New Prospects for Epidemiologic Investigations

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Epidemiology has evolved from its historic origins as the study of major epidemics and vital statistics to a contemporary focus on the study of the distribution and determinants of health and disease in humans. This evolution reflects changes in the patterns of diseases and deaths that have occurred in our time and has placed new emphasis on preventing avoidable, premature deaths. Advances in clinical medicine, laboratory science, statistical and data handling methods, and in our basic understanding of the pathogenesis of disease have enabled epidemiologists to better examine causes of disease and to propose more effective strategies for prevention and control.

IN RECENT YEARS, MANY EPIDEMIOLOGIC INVESTIGATIONS have captured widespread public attention and have been the focus of considerable scientific interest and debate. Epidemiologists have led the assault on many new infectious diseases including the acquired immune deficiency syndrome (AIDS) and Legionnaires' disease, and spearheaded the global eradication of smallpox. They have used methods as diverse as simple case finding and molecular genetics to determine, for example, that cholera is endemic in the United States (*1*) and that *Salmonella* can be spread by smoking contaminated marijuana (*2*). Epidemiologic studies have been used to assess the health risks of exposure to a wide variety of toxic substances in the environment and to examine the health benefits of reducing smoking, increasing exercise, and treating hypertension. From the perspective of public health policy, epidemiologists have suggested that our national priorities need to be reordered so that problems such as injuries and accidents, smoking, substance abuse, and violence become an important focus of attention (*3*).

Epidemiology is evolving as a discipline in response to changing patterns of morbidity, advances in clinical and laboratory science, and improvements in statistics and data handling methods. Originally defined as the study of epidemics of infectious diseases (for example, cholera, plague, typhus, typhoid, and polio), epidemiology has become the study of today's afflictions, and these include, in addition to infectious diseases, chronic diseases, injuries, and social problems (such as drug abuse, unintended pregnancy, and homicide). In the past, epidemiologists could focus their attention only on patients with severe or fatal illness. With the development of more sophisticated laboratory techniques and refinements in diagnostic tools, epidemiologists can now investigate a disease early in its course and follow its natural progression. Classic case finding methods have been refined so that epidemiologists can trace a subclinical exposure, infection, or even small fragments of genetic material that may have important implications for disease causation in man. The definition of epidemiology has been broadened to include the study of the distribution and determinants of disease and health-related states in populations and the application of results to the prevention and control of health problems (*4*). In this article, I examine some of the changes responsible for broadening the scope of epidemiology—changes both in the types of health problems that are being addressed and in the methods used to study them.

Background

Epidemiology, like clinical medicine and laboratory science, is concerned with understanding health and disease in humans, but it is distinguished by its focus on health problems in populations rather than individual patients or laboratory experimentation. Population-based measurements such as rates of disease or risk factors are gathered from surveys, special investigations, or health information systems (for example, registries of vital statistics or laboratory tests). Differences in rates between groups are used to generate hypotheses or to explain causality or mode of transmission. Epidemiologists often work closely with clinicians, laboratory scientists, and statisticians in generating and testing hypotheses about causes of disease and in learning enough about the illness or its antecedent risk factors to plan a control or prevention program. 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. In smaller, more limited investigations, epidemiologists focus on a specific disease or epidemic and try to identify the causative agent or risk factors for disease that might ultimately provide lessons related to understanding pathogenesis, control, and prevention. Much of the broadened scope of epidemiology reflects changes in the patterns of morbidity and mortality in industrialized countries of the world and in the clinical tools and diagnostic tests that have recently become available for use in population-based studies.

New Directions for Measuring Health and Setting Priorities

Historically, epidemiology is rooted in the work of John Graunt (1662), the first person to apply numerical methods to the study of vital statistics, and William Farr (1885), who delineated many of the concepts important to the handling of these data (such as life table analysis, standardized mortality rates, person-years at risk, dose-response relationships, and the interrelation of incidence and prevalence) (*5*). In the United States, crude and age-adjusted death rates have been a prime measure of the nation's health. Over the years, these rates have documented the prolongation of life and the change in the primary causes of death from acute infectious diseases to

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chronic diseases, injuries, violence, and substance abuse. At the same time, as the population has aged, these crude death rates are dominated by the many chronic diseases common to the elderly. They do not adequately reflect the premature deaths of people who die young with many productive years of life remaining.

In 1982, the Centers for Disease Control began ranking the causes of premature death according to the years of potential life lost (YPLL), that is, the number of years of life lost for anyone who dies before completing a normally productive life, an end point arbitrarily defined as 65 years (*6*). For example, the premature death of a 25-year-old in an automobile accident contributes 40 YPLL whereas the death of a 75-year-old man from pneumonia contributes none. Health priorities ranked with YPLL rather than traditional morbidity rates give quite different results (Table 1) (*7*). With traditional methods, heart disease and cancer are the two leading causes of death and no other single cause lies in the same range. With the YPLL method, unintentional injuries, cancer, heart disease, and violence (homicide and suicide), in that order, account for the most potential years of life lost before age 65.

Use of the YPLL method points out that premature deaths are a considerable problem that might be avoided by more directed health interventions. For example, epidemiologists during a recent consultation on health policy were asked to identify the burden of health problems that are unnecessary in light of knowledge that is already at hand (Fig. 1) (*3*). Smoking ranked first by traditional criteria of crude death rate and the newer measure YPLL. Alcohol-related deaths, however, were the second most important cause of premature deaths accounting for 1.5 million YPLL but only fifth as a cause of death. Accidents, previously considered to be random, individual events outside the reach of control activities are now classified as unintended injuries, well suited for epidemiologic study and an important cause of premature death in the younger age groups. Unintended pregnancy, a minor cause of the total mortality in the United States, is, in fact, a significant contributor to YPLL for teenagers and their children. Many of these areas represent particularly fruitful fields for future epidemiologic investigations and public health intervention because they provide the greatest opportunity to intervene and decrease premature mortality and morbidity in this country.

Because of this redirection of attention toward causes of today's unnecessary morbidity and mortality, epidemiologists now study issues that have not previously received much attention. Some of these represent behavioral problems—substance abuse, violence, unintended pregnancy—whose risk factors may lie in the social environment, the family setting, and education. For instance, although many epidemiologic studies have determined that smoking is the most important cause of preventable death from cancer, heart disease, and stroke, we have yet to learn how to help people alter their behavior accordingly. Other problems, such as injuries from accidents, natural disasters, and violence, are now recognized as important public health problems in terms of YPLL and are receiving closer scrutiny. Examination of risk factors that distinguish victims from survivors has suggested solutions that include setting up smoke-free zones, speed and seat-belt laws, and programs to prevent driving when intoxicated.

Table 1. Causes of deaths in the United States in 1984 ranked by estimated years of potential life lost before age 65 and by deaths per 100,000 population. [Reprinted from (*7*) with permission]

Cause of death	Years of potential life lost (rank)	Deaths per 100,000 (rank)
All causes (total)	11,761,000	866.7
Unintentional injuries	2,308,000 (1)	40.1 (4)
Malignant neoplasms	1,803,000 (2)	191.6 (2)
Heart diseases	1,563,000 (3)	324.4 (1)
Suicide, homicide	1,247,000 (4)	20.6 (7)
Congenital anomalies	684,000 (5)	5.6 (10)
Prematurity	470,000 (6)	3.5 (11)
Sudden infant death syndrome	314,000 (7)	2.4 (12)
Cerebrovascular diseases	266,000 (8)	65.6 (3)
Chronic liver diseases and cirrhosis	233,000 (9)	11.3 (9)
Pneumonia and influenza	163,000 (10)	25.0 (6)
Chronic obstructive pulmonary diseases	123,000 (11)	29.8 (5)
Diabetes mellitus	119,000 (12)	15.6 (8)

Examples of field investigations in these newer areas include studies that helped explain the child murders in Atlanta in 1983 (*8*), deaths due to heroin in Washington, D.C. (*9*), and clusters of deaths associated with improper medical practices by hospital staff (*10*). In each of these events, the epidemiologist identified the victims as a cluster and used classical methods to describe the victims in time, place, and person to develop different hypotheses for the cause of the adverse outcomes. Epidemiologists have also examined environmental hazards such as the risk of death or injury from hot weather in the elderly (*11*), from the volcanic eruption at Mount St. Helens (*12*), and from the Wichita Falls tornado for occupants of automobiles and mobile homes (*13*). In each of these instances, a cluster of deaths or health effects were related to factors that placed victims at high risk. On the basis of these studies, warnings were changed and the public was notified. These examples represent a new assault on groups of hazards that contribute to the sum of potentially avoidable deaths.

Epidemiology in Epidemic Investigations

Epidemiologists have received their greatest public recognition in recent years for their role in investigating epidemics of newly recognized health problems. These have included (i) some unusual infectious diseases (toxic shock syndrome, Lyme arthritis, and Lassa fever), (ii) problems due to environmental or occupational exposures (for example, low dose radiation, asbestos, smoking, and pesticides), and (iii) diseases for which no agent has yet been identified (for example, Reye's syndrome, Kawasaki's disease, necrotizing enterocolitis, and toxic oil syndrome in Spain).

The epidemiologic methods used to investigate these new diseases are similar to these described more than 100 years ago by John Snow, the father of modern epidemiology, to investigate the transmission of cholera in England (*14*). At that time when microbial agents were not yet recognized, Snow successfully tested hypotheses to establish how the disease was spread and to identify common events that linked patients with cholera and that distinguished them from healthy controls. By tracing cases, he established that in one outbreak in London, most victims drank water from a single point source, the Broad Street pump. He hypothesized that cholera was transmitted by water contaminated with feces from infected humans. In testing this hypothesis, he demonstrated that persons who consumed dirty water drawn from the Thames River in Central London had a rate of cholera that was significantly greater than that observed in consumers of cleaner water drawn upstream. The essence of an epidemiologic investigation remains as the gathering of population-based data that can compare disease rates between groups with different exposures. In general, as the relative risk of disease increases in one exposure group compared with the other, the greater is the strength of association and the closer is the link to causality.

Snow's methods are still applied today in the search for causes and means of preventing diseases where no etiologic agent has yet been identified. One example is Reye's syndrome, a disease of children that was first described in 1963 by R. D. K. Reye as encephalopathy and fatty degeneration of the viscera (*15*). The epidemiology of Reye's syndrome was first studied in an outbreak that occurred in North Carolina (*16*). Hundreds of cases have been reported through a nationwide system of surveillance begun in 1973. Although the cause of the disease is still unclear, the viral-like prodrome to the illness has led epidemiologists to seek a virus as the etiologic agent. A significant association both temporally and geographically has been identified with outbreaks of influenza B, influenza A, and varicella (*17*).

In 1980, several small case-control studies based on surveillance data suggested that ingestion of salicylates during antecedent illnesses was associated with Reye's syndrome (*18*). This association was confirmed in a larger case-control study conducted under the auspices of the Institute of Medicine (*19*). These findings led to the recommendations of the Surgeon General of the Public Health Service and the Committee on Infectious Diseases of the American Academy of Pediatrics that children with flulike illness or chickenpox should not be given aspirin. Since the initial association was identified, aspirin use among children in the United States has declined by more than half and the number of cases of Reye's syndrome has similarly decreased (*20*). Through this intense series of epidemiologic studies, a major stride toward preventing this disease has been made, even though our understanding of the cause remains incomplete.

For other new diseases, the identification of pathogens by laboratory scientists was made possible by the thoroughness of the original epidemiologic investigation. For example, in 1980, epidemiologists in Minnesota and Wisconsin reported two clusters of patients with toxic shock syndrome (TSS) shortly after the syndrome was first described (*21*). Women whose symptoms met stringent requirements for TSS and controls who were healthy, age-matched friends of patients were queried about a number of potential risk factors. All 52 patients but only 44 of the 52 controls used tampons during the period of recall. These patients and a subsequent group of TSS patients were significantly more likely than controls to have had vaginitis associated with *Staphylococcus aureus*. Since blood cultures from the patients were negative, the investigators suggested that TSS was caused by *S. aureus* elaborating a toxin that was predominantly found in women using tampons. The investigators informed public health authorities and clinicians that using certain types of tampons placed women at high risk of TSS. After the recall of one brand of tampons, laboratory investigators working with field specimens found the toxin in *S. aureus* that confirmed the epidemiologic hypothesis.

Epidemiologists were able to begin the TSS investigation with the cooperation of clinicians. Later work of laboratory scientists led to identification of the pathogen and its toxin and confirmed the epidemiologic conclusions. There are many similar examples of in-depth epidemiologic studies that led to the discovery of a new pathogen in the laboratory. Some of these new pathogens include the Norwalk family of viruses, *Legionella pneumophila, Borrelia burgdorferi*, enteroinvasive and enterotoxigenic *Escherichia coli*, and *Cryptosporidia*.

The AIDS epidemic has provided a continuing view of the use of epidemiologic studies to identify and characterize a new disease and to establish modes of transmission and control. It has also demonstrated the advantage of collaboration among epidemiologists, laboratory investigators, and clinicians. In 1981, five reports of *Pneumocystis carinii* pneumonia (PCP) in young males at three hospitals in Los Angeles were noted by epidemiologists who established that an epidemic had begun (*22*). PCP normally occurs

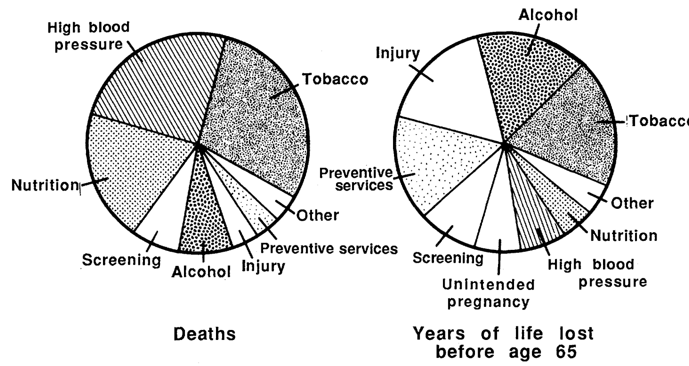

Fig. 1. Causes of unnecessary mortality in the United States by relative number of deaths and years of life lost. Preventive services refers to deaths due to diseases that can be prevented by early medical intervention. [Reprinted from (*3*) with permission]

in immunocompromised hosts, so its occurrence in previously healthy men was unusual and the clustering of five cases gave cause for concern. Before the virus associated with AIDS was discovered, epidemiologists gathering individual case reports had linked the syndrome to Kaposi's sarcoma, persistent generalized lymphadenopathy, and cryptosporidiosis. Additionally, several major risk groups—homosexuals, persons with hemophilia, intravenous drug users, and transfusion recipients—had been identified (*23*). The categorization of the patients into high-risk groups allowed epidemiologists to test hypotheses about transmission by blood and blood products and by sexual practices. Establishment of a national surveillance system documented the magnitude of the epidemic and the high case-fatality ratio for patients (*24*).

The discovery of the AIDS-associated virus and development of a serodiagnostic test allowed epidemiologists to expand their investigations. They have now estimated that more than 1 million persons in the United States have been exposed to the virus. Investigations now focus on the transmission of subclinical infections with a short incubation period rather than overt disease, which may take years to present. Control measures, including the screening of blood and blood products used for transfusions and therapy, have been implemented. Public health initiatives have been organized to promote safer sexual practices by homosexuals and bisexuals. Throughout this epidemic, epidemiologists have linked clinicians and their individual patients with laboratory scientists and diagnostic tests. Together they are striving to provide a global perspective on this disease, to identify its modes of transmission, and to implement strategies for control.

Epidemiologic Ties to Laboratory Science

In earlier periods, epidemiologists were limited to counting disease cases among the sick or dead and linking the cases to exposures or other risk factors identified by verbal history alone. With improvements in diagnostic tests, persons with subclinical conditions, early signs or precursors of disease, abnormal laboratory values, or asymptomatic infections have become appropriate for study because they represent all aspects of the natural history of a disease. Many potential causes, risk factors, and exposures can be suggested by a patient's history and confirmed by laboratory analysis; some biological risk factors can be assessed by laboratory tests alone.

Some of the most exciting advances in epidemiology can be attributed directly to discoveries made in the laboratory. In 1968, epidemiologists investigated an explosive outbreak of acute febrile myalgia that struck 90% of employees of the Pontiac office of the Oakland County Michigan Health Department. No causative agent was found, and the epidemic went unresolved and unheralded (*25*). In 1976, the same agent struck participants at the American Legion convention in Philadelphia (*26*). Laboratory scientists, after working for 6 months with specimens and clues provided by both epidemiologic investigations, were able to identify the causative organism, *Legionella pneumophila*, and thus resolve the mystery of both epidemics. Similarly, an outbreak of winter vomiting disease attacked 80% of 200 children at an elementary school in Norwalk, Ohio, in 1968. The epidemiologists described the illness, the common source of exposure, and the transmission to family members but never established the cause (*27*). Four years later, the Norwalk virus was identified by scientists using new techniques of immune electron microscopy (*28*). This virus is now recognized as the most common cause of outbreaks of nonbacterial gastroenteritis among adults in the United States (*29*).

Recent advances in molecular biology and immunology and new knowledge at the genetic and cellular level about the pathogenesis of disease have been applied by epidemiologists to study molecular epidemiology. Epidemiologic methods previously used to trace the spread of diseases or infectious agents between humans and the environment are now used to examine the distribution and spread of fragments of genetic material that have relevance to disease. Molecular techniques, including analyses with genetic probes and hybridization and sequence analyses, have been used for rapid diagnosis and characterization of microorganisms causing infectious diseases and genes involved in genetic diseases and cancer. The development of probes for the diagnosis of toxigenic strains of *E. coli*, for example, has permitted study of the spread of the organism within the family and from contaminated food and water to man, an effort that would have been impossible with more traditional tests (*30*). When *Vibrio cholerae* serogroup 01 was isolated from four distant sites around the Gulf of Mexico over a 10-year period, molecular analysis of the gene for cholera toxin together with phage typing showed that the four isolates were identical to each other but distinct from strains isolated in other parts of the world. These results supported the hypothesis that the American isolates were derived from a single clone that has a free-living cycle in the environment and provided evidence against a previous theory that the cases represented multiple introductions by travelers returning from areas of endemic cholera (*1*). As a final example, when cases of polio occurred in Missouri and North Carolina, oligonucleotide fingerprint analysis identified the strain as a wild type that had not been found in the United States for several years (*31*). Analysis of the genetic sequence of these isolates demonstrated that they were recombinants of the vaccine strains and did not represent a reintroduction of polio.

Molecular genetics has also been applied to the study of chronic diseases. Chromosomal and genetic markers have already been used for prenatal diagnosis and characterization of types of cancers. The identification of viral oncogenes in the genetic material of man may permit genetic risk analysis of some cancers. Proposals for sequencing the entire human genome raise the possibility that future generations of molecular epidemiologists may be able to place people in health risk groups by directly probing their genes.

New, simplified assays, such as those for specific classes of antibodies, local immunity, specific T-cell responses, cell-mediated immunity, HLA type, and genetic modulators, are used by epidemiologists to study an individual's immune response to disease. For some diseases, these assays may provide clues to understanding what functions must be simulated to develop a protective immune response and lead to construction of a new generation of vaccines. Modern technology is making epidemiology more interesting and versatile by providing the tools to refine population-based studies of risk factors, disease associations, and causality. This new methodology is already having an impact on the prevention and control of diseases in humans.

Epidemiologic Ties to Biostatistics and Computer Science

For many diseases and, in particular, the chronic diseases, the web of causality is complex, involving multiple risk factors, dose-response relationships, intricate interactions between the human host and the environment, a long latency period from exposure to the development of disease, and a wide spectrum of disease outcomes. Many epidemiologists investigating causes and risk factors associated with chronic diseases are participating in large-scale intervention trials to decrease risk factors associated with disease, to survey entire population groups for potential risk factors for disease, and to conduct longitudinal studies following thousands of people for many years. These studies have become possible because of developments in both the statistical methods and computer techniques required to manage and analyze large data sets.

The need for computerized data management was clear when A. B. Hill and Richard Doll began their survey of British doctors, a study of 34,440 physicians queried in 1951 about their smoking habits and followed for 20 years (*32*). This study documented that between a half and a third of all cigarette smokers died because of their smoking and that these deaths were associated chiefly with heart disease, lung cancer, chronic obstructive lung disease, and various vascular diseases. Detailed analysis of these data by age, smoking history, inhaling habits, and cause of death would have been unthinkable without computerized assistance.

Techniques for multifactorial analysis were developed in part in response to statistical demands of large-scale longitudinal studies. The Framingham Study was conceived to investigate the effects of a large number of variables, both singly and jointly, on the risk of developing coronary heart disease. Traditional analytic methods of multiple cross-classification were impractical as the number of variables to be investigated increased. The multiple logistic function was first applied to observational data from this study in order to model, describe, and summarize the wealth of data in a comprehensive fashion (*33*). Log-linear models have been perfected to analyze clinical trials with categorical outcomes such as deaths from a particular cancer (*34*). Proportional hazard models and a variety of multivariate techniques have been developed to deal with confounding factors, a variety of covariates, and risk estimates. These new methods for data management and advanced statistical analysis are readily available as computer software packages. They represent robust tools permitting epidemiologists to conduct studies of large population groups with multiple risk factors that would have been difficult a decade ago and nearly impossible before 1960.

New Prospects for Epidemiologic Investigations

The prospects for new epidemiologic investigations are expanding. In the arena of public health policy, national priorities are being redefined so that new issues, such as attempts to control premature deaths, are receiving increased attention. In the investigation of new or poorly understood diseases, epidemiologists continue to play an important role in the discovery of new agents, understanding pathogenic mechanisms, and attempting to implement control methods. Their activities have been facilitated by advances in laboratory science and the molecular understanding of disease. In chronic diseases, new methods for data handling and statistical analysis are making it possible for epidemiologists to investigate more complex causal relationships among exposures, host factors, and disease. The focus of all these efforts remains in furthering our understanding of disease causality and the prevention of premature morbidity and mortality.

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AIDS in Africa: An Epidemiologic Paradigm

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Cases of the acquired immune deficiency syndrome (AIDS) have been reported in countries throughout the world. Initial surveillance studies in Central Africa suggest an annual incidence of AIDS of 550 to 1000 cases per million adults. The male to female ratio of cases is 1:1, with age- and sex-specific rates greater in females less than 30 years of age and greater in males over age 40. Clinically, AIDS in Africans is often characterized by a diarrhea-wasting syndrome, opportunistic infections, such as tuberculosis, cryptococcosis, and cryptosporidiosis, or disseminated Kaposi's sarcoma. From 1 to 18% of healthy blood donors and pregnant women and as many as 27 to 88% of female prostitutes have antibodies to human immunodeficiency virus (HIV). The present annual incidence of infection is approximately 0.75% among the general population of Central and East Africa. The disease is transmitted predominately by heterosexual activity, parenteral exposure to blood transfusions and unsterilized needles, and perinatally from infected mothers to their newborns, and will continue to spread rapidly where economic and cultural factors favor these modes of transmission. Prevention and control of HIV infection through educational programs and blood bank screening should be an immediate public health priority for all African countries.

THE ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) has become recognized as a global health problem. Cases have now been reported in 74 countries with more than 25,000 cases in the United States, nearly 3,000 cases in other countries of the Americas, more than 3,000 cases in Europe, and several thousand cases suspected and many more unrecognized in Africa (*1, 2*). It is estimated that at least several million people worldwide have been infected with the causative agent, referred to as human T-lymphotropic virus type III (HTLV-III)/lymphadenopathy virus (LAV), or more recently as human immunodeficiency virus (HIV) (*3*). As many as 10 to 30% of these HIV-infected individuals may develop AIDS within the next 5 to 10 years (*4–6*). With the present lack of a curative therapy or vaccine, this disease now ranks as the most serious epidemic of the past 50 years.

Although the immunopathogenesis of HIV infection is similar in most AIDS patients (*7*), the epidemiology and clinical features of the infection in different countries may vary, depending on cultural

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