on the methodology of epidemiology and the technical advances that have furthered the discipline.

* * * * *

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