New Edition

Population and Health: An Introduction to Epidemiology

by Ian R.H. Rockett

Epidemiologists search for the who, when, where, and why of health problems.

Health surveys have the capacity to access hard-to-reach populations.

Epidemiologic research gauges whether specific medicines or behaviors prevent disease.

PRB

Population and Health: An Introduction to Epidemiology

About the Author

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Most people are concerned about their health. When they are well, they wonder how to remain that way. Will regular exercise decrease their risk of cardiovascular disease later in life? Will beta-carotene or vitamin C reduce their risk of getting cancer? Does living near overhead power lines increase that risk? When they, their families, or friends are ill, they wonder which treatments would be best. Is chemotherapy more effective than surgery and radiation in treating cancer? Is angioplasty more appropriate than heart bypass surgery for treating blocked arteries?

Television, newspapers, and magazines fuel this widespread curiosity about the mysterious world of health risks and hazards. How dangerous is radiation exposure? Which populations face the greatest risks? What are the risks of injury in an automobile crash when driving intoxicated versus driving sober, and how are those risks modified in cars with airbags?

All too often, discussions of these and similar questions are characterized more by ignorance or fear than by scientific knowledge. But, the quality of these discussions is being enhanced as scientific research becomes more accessible to the public. The science of epidemiology is a major contributor to this growing body of knowledge about how to prevent and treat disease and injury.
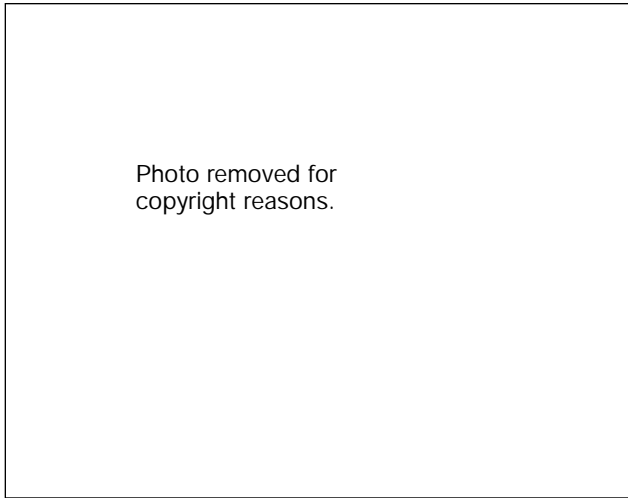
Epidemiology draws on lab sciences as well as social sciences to learn what determines the health of populations.

What is epidemiology? It may be formally defined as the "study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems."[1] In other words, epidemiology is the study of our collective health. Epidemiology offers insight into why disease and injury afflict some people more than others, and why they occur more frequently in some locations and times than in others—knowledge necessary for finding the most effective ways to prevent and treat health problems.

The term "epidemiology" springs directly from "epidemic," which originally referred to communicable disease outbreaks in humans. Epidemic is derived from the Greek roots *epi* (upon) and *demos* (people). The third component of epidemiology, the Greek root *logos*, means study. *Demos* and another Greek root, *graphein* (to write, draw), combine to form the term demography, a kindred population-based science. Not only do epidemiology and demography share a linguistic heritage and other historical origins, they also overlap considerably in their data sources and research domains.

Epidemiology has a descriptive dimension that involves the identification and documentation of patterns, trends, and differentials in disease, injury, and other health-related phenomena. This science also has an analytic dimension, in which the **etiology**, or causes, of these phenomena are investigated. Epidemiology also helps investigate how well specific therapies or other health interventions prevent or control health problems.

Because health is multifaceted, epidemiology is interdisciplinary. Epidemiology is substantively and traditionally connected to the health and biomedical sciences such as biology, chemistry, anatomy, physiology, and pathology; and it is closely tied to statistics or, more precisely, biostatistics. In the search for solutions to health problems, however, the interdisciplinary net of epidemiology is often cast beyond these traditional boundaries to incorporate still other disciplines, such as social and behavioral sciences, communications, engineering, law, cartography, and computer science. The complexity of health problems has even spawned specialties within the discipline, including clinical epidemiology, genetic epidemiology, nutritional epidemiology, reproductive epidemiology, injury epidemiology, environmental epidemiology, social epidemiology, and veterinary epidemiology.

Many epidemiologists have earned degrees in medicine or some other specialty as well as graduate degrees or certificates in epidemiology. They work in diverse occupational settings—including international, national, and local health agencies and universities; teaching hospitals; and private corporations. Epidemiologists may be found, for example, in the chemical, pharmaceutical, electronics, energy, automotive manufacturing, and air travel industries.

Epidemiology provides a unique way of viewing and investigating disease and injury. The keys to understanding health, injury, and disease are embedded in the language and methods of epidemiology. Many of the basic epidemiologic concepts are familiar to most people, although only superficially understood. They reside in such everyday terms as **exposure, risk factor, epidemic,** and **bias**. This *Population Bulletin* explains the terms, methods, and materials scientists use to study the health of populations, as well as the historical underpinnings of the modern-day science of epidemiology.

Auspicious Origins

The epidemiologic way of thinking originated in writings ascribed to the Greek philosopher-physician Hippocrates in the fifth century B.C. In *On Airs, Waters, and Places,* Hippocrates displayed an extraordinary awareness of the impact of environment and behavior on personal well-being.[2] In pinpointing these factors, Hippocrates identified forces that epidemiologists today recognize as major determinants of human health. However, Hippocrates overlooked the importance of quantification, which is necessary for assessing the nature and severity of health problems as well as for understanding their etiology.

Some 800 years after Hippocrates, during the third century, the Romans began to record apparent numerical patterns in their everyday lives.[3] As part of this work, they developed an ancient precursor of the life table—a

table that displays the proportions of a population surviving to various ages and the life expectancy for people at these ages. The Romans used such tables to aid in computing annuities. Their table contained a series of five-year life expectancy calculations for people ages 20 and older.

Despite these Greek and Roman contributions, it was not until the 17th century that the quantification and manipulation of health data began in earnest. The most important advances occurred thanks to the talent and imagination of the Englishman John Graunt (1620-1674). In his pioneering research, Graunt noted that biological phenomena, such as births and deaths, varied in predictable and regular ways. His research laid the groundwork for the disciplines of both epidemiology and demography. He observed, for example, that male births consistently outnumbered female births. Graunt further observed that males no longer outnumbered females by the time they reached their childbearing ages. He attributed this to the greater tendency of males than females to migrate or to die because of war, execution, or unintentional injury. In addition to the excess of male deaths, Graunt detected a relatively higher urban than rural death rate and seasonal variation in mortality rates. His work is summarized in *Natural and Political Observations . . . Upon the Bills of Mortality*, which was first published in England in 1662.[4]

This publication also laid out another Graunt legacy, a primitive version of the life table. About 30 years later, the famous astronomer Edmond Halley improved on the life table concept, using data from 1687-1691 for the city of Breslau, now in Poland. The first complete life table appeared much later, in 1815. Its best-known product is life expectancy at birth, which is a leading indicator of a population's health status. Epidemiologists today use life table methodology to analyze how long a patient with a particular disease diagnosis or treatment is likely to survive.[5]

Photo removed for copyright reasons.

John Snow's revolutionary methods for tracking the source of cholera led the way for modern epidemiologists.

Founders of Modern Epidemiology

Two English physicians, John Snow and William Farr, and a Hungarian physician, Ignaz Semmelweis, can be considered the founders of modern epidemiology because they jointly carried epidemiology beyond description into analysis or explanation. Indeed, the epidemiologic legacies of all three include the crucial concept of hypothesis testing, upon which progress in any science ultimately depends. Each man made seminal contributions to epidemiology, public health, and preventive medicine.

John Snow (1813-1858) defied contemporary medical thinking and succeeded in slowing the spread of cholera in London, which was beset with cholera epidemics in the late 1840s and again in 1853-1854. This disease afflicts victims with violent diarrhea and vomiting, and it can be fatal. Europe had suffered from periodic cholera epidemics since at least the 16th century. During the mid-19th century, most physicians attributed the disease to miasma—"bad

Figure 1
Cluster Map of Fatal Cholera Cases in London, 1854

Source: Adapted from John Snow, *Snow on Cholera* (New York: Hafner, 1965).

air" believed to be formed from decaying organic matter. Snow held a radically different view. Snow, who was also well known as the founder of anesthesiology, suspected that the real culprit was drinking water contaminated by fecal waste.

In September 1854, Snow determined that the cholera deaths in a recent outbreak clustered around a popular source of drinking water, the Broad Street pump (see Figure 1). He shared this finding with local authorities, along with his hunch as to the cause. His disclosures prompted the removal of the pump handle, and thus shut down the suspected disease source. Shortly thereafter, the Broad Street outbreak subsided. Because cholera fatalities were already declining in London, however, Snow was un-

able to attribute the end of the outbreak directly to the closing of the pump.

The cholera-water connection remained in doubt only until 1855, when Snow published the results of his carefully controlled test of the hypothesis that sewage in drinking water causes cholera. For this research, Snow obtained information on cholera mortality occurring among 300,000 residents of a specified area of London whose water suppliers could be identified. Because he could link the cholera cases to a population base and because the allocation of the water source to households seemed random, Snow's study has been called a natural experiment. By walking door-to-door, Snow acquired the names of the specific water companies

servicing the houses where cholera fatalities had occurred—an approach to data collection that scientists now call **shoe-leather epidemiology**. Snow's research demonstrated that the cholera fatality rate in households receiving contaminated water was higher than the rate in households getting cleaner water. This finding confirmed his hypothesis.

Snow's results were unacceptable to the medical establishment primarily because they contradicted miasmic theory. Professional resistance to Snow's cholera theory was also related to his inability to identify and specify cholera's **disease agent**—the essential causal ingredient. It was not until 1883 that this agent, *Vibrio cholerae*, was isolated under the microscope by the German bacteriologist Robert Koch. Koch—best known for his research on tuberculosis and for confirming that "germs" (or microorganisms) cause infectious disease—filled in the missing piece of the cholera puzzle.[6] Snow's efforts showed, however, how epidemiology can play a preventive role even when the specific microorganism responsible for a disease is unknown.

John Snow's contemporary, William Farr (1807-1883), was a leader in developing health and vital statistics records for the Office of the British Registrar General. His many innovations include the refining of life table analysis by relating disease prevention to life expectancy, devising standardized measures to capture occupational and residential differences in mortality, and creating a system to classify disease and injury.[7] His classification system was the forerunner of the International Classification of Diseases (ICD), the standard system used throughout the world today to record the causes of mortality and morbidity (or the occurrence of disease).

Like Snow, Farr conducted an exhaustive analysis of cholera. He ascertained that cholera death rates were inversely related to altitude. But, misled by miasmic theory, Farr erred in concluding that altitude was causally connected to water contamination, and therefore to the spread of cholera. Farr provided the mortality data for the more famous Snow study of cholera in London, a testimony to his consummate professionalism. Farr also later confirmed the Snow hypothesis by showing that a specific water company had negligently marketed and supplied the unfiltered water through which cholera bacteria had been transmitted.

Ignaz Semmelweis (1818-1865), the third founder of modern epidemiology, helped revolutionize hospital practices because of his discoveries about the causes of infections. Before the introduction of antibiotics and high standards of personal hygiene, nosocomial (or hospital-acquired) infection was so common that hospitals were hazardous places to seek health care. Medical and hospital hygiene practices were dramatically improved thanks to the work of Semmelweis in the maternity wards at the General Hospital in Vienna.[8] Maternal mortality from puerperal (childbirth) fever often reached epidemic heights in Europe between the 17th and 19th centuries. Between 1841 and 1846, puerperal fever at times killed up to 50 percent of the women giving birth in the General Hospital's maternity wards staffed by medical students. The average fatality rate in these wards was about 10 percent in the 1840s—three times higher than the rate in a second set of maternity wards staffed by midwifery students.

While pursuing an obstetrical residency at the General Hospital in the late 1840s, Semmelweis became concerned about the problem of puerperal fever. He was intrigued by the vastly different maternal mortality rates in the two sets of wards. He hypothesized that the differential resulted from the failure of medical students to cleanse their hands after dissecting unrefrigerated cadavers just before examining maternity patients. He believed that puerperal fever was a septicemia, a form of blood poisoning. His belief arose from observing the similarity between symptoms of the mothers who

Ignaz Semmelweis' discoveries helped revolutionize hospital practices.

Top 10 Causes of Death in the United States, 1900 and 1998

Rank	Cause of death	Deaths per 100,000	Percent of all deaths
		1900	
1	Pneumonia	202	12
2	Tuberculosis	194	11
3	Diarrhea and enteritis	140	8
4	Heart disease	137	8
5	Chronic nephritis (Bright's disease)	81	5
6	Unintentional injury (accidents)	76	4
7	Stroke	73	4
8	Diseases of early infancy	72	4
9	Cancer	64	4
10	Diphtheria	40	2
		1998	
1	Heart disease	268	31
2	Cancer	199	23
3	Stroke	59	7
4	Lung diseases	42	5
5	Pneumonia and influenza	35	4
6	Unintentional injury (accidents)	35	4
7	Diabetes	24	3
8	Suicide	11	1
9	Nephritis, kidney diseases	10	1
10	Liver diseases	9	1

Source: Robert D. Grove and Alice M. Hetzel, *Vital Statistics Rates of the United States, 1940-1960* (Washington, DC: U.S. GPO, 1968); and National Center for Health Statistics, *National Vital Statistics Report* 47, no. 25 (1999): 6.

died of puerperal fever and those of a colleague who died of illness associated with a knife wound sustained while performing an autopsy.

Semmelweis reached his conclusion after he logically refuted a series of alternative explanations: soiled bed linen, crowding, atmospheric conditions, poor ventilation, and diet. None of these factors differed between the two maternity wards. This strengthened his original hypothesis that the disease was transmitted through the medical students. To test his hypothe-

sis, Semmelweis insisted that the students and other medical personnel in his wards scrub their hands in soap and water and then soak them in chlorinated lime before conducting pelvic examinations. Within seven months of this controversial intervention, puerperal fever fatalities in the ward plummeted tenfold, from 120 deaths per 1,000 births to 12 deaths per 1,000 births. For the first time, the mortality rate in the wards staffed by medical students dipped below that in the wards of the student midwives.

The medical community in Europe and the United States—still heavily invested in miasmic theory—rejected Semmelweis' powerful evidence that puerperal fever was transmitted through direct physical contact between caregiver and patient. The U.S. medical establishment had ignored an earlier warning about the contagious nature of puerperal fever given by Oliver Wendell Holmes Sr., the celebrated physician and author.[9] Some support for a miasmic explanation of the disease lingered even after the 1870s, when Louis Pasteur isolated its bacterial agent.[10]

Demographic and Epidemiologic Transitions

Disease patterns have changed dramatically in the industrialized world since the era of Snow, Farr, and Semmelweis. Chronic diseases, such as cancer and heart disease, displaced communicable diseases as the leading causes of mortality and morbidity in industrialized nations.[11]

In 1900, the three leading causes of death in the United States were pneumonia, tuberculosis, and diarrhea and enteritis (see Table 1). All are communicable diseases. Collectively they accounted for nearly one-third of all deaths at the beginning of the century. In 1998, the top three causes were all chronic diseases: heart disease, cancer, and stroke.

Together they were responsible for 61 percent of all U.S. deaths. These three diseases also numbered among the top 10 killers in 1900, but then they accounted for less than one-sixth of the death toll.

Epidemiologists refer to this secular, or long-term, change in disease and mortality patterns as the **epidemiologic transition**, adapting terminology developed earlier by demographers to describe the **demographic transition**. The four-stage demographic transition model describes a process during which slow or stagnant population growth gives way to a period of rapid population growth and then reverts to slow or stagnant growth.

In the pretransitional stage, both fertility and mortality rates are high. Mortality rates rise higher during intermittent epidemics, wars, and famines. During the early transition, the death rate plummets while the birth rate remains high. Fertility's decline occurs in the late transition stage. Finally, in the post-transitional stage, fertility rates converge with mortality rates. The near equilibrium between birth and death rates that occurred in the pretransitional stage is restored. Mortality rates are low and constant, while fertility rates are low and fluctuating—often in response to changing economic conditions.[12]

The original epidemiologic transition theory largely parallels the stages of the demographic transition model, upon which it is based. It outlines a progression from the **Age of Pestilence and Famine**, through the **Age of Receding Pandemics,** and culminates in the **Age of Degenerative and Manmade Diseases** (see Figure 2).[13]

A fourth stage, termed the **Hybristic Stage**, has been incorporated into epidemiologic transition theory.[14] Hybristic derives from the Greek word *hybris*, meaning a feeling of invincibility or overweening self-confidence. The United States and many other industrialized countries are in this fourth stage of the epidemiologic transition, in which personal behavior and lifestyle influence the patterns and levels of disease and injury. So-

Figure 2
Demographic/Epidemiologic Transition Framework
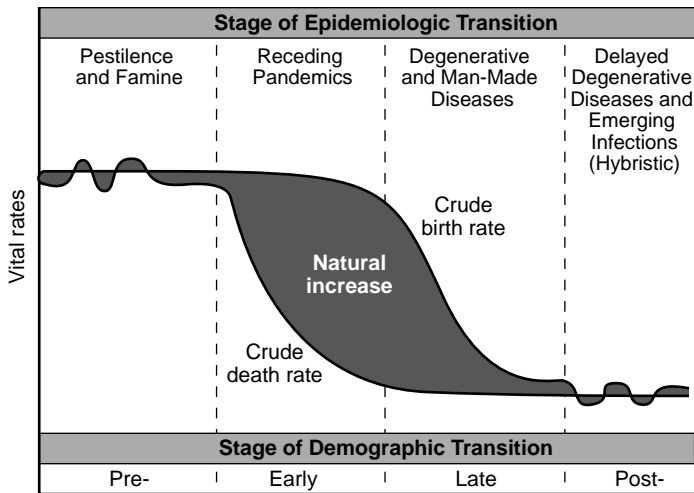
called "social pathologies" such as homicide, cirrhosis of the liver, suicide, and HIV/AIDS were among the leading killers of Americans in the 1980s and 1990s. Tuberculosis is undergoing a resurgence in the United States, as are several other communicable diseases associated with poverty and unhealthy lifestyles.[15]

Like the demographic transition, the epidemiologic transition reflects the varying forces of socioeconomic development, sanitation, and public health, and, to a much lesser extent, advances in clinical medicine.[16] Socioeconomic factors initiated the epidemiologic transition in the United States and western European countries—where the transition first began. Explicit public health measures, such as immunization, water purification, and application of insecticides, were more important to the achievement of the transition in non-Western countries such as Japan and Taiwan than in the West. Although most of these public health measures had been developed in Western countries, they were introduced after the West's mortality rates had already dropped substantially.

Between 1900 and 1998, life expectancy at birth rose from 47 to 77

Figure 3
The Epidemiologic Triad

Epidemiologic Triad: Host, Agent, and Environment

The most familiar disease model, the epidemiologic triad, depicts a relationship among three key factors in the occurrence of disease or injury: **agent**, **environment**, and **host** (see Figure 3).

An agent is a factor whose presence or absence, excess or deficit, is necessary for a particular disease or injury to occur. General classes of disease agents include chemicals such as benzene, oxygen, and asbestos; microorganisms such as bacteria, viruses, fungi, and protozoa; and physical energy sources such as electricity and radiation. Many diseases and injuries have multiple agents.

People who are not epidemiologists often confuse a disease or injury agent with its intermediary— its **vector** or **vehicle**. A vector is a living organism, whereas a vehicle is inanimate. The female of one species of mosquito carries the protozoa that are parasitic agents of malaria. The mosquito is the vector or intermediate host of malaria, but not the agent. Similarly, an activated nuclear bomb functions as a vehicle for burns by conveying one of its agents, ionizing radiation.

The environment includes all external factors, other than the agent, that can influence health. These factors are further categorized according to whether they belong in the social, physical, or biological environments. The social environment encompasses a broad range of factors, including laws about seat belt and helmet use; availability of medical care and health insurance; cultural "dos" and "don'ts" regarding diet; and many other factors pertaining to political, legal, economic, educational, communications, transportation, and health care systems. Physical environmental factors that influence health include climate, terrain, and pollution. Biological environmental influences include disease and injury vectors; soil, humans, and plants serving as reservoirs of infection; and plant and animal sources of drugs and antigens.

years in the United States.[17] The decline in communicable disease mortality rates, along with falling birth rates, increased the share of the elderly in the U.S. population. Americans ages 65 or older constituted 4.1 percent of the U.S. population in 1900. By 1998, they represented three times that number, or 12.7 percent.[18]

The predominance of degenerative and man-made diseases in more developed countries has transformed the scope of epidemiology. Although HIV infection is a notable exception, epidemiologists in industrialized countries today are more likely to study the morbidity and mortality of chronic disease than of communicable disease. In the search for the causes of chronic diseases such as lung cancer and heart disease, epidemiologists focus more attention on environmental or lifestyle factors than on microorganisms. The long latency period between exposure to the risk of getting a chronic disease and subsequent diagnosis complicates this search. Especially since World War II, epidemiologists have devised or adapted special techniques for collecting and analyzing chronic disease data that address the latency problem.[19] These techniques will be presented in the section on analytic epidemiology.

Disease Models

How do diseases develop? Epidemiology helps researchers visualize disease and injury etiology through models. The epidemiologic triad and the web of causation are among the best known of these models.

The host is the actual or potential recipient or victim of disease or injury. Although the agent and environment combine to "cause" the illness or injury, host susceptibility is affected by personal characteristics such as age, occupation, income, education, personality, behavior, and gender and other genetic traits. Sometimes genes themselves are disease agents, as in hemophilia and sickle cell anemia.

From the perspective of the epidemiologic triad, the host, agent, and environment can coexist fairly harmoniously. Disease and injury occur only when there is interaction or altered equilibrium between them. But if an agent, in combination with environmental factors, can act on a susceptible host to create disease, then disruption of any link among these three factors can also prevent disease.

Smallpox was eradicated globally through this kind of disruption.[20] Smallpox is almost always spread by human face-to-face contact, but is less contagious than influenza, measles, chickenpox, and some other communicable diseases. Health personnel severed the link between disease agent and host by isolating each smallpox case upon diagnosis and then vaccinating everyone within a three-mile radius. This highly effective method, known as the **case-containment and ring-vaccination strategy**, proved to be a relatively low-cost way to eradicate smallpox.

Web of Causation

Although the epidemiologic triad has contributed to the understanding of disease etiology, the process that actually generates disease or leads to injury is much more complex. This complexity is better portrayed in a second model used by epidemiologists: the web of causation.[21]

The web of causation was developed especially to enhance understanding of chronic disease, such as cardiovascular disease. However, it can also be applied to the study of injury and communicable disease. The web of causation de-emphasizes the role of

Figure 4
Simplified Web of Causation Applied to Cardiovascular Disease
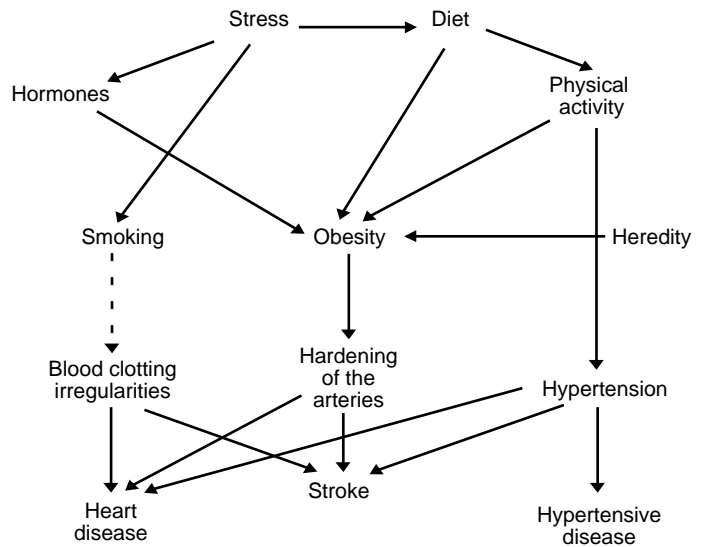
Note: Some intermediate links were omitted in this example.
Source: Adapted from R.A. Stallones, *Public Health Monograph* 76 (1966): 53.

the agent and highlights other factors that encourage the onset of disease. Using this model, scientists can diagram how factors such as stress, diet, heredity, and physical activity relate to the onset of the three major types of cardiovascular disease: coronary heart disease, cerebrovascular disease (stroke), and hypertensive disease (see Figure 4). In addition, the approach reveals that each of these diseases has a precursor, for example, hypertension, that can alert a diagnostician to the danger of a more serious underlying condition.

Compiling Epidemiologic Evidence

Models are useful in guiding epidemiologic research, but health scientists cannot answer the underlying questions about the causes of disease or injury without appropriate data.

By linking information on exercise habits to such health outcomes as hypertension, researchers can measure the health benefits of physical activity.

Researchers need a myriad of data on the personal and medical backgrounds of individuals to determine, for example, whether physicians are more likely to have hypertension than construction workers—and whether one group is more likely than the other to develop a related disease.

Original data collected by or for an investigator are called **primary data.** Because primary data collection is expensive and time consuming, it usually is undertaken only when existing data sources—or **secondary data**—are deficient. Most descriptive epidemiologic studies use secondary data, often data collected for another purpose. Analytic epidemiologic studies usually require primary as well as secondary data.

Risk Factors and Outcome Variables

Two core categories of variables are used in epidemiologic research: risk factors and health outcome (or health status) variables.

Risk factors are associated with or explain a particular health outcome, such as disease or injury. The term risk factor embraces direct causes or disease agents, but it also covers personal characteristics that make indi-

viduals more or less prone to a particular disease or injury. Personal characteristics include sociodemographic factors such as age, gender, and race, and behavioral factors such as exercise, diet, and use of alcohol and other drugs.

Health outcome (or health status) variables measure the presence or absence of disease, injury, physical disability, or death. While morbidity and mortality are the principal outcome variables used in epidemiologic research, epidemiologists also study a host of morbidity indicators. These may include prescription drug use, restricted activity days, or work and school absences because of sickness, and health care service utilization. Outcome variables may also consist of health indicators such as lung function, blood pressure, cholesterol levels, and mental status.

Major Data Sources

Sources of epidemiologic data are numerous and varied. They include population censuses and surveys, vital statistics, disease registries, and health care utilization records.

Censuses

In the United States and other countries, national censuses are conducted to obtain an accurate count of the total population, along with sociodemographic characteristics such as age, gender, race, and place of residence. Census counts often provide the denominator, or the population at risk, for computing epidemiologic rates and proportions. Some countries, such as Sweden, Japan, and Israel, maintain universal population registers through which they continually adjust their population counts in response to new "vital" events—including births, deaths, marriages, divorces, military enlistment, imprisonment, and migration.

Vital Statistics: Births and Deaths

In the United States, nearly every death is recorded in a national reg-

istry. The death certificate completed for each recorded death is a rich source of data for epidemiologic research. The certificate contains information about the circumstances of death (time, date, and place), sociodemographic characteristics of the person who died, and specifics about the cause of death. These specifics include the immediate, intervening, and underlying causes of death, and other conditions that might have contributed to the death (see Figure 5, page 14).

Death certificates may be easily retrieved through a centralized, computerized system called the National Death Index (NDI).[22] Unfortunately, death certificates often contain inaccurate information. These inaccuracies are compounded when the individual preparing the certificate (generally a physician, medical examiner, or coroner) did not know the decedent.

The death certificate solicits a single underlying cause of death—stroke, for example—although other causes, such as malnutrition or pneumonia, might have contributed directly to a given individual's death. For the physician or other person completing the certificate, the decision to choose stroke as the single underlying cause of death—rather than one of the contributing causes—may be quite arbitrary. Because of this, some epidemiologists consider all the contributing or other significant conditions included on a death certificate when doing mortality research.[23] Nevertheless, most studies of cause-specific mortality rely on the single underlying cause data rather than the multiple causes. This approach tends to underestimate the role of diabetes, nutritional deficiencies, and other important factors that directly contributed to an individual's death. Researchers can check the accuracy of death certificates and improve their chances of learning the true underlying cause of death through careful review of medical records; through interviews with family, friends, and acquaintances of the decedent (verbal

autopsies); and especially through an autopsy, an invasive physical examination of the body.

Epidemiologists use a second product of the vital registration system, the birth certificate, to investigate complications of pregnancy and childbirth such as spontaneous abortion, low birth weight, preterm birth, Caesarean delivery, birth defects, maternal mortality, and infant mortality. Nearly every U.S. birth is recorded in a national registry. Birth certificates also contain sociodemographic characteristics, such as age, marital status, race, and length of gestation, that are associated with the health status of mothers and babies.[24] Like death certificates, however, birth certificates may contain inaccurate or incomplete information.

Disease Registries

The best sources of information on the occurrence of disease in the United States are population-based disease registries established to record cases of certain serious diseases, such as HIV/AIDS, tuberculosis, and cancer.[25] These registries are particularly useful to epidemiologists because disease cases can be directly related to a population within specified geographic or political boundaries; that is, to a population at risk. Moreover, because physicians are legally required to report all new cases to the appropriate registries, the records are relatively complete and reliable.

One of the most important of these registries is the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. SEER, established in 1972, contains data from five states and four metropolitan areas that represent one-tenth of the U.S. population. It is the most comprehensive source of cancer data in the United States. SEER enables researchers to study national cancer morbidity and mortality trends and provides data for analytic studies into the causes of cancer.

Registries can help health personnel detect epidemics by revealing an

The best sources of information on the occurrence of disease in the United States are population-based disease registries.

Figure 5
Standard U.S. Death Certificate

U.S. STANDARD
CERTIFICATE OF DEATH

TYPE/PRINT IN PERMANENT BLACK INK FOR INSTRUCTIONS SEE OTHER SIDE AND HANDBOOK

LOCAL FILE NUMBER

STATE FILE NUMBER

DECEDENT

1. DECEDENT'S NAME *(First, Middle, Last)*

2. SEX

3. DATE OF DEATH *(Month, Day, Year)*

4. SOCIAL SECURITY NUMBER

5a. AGE—Last Birthday *(Years)*

5b. UNDER 1 YEAR — Months / Days

5c. UNDER 1 DAY — Hours / Minutes

6. DATE OF BIRTH *(Month, Day, Year)*

7. BIRTHPLACE *(City and State or Foreign Country)*

8. WAS DECEDENT EVER IN U.S. ARMED FORCES? *(Yes or no)*

9a. PLACE OF DEATH *(Check only one; see instructions on other side)*
HOSPITAL: ☐ Inpatient ☐ ER/Outpatient ☐ DOA
OTHER: ☐ Nursing Home ☐ Residence ☐ Other *(Specify)*

9b. FACILITY NAME *(If not institution, give street and number)*

9c. CITY, TOWN, OR LOCATION OF DEATH

9d. COUNTY OF DEATH

10. MARITAL STATUS — Married, Never Married, Widowed, Divorced *(Specify)*

11. SURVIVING SPOUSE *(If wife, give maiden name)*

12a. DECEDENT'S USUAL OCCUPATION *(Give kind of work done during most of working life. Do not use retired.)*

12b. KIND OF BUSINESS/INDUSTRY

13a. RESIDENCE—STATE

13b. COUNTY

13c. CITY, TOWN, OR LOCATION

13d. STREET AND NUMBER

13e. INSIDE CITY LIMITS? *(Yes or no)*

13f. ZIP CODE

14. WAS DECEDENT OF HISPANIC ORIGIN? *(Specify No or Yes—If yes, specify Cuban, Mexican, Puerto Rican, etc.)* ☐ No ☐ Yes Specify:

15. RACE—American Indian, Black, White, etc. *(Specify)*

16. DECEDENT'S EDUCATION *(Specify only highest grade completed)* Elementary/Secondary (0-12) College (1-4 or 5+)

PARENTS

17. FATHER'S NAME *(First, Middle, Last)*

18. MOTHER'S NAME *(First, Middle, Maiden Surname)*

INFORMANT

19a. INFORMANT'S NAME *(Type/Print)*

19b. MAILING ADDRESS *(Street and Number or Rural Route Number, City or Town, State, Zip Code)*

DISPOSITION

20a. METHOD OF DISPOSITION ☐ Burial ☐ Cremation ☐ Removal from State ☐ Donation ☐ Other *(Specify)*

20b. PLACE OF DISPOSITION *(Name of cemetery, crematory, or other place)*

20c. LOCATION—City or Town, State

21a. SIGNATURE OF FUNERAL SERVICE LICENSEE OR PERSON ACTING AS SUCH

21b. LICENSE NUMBER *(of Licensee)*

22. NAME AND ADDRESS OF FACILITY

SEE DEFINITION ON OTHER SIDE

PRONOUNCING PHYSICIAN ONLY

Complete items 23a-c only when certifying physician is not available at time of death to certify cause of death. Signature and Title ▶

23a. To the best of my knowledge, death occurred at the time, date, and place stated.

23b. LICENSE NUMBER

23c. DATE SIGNED *(Month, Day, Year)*

ITEMS 24-26 MUST BE COMPLETED BY PERSON WHO PRONOUNCES DEATH

24. TIME OF DEATH M

25. DATE PRONOUNCED DEAD *(Month, Day, Year)*

26. WAS CASE REFERRED TO MEDICAL EXAMINER/CORONER? *(Yes or no)*

SEE INSTRUCTIONS ON OTHER SIDE

CAUSE OF DEATH

27. PART I. Enter the diseases, injuries, or complications that caused the death. Do not enter the mode of dying, such as cardiac or respiratory arrest, shock, or heart failure. List only one cause on each line.

Approximate Interval Between Onset and Death

IMMEDIATE CAUSE (Final disease or condition resulting in death) ▶ a. ____ DUE TO (OR AS A CONSEQUENCE OF):

Sequentially list conditions, if any, leading to immediate cause. Enter UNDERLYING CAUSE (Disease or injury that initiated events resulting in death) LAST

b. ____ DUE TO (OR AS A CONSEQUENCE OF):

c. ____ DUE TO (OR AS A CONSEQUENCE OF):

d. ____

PART II. Other significant conditions contributing to death but not resulting in the underlying cause given in Part I.

28a. WAS AN AUTOPSY PERFORMED? *(Yes or no)*

28b. WERE AUTOPSY FINDINGS AVAILABLE PRIOR TO COMPLETION OF CAUSE OF DEATH? *(Yes or no)*

29. MANNER OF DEATH ☐ Natural ☐ Accident ☐ Suicide ☐ Homicide ☐ Pending Investigation ☐ Could not be Determined

30a. DATE OF INJURY *(Month, Day, Year)*

30b. TIME OF INJURY M

30c. INJURY AT WORK? *(Yes or no)*

30d. DESCRIBE HOW INJURY OCCURRED

30e. PLACE OF INJURY—At home, farm, street, factory, office building, etc. *(Specify)*

30f. LOCATION *(Street and Number or Rural Route Number, City or Town, State)*

CERTIFIER

31a. CERTIFIER *(Check only one)*

☐ CERTIFYING PHYSICIAN *(Physician certifying cause of death when another physician has pronounced death and completed item 23)* To the best of my knowledge, death occurred due to the cause(s) and manner as stated.

☐ PRONOUNCING AND CERTIFYING PHYSICIAN *(Physician both pronouncing death and certifying to cause of death)* To the best of my knowledge, death occurred at the time, date, and place, and due to the cause(s) and manner as stated.

☐ MEDICAL EXAMINER/CORONER On the basis of examination and/or investigation, in my opinion, death occurred at the time, date, and place, and due to the cause(s) and manner as stated.

31b. SIGNATURE AND TITLE OF CERTIFIER ▶

31c. LICENSE NUMBER

31d. DATE SIGNED *(Month, Day, Year)*

32. NAME AND ADDRESS OF PERSON WHO COMPLETED CAUSE OF DEATH (ITEM 27) *(Type/Print)*

REGISTRAR

33. REGISTRAR'S SIGNATURE ▶

34. DATE FILED *(Month, Day, Year)*

NAME OF DECEDENT: For use by physician or institution

SEE INSTRUCTIONS ON OTHER SIDE

1989 REVISION   PUBLIC HEALTH SERVICE – NATIONAL CENTER FOR HEALTH STATISTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PHS T-003
REV 1/89

unanticipated sharp rise in disease or injury rates. Registries can also facilitate the planning, implementation, and evaluation of disease and injury control programs.

Health Surveys

Health surveys are another valuable source of epidemiologic data.[26] One prime example is the National Health Interview Survey (NHIS or HIS), conducted on behalf of the U.S. National Center for Health Statistics. The HIS provides an annual snapshot of Americans' health status and patterns of health service utilization. Each year, the HIS surveys up to 47,000 households representing 125,000 individuals to obtain information on the frequency of medical visits and short hospital stays and on special topics such as smoking habits or knowledge and attitudes about HIV/AIDS. Some surveys, such as the National Health and Nutrition Examination Survey (NHANES), incorporate medical examinations to complement information on personal attributes, knowledge, attitudes, beliefs, and behavior.

Health surveys combine flexibility with a capacity to penetrate hard-to-reach populations, such as the inner-city poor and rural mountain inhabitants. Surveys can also elicit information on sensitive topics, such as use of contraceptives or illegal drugs. They provide data important for identifying high-risk populations and planning health intervention programs.

Survey results can be generalized to a larger population only if the sampling units are representative of that population—that is, each individual, household, hospital, or other sampling unit in that population has a known chance of being included in the survey. There are various methods for obtaining representative sample units, including simple random sampling, systematic sampling, stratified sampling, and cluster sampling.[27] Regardless of the method of sampling, all surveys contain sampling error. Researchers often publish estimates of sampling error along with survey results.

Information about a baby's birth, such as birth weight, complications during delivery, and general health status are recorded on the birth certificate, along with information about the mother.

The types and wording of questions also influence the results. Researchers usually take great care to ensure that survey questions are **valid** (they measure what they purport to measure) and **reliable** (they measure the same thing when they are asked of different respondents or when asked by different interviewers).

The way the survey is conducted affects the **response rate**—the percent of the sample responding to a survey. Rates are usually higher when interviewers conduct the survey in person rather than over the telephone or through the mail. The response rate for a survey is another indication of whether the results truly apply to the study population. Nonrespondents often differ from respondents in critical ways. Young adults (especially young single men), the poor, and members of ethnic minorities, for example, are less likely than other people to respond to a survey. Hence, these groups often are underrepresented in survey research. Response rates are generally calculated for each survey item and for the survey as a whole to guide analysts in interpreting the results.

Health Care Utilization Records

Records of professional encounters between patients and health care providers are known as utilization da-

Figure 6
Suicide Rates for Men in Selected Countries, 1995
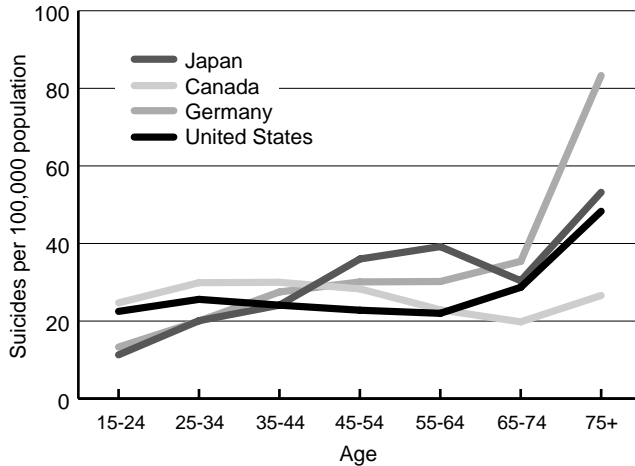
Source: World Health Organization, *1996 World Health Statistics Annual* (1997); U.S. National Center for Health Statistics, unpublished data; and Japan, National Institute of Population and Social Security Research, unpublished data.

ta. Hospital discharge records, which are based on inpatient medical charts, are the most prominent type of utilization data. Discharge records allow hospitals to evaluate the effectiveness and outcome of a patient's treatment. Computerized discharge systems, such as the Professional Activity Study (or PAS) and the Uniform Hospital Discharge Data Set (or UHDDS), are more useful for epidemiologic research, however. These standardized systems permit researchers to compare hospitals, for example, according to the proportion of patients admitted who had private health insurance or who died while under care. Comparisons can extend to other characteristics of patients, such as age, gender, race, or reason for admission.

The value of utilization data is affected by the feasibility of connecting them to a population at risk, ability to distinguish new cases from repeat cases, completeness of reporting, and quality of data.

Supplemental Sources
Scientists may use various other sources of data in health research. They sometimes obtain data, for example, from the mass media, insurance companies, work sites, police, schools, social workers, and psychologists.

Linking Data Records
When researchers link records from different sources, they may obtain valuable clues about a health problem. Knowledge of homicide in a community, for example, is expanded if autopsy records or death certificates are individually matched with police and court records. By exploring the nature of the relationship between victims and assailants, epidemiologists and criminologists become better equipped to help prevent future homicides or assaults. Similarly, with an essentially closed health-care system, such as the National Health Service in the United Kingdom or a health maintenance organization (HMO) in the United States, family medical records can be linked to show how health problems in parents may affect their children. One such study, using HMO medical records on intact nuclear families, demonstrated that children with an alcoholic parent faced a higher risk than other children of injury and of emotional and psychosomatic problems.[28]

Electronic storage of administrative and health records has increased the potential for linking records from myriad sources, opening up rich possibilities for new epidemiologic research. These exciting new prospects for enhancing public health must be balanced, however, against the importance of protecting the privacy of the individual.

Epidemiology draws on many diverse data sources. Some are readily available and accessible, while others can be accessed only after prolonged negotiations with those responsible for the data or after ensuring the confidentiality of individuals' records. Still other sources need to be specially created, which may require careful negotiations to elicit cooperation from the targets of the research as well as the people or institutions that control access to the subjects.

In general, the hurdles to collecting data for analytic epidemiologic research are higher than for purely descriptive research.

# Finding Patterns: Descriptive Epidemiology

People's lives seem besieged by health risks at any given moment, yet the health environment is relatively benign in most industrialized countries. Nearly two-thirds of U.S. deaths in 1998 were attributed to heart disease, cancer, and stroke—all diseases associated with old age. There is only a small chance that an individual will commit suicide, die in a motor vehicle crash, or be murdered. National-level figures, however, mask much higher risks for certain groups of people. Men ages 75 or older, for example, turn to suicide at a much higher rate than men in other age groups in the United States. This same pattern is found in many other industrialized countries. Japanese and German men, for example, generally have higher suicide rates than the U.S. men, but the rates rise at older ages in all three countries (see Figure 6). In Canada, reported suicide rates are highest in the young adult years, but the likelihood of suicide rises again in the oldest age group.

Teenagers and young adults, on the other hand, face a higher risk of dying or being injured in an automobile crash than people in other age groups. A Rhode Island study in the 1980s showed, for example, that men ages 15 to 34 and women ages 15 to 24 were much more likely to be hospitalized or killed in an automobile crash than people in other age groups (see Figure 7). A male's risk of being a homicide victim is much higher in the United States than in other populous industrialized countries, as shown in Figure 8.

Predicting health risks is one of the prime tasks of epidemiology.

Figure 7
Age-Sex Pyramids for the Rhode Island Population and Motor Vehicle Trauma Cases, 1984–1985
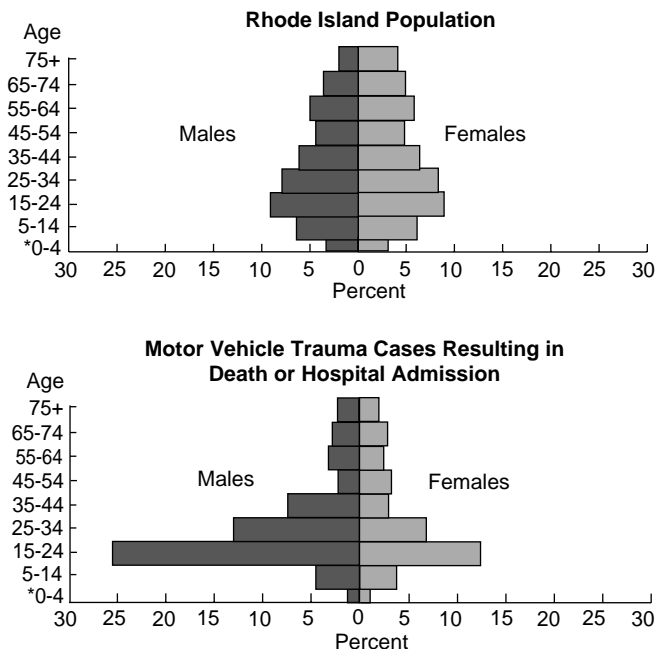
* The bottom bar shows a five-year age group while the other bars refer to 10-year age groups up to age 75.

Source: Adapted from Ian R.H. Rockett, Ellice S. Lieberman, William H. Hollinshead, Sandra L. Putnam, and Henry E. Thode, "Profiling Motor Vehicle Trauma in Rhode Island," *Rhode Island Medical Journal* 73, no. 12 (1990).

Figure 8
Male Homicide Rates by Age in Selected Countries, 1995
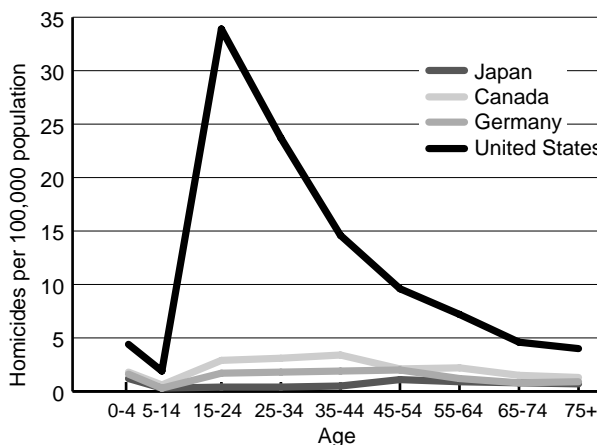
Source: World Health Organization, *1996 World Health Statistics Annual* (1997); U.S. National Center for Health Statistics, unpublished data; and Japan, National Institute of Population and Social Security Research, unpublished data.

Before making predictions about a given health problem, however, scientists need to learn how frequently it occurs within a specific population group or geographic area. Tracking the occurrence of disease and injury is the job of descriptive epidemiology. Descriptive epidemiology shows that certain groups face a higher risk than others; that is, that disease and injury are not random phenomena. It can also identify the risk factors. Descriptive epidemiology documents patterns, trends, and differentials in risk factors and health outcomes. This information is critical for

developing policy; allocating scarce economic and manpower resources; and planning, implementing, and evaluating prevention and treatment programs.

Descriptive epidemiology is a two-step process. The first step involves the rather mechanical task of amassing all the facts about a situation or problem. The second is the more contemplative step of conceiving a plausible explanation for why the situation exists. This second phase, known as hypothesis formulation, involves examining all the facts and asking questions from different perspectives. It is

the bridge between descriptive and analytic epidemiology. Analytic epidemiology is responsible for testing the hypotheses—for addressing the question of why certain groups are at higher or lower risk of a particular disease or injury than others. But before testing a hypothesis, researchers must describe the problem in standard terms.

Mapping the Parameters

Epidemiologists quantify the health status of populations by recording the stock and flow of diseases, injuries, and other health problems. To do this, they measure the prevalence and incidence of health problems, and document the who, where, and when of specific kinds of cases.

Prevalence and Incidence

Epidemiologists describe the magnitude of a health problem in two ways: in terms of prevalence and incidence (see Box 1). Prevalence reveals how many cases exist in a population at a given time. The incidence rate records the rate at which new cases are appearing within that population over a specific period.

time each of the noncases was at risk of contracting a disease, plus the total amount of time all the people with the disease (cases) had remained disease-free (noncases). If each of the seven cases in this example were disease-free for five months, they would add a total of 35 months (2.9 person-years) to the person-years at risk.

It is often difficult to track a true population at risk, especially a large population. Births, deaths, and moves in and out of a given area change the size and composition of the population. In addition, the members of a study population may not cooperate with the investigators for the entire duration of a study. For states, countries, or other large populations, the incidence rate generally is computed using the mid-period population rather than person-time at risk as the denominator. The rate is therefore expressed in population units rather than person-time units. Strictly speaking, such a measure is really an index or pseudorate, not a rate. A true rate measures how frequently a phenomenon (for example, the number of disease cases) occurs per unit of time. Rates are dynamic, not static.

Although prevalence is sometimes called a prevalence rate, it is not a true rate because prevalence cases cannot be related to time at risk for becoming a case. Unlike incidence rates, prevalence cannot be used to study the etiology of disease because the lack of a person-time dimension makes it impossible to link disease cases to risk factors. However, prevalence data are valuable to health planners and administrators who allocate scarce resources and plan and provide needed services. Also, incidence rates are essential for evaluating the effectiveness of specific interventions in preventing disease and injury.

If a disease is rare, its incidence rate is fairly stable over time, and it lasts for a predictable length of time, then prevalence can be estimated by multiplying the incidence rate by the average duration of the disease:

$$\text{Prevalence} \approx \text{Incidence rate} \times \frac{\text{Average}}{\text{duration}}$$

Thus, if a researcher knows the value of any two of the three measures (incidence, prevalence, and average duration), he or she can estimate the third.

Another epidemiologic measure of frequency is the **cumulative incidence**, normally expressed as a percentage. This measures the percentage of individuals in a population who develop a disease or become injured within a specified time interval. Cumulative incidence is particularly useful in investigating an infectious disease outbreak:

$$\frac{\text{Cumulative}}{\text{incidence}} = \frac{\text{Number of new cases}}{\text{Persons at risk}} \times 100$$

Prevalence data reveal the extent of a given health problem and can help guide decisions about allocating resources and providing services. They do not, however, shed light on possible causes of the health problem or on whether interventions are effective in curbing it. Incidence data, by contrast, can be linked with data on risk factors and used to investigate the causes of disease and to evaluate the effectiveness of disease treatments or other interventions.

Person, Place, and Time

Knowing the magnitude of disease or injury is only the beginning of the epidemiologist's work. The next step is to answer the following three questions: Who has the disease or injury? Where did the cases occur? When did they occur?

Specifying person, place, and time is crucial for identifying risk groups, narrowing the search for risk factors, and targeting and evaluating interventions. People may be identified by sociodemographic characteristics that promote or inhibit susceptibility to disease or injury. They may also be identified by habits or lifestyles that influence the likelihood of harmful or beneficial exposures. Place can be described geographically (for example, by country or state) and institutionally (for example, by type of school or branch of military service). The date or time that disease or injury occurred can help document secular (or long-term) trends, seasonal, and other periodic effects or the presence of epidemics or case clusters.

Designing Research

Descriptive studies can be classified according to three categories of research design: **case report**, **cross-sectional survey**, and **correlational study**.

Case Report and Case Series

The case report is the simplest kind of descriptive study. It is written by a physician or other health care provider to describe an exceptional

'Frisbee finger,' and 'Space Invaders' wrist,' for example, have found their way into the annals of medicine.

clinical experience. For example, in 1933, a case report was prepared on a child who had recovered from bacterial meningitis, an infection of the coverings of the brain and spinal cord that, until the appearance of sulpha drugs, was almost invariably fatal.[29] Although most case reports focus on serious, life-threatening conditions, some reflect the hazards of popular pastimes. "Break-dancing neck," "Frisbee finger," and "Space Invaders' wrist," for example, have found their way into the annals of medicine.[30]

A single case usually raises more questions than it answers. A series of similar cases, however, may provide the basis for a new hypothesis or even evidence of a new disease (see Box 2, page 22). AIDS was first identified in this manner. Epidemiologists from the U.S. Centers for Disease Control and Prevention (CDC) were called in when five young homosexual men in Los Angeles were diagnosed with *Pneumocystis carinii* pneumonia between October 1980 and May 1981.[31] This series of cases was highly irregular because this form of pneumonia did not normally affect young, healthy individuals. Around the same time, physicians also began finding young homosexual men afflicted with another atypical disease: Kaposi's sarcoma. The discovery of these two clusters led the CDC to initiate the classification and quantification of AIDS.

Case reports and case series themselves cannot demonstrate that exposure to a suspected risk factor causes a particular health outcome because they lack an appropriate comparison or control group. Nevertheless, case reports can offer clinicians theories that can be confirmed or refuted by further study.

It is simpler to investigate a case of an acute disease than a chronic disease because of the shorter lag time between exposure to disease risk and the onset of the disease. Scientists find it easier to trace a case of food poisoning to contaminated chicken eaten the previous evening in a restaurant than to trace a lung cancer case back to employment in a nickel

refinery decades before the diagnosis. The physician who, after looking at a mere three cases, detected the connection between angiosarcoma (cancer of the blood vessel tissue of the liver) and previous employment in a vinyl chloride plant, was a rare exception.[32]

Cross-Sectional Survey

A population-based health survey is cross-sectional when the investigators collect data simultaneously on individuals' exposure to the suspected risk factor for a disease and on whether they have that disease. With these cross-sectional data, epidemiologists can find out whether that exposure was more common in a group of individuals who have the disease than in a comparison group without the disease. Survey results might show, for example, that subjects with esophageal cancer are twice as likely to drink alcoholic beverages as are those without the disease. Similarly, epidemiologists can compare the intensity of the condition with the intensity of the exposure; subjects with higher blood-lead levels may be found to live closer to a battery plant than those with lower levels.

Cross-sectional survey data, however, cannot indicate whether exposure to disease risk factors preceded the onset of the disease in an individual because these data are collected at one point in time. To address this problem, surveys are sometimes repeated within the same population or sample. Such a series of surveys, known as a **panel study**, go beyond the purely descriptive to the analytic dimension of epidemiology. Panel studies allow analysts to separate the period of exposure from the time of disease onset, affording a deeper understanding of the disease process.

Correlational Study

In a correlational (or ecological) study, the association between the incidence of injury or disease in a population and a suspected risk factor is examined for a population as a whole, rather than for individuals. Correla-
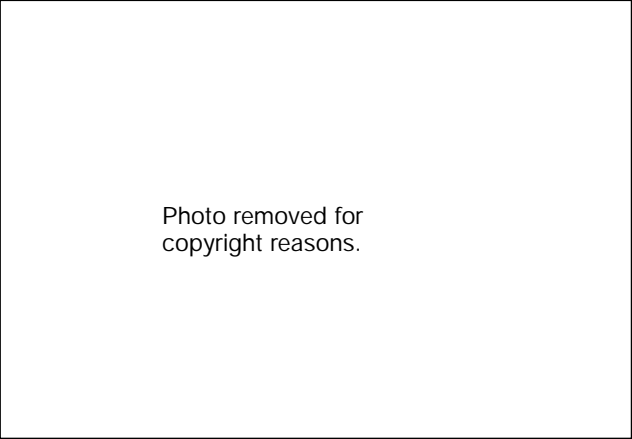
The practice of washing food in a river can be part of the web of causation that brings disease to humans.

tional studies generally use routinely collected data, such as infant mortality rates and per capita income. As a result, they tend to be relatively cheaper and easier to conduct than cross-sectional surveys.

Because correlational studies do not rely on individual-level data, the relationships between variables that emerge from such studies may be misinterpreted because of the ecological fallacy—the attribution of population or group characteristics to individuals within the group.

The ecological fallacy can be illustrated using a hypothetical example. Suppose a correlational study of the eastern United States shows that, as the Hispanic share of a state's population rises, the incidence rate of Alzheimer's disease also rises. This finding appears to imply that Hispanics are at greater risk of Alzheimer's than other Americans. However, the finding probably reflects the fact that some states with relatively old populations, such as Florida and Rhode Island, also have attracted substantial numbers of Hispanics in recent years. Elderly people are known to be a high-risk group for Alzheimer's disease; Hispanics are not. In fact, the Hispanics in Florida and Rhode Island are probably less likely to have Alzheimer's than other state residents because many Hispanics are recent

migrants. Migrants tend to be relatively young, and therefore less likely to have Alzheimer's than older individuals.

Correlational studies can generate research hypotheses, as will be discussed in the next section, but analytic studies are necessary to test them. Analytic studies can avoid the pitfalls of the ecological fallacy by tapping into exposure and disease data at the individual level and documenting the timing and sequence of events.

Formulating a Hypothesis

Research hypotheses rarely spring from the intuitive genius of a scientist. Formulating a research hypothesis is often an arduous and methodical process—involving experimentation with one approach and then another, until one fits. There are various approaches to epidemiologic hypothesis

formulation. These include:
- the method of difference
- the method of agreement
- the method of concomitant variation
- the method of analogy
- the method of detection of conflicting observations.

Of these, the first three reflect the work of 19th-century English philosopher and economist John Stuart Mill, whose *System of Logic* revolutionized the application of inductive reasoning to the natural world.[33] Although the terms may seem intimidating, they are really a formal description of the way people subconsciously draw conclusions about cause and effect in their everyday lives.

The **method of difference** examines the differences among groups for clues as to why the groups' disease rates or other health problems vary. For example, the United States has

Onset of Illness in Des Moines, Iowa, Trichinosis Outbreak, July to September 1990
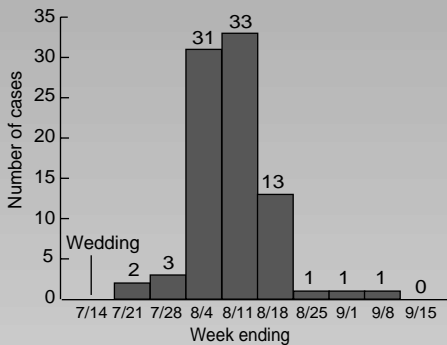
Source: James B. McAuley, et al, "A Trichinosis Outbreak Among Southeast Asian Refugees," *American Journal of Epidemiology* 135, no 12 (1992): 1404-10.

who were exposed to the suspected risk factor with the cumulative incidence of those who were not exposed. Investigators' conclusions based on the weight of the accumulated evidence are then written up in a report. Control measures need to be applied as soon as possible after an outbreak begins to minimize the number of victims.

An outbreak investigation may be initiated by an analytic study. In the Iowa trichinosis example, a case-control study enabled the investigators to ascertain which of three social events was the source of the contaminated pork whose consumption triggered the outbreak.

Clusters of noninfectious health events, including youth suicides, childhood leukemias, and birth defects, sometimes occur in local communities. CDC defines a cluster as "an unusual aggregation, real or perceived, of health events that are grouped together in time and space and that are reported to a health agency."[5] CDC has developed a series of specific guidelines to help health officials manage and investigate disease and injury clusters.

References
1. John M. Last, ed., *A Dictionary of Epidemiology*, 3d ed. (New York: Oxford University Press, 1995): 54.
2. Sir MacFarlane Burnet and David O. White, *Natural History of Infectious Disease*, 4th ed. (London: Cambridge University Press, 1972).
3. David W. Fraser, Theodore F. Tsai, Walter Orenstein, W.E. Parkin, H.J. Beecham, R.G. Sharrar, J. Harris, G.F. Mallison, S.M. Martin, Joseph E. McDade, C.C. Shepard, and P.S. Brachman, "Legionnaire's Disease: Description of an Epidemic of Pneumonia," *New England Journal of Medicine* 297, no. 22 (1977): 1189-97.
4. Robert G. Sharrar, "General Principles of Epidemiology," in *Preventive Medicine and Public Health*, 2d ed., ed. Brett J. Cassens (Baltimore: Williams and Wilkins, 1992): 1-28.
5. U.S. Centers for Disease Control and Prevention, "Guidelines for Investigating Clusters of Health Events," *Morbidity and Mortality Weekly Report* 39, no. RR-11 (1990): 2.

relatively lax gun control laws and high homicide rates. Canada, Germany, and Japan, in contrast, have far lower homicide rates and they have stringent gun control laws and lower rates of firearm ownership. It may seem reasonable to conclude that the gun laws account for the differences in homicide rates shown in Figure 8 (page 17)—a position adopted by many gun-control advocates in the United States. Without further data, however, this conclusion remains a hypothesis. Researchers cannot yet rule out alternative explanations for the higher U.S. homicide rates—for example, national differences in income inequality, illicit drug use, racial heterogeneity, and discrimination.

The **method of agreement** looks for commonality in groups that show the same health problem. AIDS, for example, showed up among intravenous drug users, hemophiliacs, and recipients of blood transfusions at far higher rates than among the general population. This suggested that the causal agent was a virus in the bloodstream.

The **method of concomitant variation** traces how exposure varies in relation to disease or injury rates. High national rates of cigarette smoking in 1930 were associated with high lung cancer death rates 20 years later (see Figure 9). The 20-year lag in the mortality data reflects the long latency period of lung cancer. These correlational data support the hypothesis that smoking causes lung cancer.

The **method of analogy** involves applying a model that characterizes one kind of disease or injury to another kind. Scientists know, for example, that the disease agent for hepatitis B is transferred through blood products. Thus, when the high-risk groups for AIDS were found to be the same as those for hepatitis B, this knowledge led to the hypothesis that AIDS had a similar cause.

In using the **method of detection of conflicting observations**, epidemiologists take special notice when different groups of people react differently to what appears to be the same exposure to a health risk. This was what happened in the case of pellagra, a disease causing skin eruptions and digestive and nervous disorders, long thought to be a communicable disease.[34] In the early 1900s, Joseph Goldberger (1874-1929), a scientist with the U.S. Public Health Service, noted that residents of prisons and asylums suffered from pellagra, while staff members did not. His observation led to the hypothesis that the disease was not infectious, but was related to diet. Subsequent laboratory and field research revealed that pellagra was probably caused by a deficiency of meat, vegetables, and other foods rich in niacin.

Searching for Cause: Analytic Epidemiology

The ultimate purpose of epidemiology is the treatment and prevention of health problems that threaten the quality and length of people's lives. To design, target, and implement successful health interventions, scientists need to understand the etiology of specific health problems. This is the domain of analytic epidemiology. Analytic studies test hypotheses about exposure to risk factors and a specific health outcome.

Analytic Research Designs

There are two main types of research design for analytic studies: cohort and case-control.

Cohort Study

A cohort study tracks the occurrence of a disease (or other health problem) among groups of individuals within a particular population. All the members of the study cohort are assumed to be free of that disease at the beginning of the study. They are then grouped according to their exposure to the risk factor(s) under investigation. The group of individuals ex-

posed to a risk factor (for example, asbestos) is usually compared with an unexposed group. At the end of the study, researchers compare the incidence rate for the disease (for example, lung cancer) in the exposed group with the incidence rate in the unexposed group. The strength of the association between the exposure and a specific health outcome is measured by the rate ratio (see Box 3, page 26). The rate ratio indicates the likelihood that those exposed to asbestos would develop lung cancer relative to the likelihood that those not exposed would get lung cancer.

There are two basic categories of cohort studies: **concurrent prospective studies** and **historical prospective studies**. In concurrent prospective studies, subjects are followed from the beginning of the study for a given period of time—sometimes for decades. In a historical prospective study, data are collected retrospectively; that is, after the events have occurred. One retrospective study conducted in 1977 examined the association between repeated X-rays of the chest and breast cancer between 1948 and 1975.[35]

Of the two types of cohort studies, the concurrent prospective approach affords investigators greater control over the quality of the data collected. The most famous concurrent prospective study in the United States is the Framingham Heart Study, which has been conducted continuously since 1949 in Framingham, Mass. In this study, researchers are keeping track of the weight, smoking habits, blood pressure, cholesterol levels, and other disease risk factors for a sample of about 5,000 town residents who were ages 30 to 59 in 1949. These risk factors are then related to the development of cardiovascular and other chronic disease among residents in the sample. The Framingham study documented the connection between obesity and the risk of sudden death from heart attack, stroke, or other cardiovascular disease. Among other findings, the study demonstrated that high blood pressure and chronic hypertension can interfere with an indi-

Figure 9
Cigarette Consumption in 1930 and Male Lung Cancer Death Rate in 1950, Selected Countries
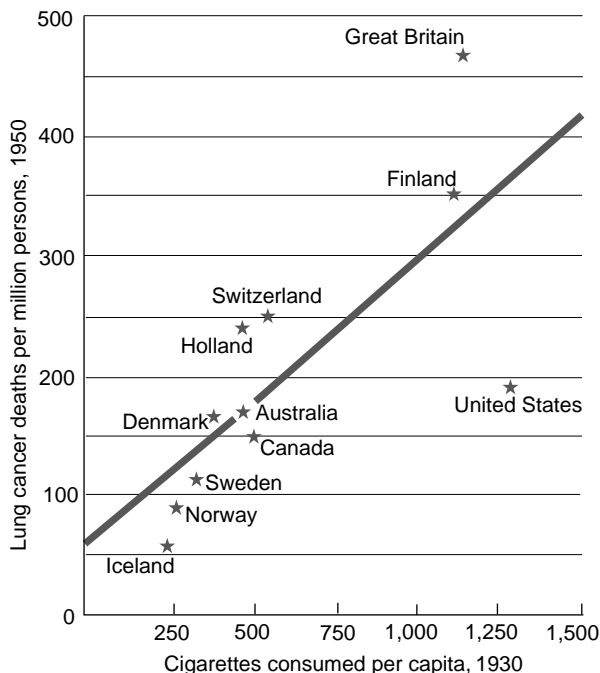
Source: Based on Richard Doll, "Etiology of Lung Cancer," *Advances in Cancer Research* 3 (1955): 1-50.

vidual's memory, attention span, and other cognitive functions.[36]

Another example of a concurrent prospective study is Health Watch, which has been conducted in Australia since 1981. This study is examining whether people who work with petroleum products face a greater risk of developing or dying from cancer than do other people.[37]

Intervention Study
Intervention or experimental studies are a special type of cohort study in which the investigator modifies risk factors to test their effects more precisely. Regular cohort studies, by contrast, are purely observational in that they track natural, not experimental, situations. Ignaz Semmelweis' study of puerperal fever in Vienna's General Hospital was an intervention study. The intervention was the scrubbing and soaking of medical students'

hands before they examined the hospital patients.

The first record of an intervention study is found in a Bible story from the Book of Daniel. Four Jewish youths in ancient Babylon were placed on a water and vegetarian diet for 10 days while training as advisors to King Nebuchadnezzar.[38] Meanwhile, a second group of non-Jewish trainees consumed the normal diet of wine and rich food. After 10 days, the Jewish youths looked superior in physical appearance to the comparison (control) group. Consequently, the Jewish youths were allowed to stay on the vegetarian and water diet.

Another famous intervention study, dating from the 18th century, focused on the high prevalence of scurvy—a disease characterized by weakness, anemia, and spongy gums—among British sailors. Sailors spent many months at sea without fresh fruits or vegetables. James Lind, a Scottish physician, experimented with adding citrus fruits rich in vitamin C to the sailors' diets to prevent scurvy.[39] The

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Box 3

Measures of Association for Cohort Studies

Cohort studies are usually used to assess the health effects of exposure to a specific health factor—for example, whether consuming alcohol increases the risk of breast cancer in women. In a cohort study, epidemiologists measure the strength of the association between exposure and health outcome using the rate ratio. The **rate ratio** (or relative risk) is the ratio of the incidence rate for the people exposed to a risk factor to the incidence rate of those who were not exposed. In the alcohol/breast cancer example, the rate ratio measures the likelihood that a drinker will develop breast cancer relative to the likelihood that a nondrinker will develop breast cancer. The rate ratio is calculated from the values shown in the table below:

$$\text{Rate ratio} = \frac{a}{e} \Big/ \frac{c}{f}$$

Rate ratios vary between zero and infinity. A value of 1 indicates no association between exposure and disease. A value greater than 1 indicates that the association is positive (in this example, that alcohol use increases breast cancer risk). A rate ratio less than 1 signals a negative association (in this example, that alcohol use protects women against breast cancer). While the rate ratio measures the strength of association, it never proves causality. Scientists need other compelling, corroborative evidence to determine whether a specific exposure contributes to a particular health outcome.

The **attributable risk** or **rate difference** measures the absolute effect of an exposure believed to contribute to a specific health outcome. It is the difference between the incidence rates of the exposed and unexposed groups:

$$\text{Attributable risk} = \frac{a}{e} - \frac{c}{f}$$

The **attributable fraction** or **etiologic fraction** measures the relative effect of the exposure—for example, the proportion of breast cancer cases attributed specifically to alcohol consumption. It is equal to the attributable risk divided by the incidence rate for the exposed group. It is often expressed as a percentage:

$$\text{Attributable fraction} = \left[\frac{a}{e} - \frac{c}{f} \right] \Big/ \frac{a}{e}$$

Two-by-Two Table for a Cohort Study

Current exposure	Subsequent disease		Person-time units	Incidence rates
	Yes	No		
Yes	a	b	e	a/e
No	c	d	f	c/f
Total	a + c		e + f	

success of Lind's experiment brought limes and lemons into the diet of British sailors, and gave birth to the term Limeys, old American slang for the British. Lind's intervention study demonstrated that appropriate nutrition could prevent scurvy.

Modern intervention studies—termed randomized controlled trials—are more highly controlled than was the Lind study, and therefore their results are more conclusive. In these studies, investigators randomly assign subjects to either an intervention group or a control group to evaluate the effects of an exposure (intervention) such as a specific dose of medicine, dietary supplement, or exercise program.[40] Because they are randomly assigned, the members of the study group are assumed to be similar to the members of the control group. The two groups differ only in whether they are exposed to the medicine, exercise program, or other intervention that is thought to affect their health. This approach strengthens the validity of the study's results.

The **preventative fraction** is analogous to the attributable fraction. It measures the impact of a protective exposure; that is, the proportion of cases prevented as a result of that exposure. The measure is simply 1 minus the rate ratio.

From a public health perspective, there is a strong economic rationale for allocating fewer resources for control of a rare lethal exposure than for a less lethal but more pervasive one. Because it incorporates the magnitude of the exposure or risk factor in the population, the **population attributable risk (PAR)** is valuable for public health planning. However, because researchers rarely have all the necessary data, it is less commonly used. The PAR represents the difference between the disease incidence rates in the total population and those in the unexposed population:

$$\text{PAR} \quad = \quad \frac{(a + c)}{(e + f)} \quad - \quad \frac{c}{f}$$

This measure can be presented as a percent (population attributable risk percent):

$$\text{Population attributable risk percent} \quad = \quad \frac{\text{PAR}}{(a + c)/(e + f)} \quad \times \quad 100$$

In a hypothetical cohort study that compared a group of healthy smokers with a group of healthy nonsmokers, the smokers' risk of developing lung cancer was 8.7 times greater than that of the nonsmokers. The smoking-related risk of developing this disease was 1,026 incidence cases per 100,000 person-years of observation. Among smokers, 88.5 percent of lung cancer cases could be attributed to smoking. In the population, smoking accounted for 67.4 percent of such cases.

Hypothetical Cohort Study of Cigarette Smoking and Lung Cancer, With Incidence Rates and Measures of Association

Cigarette exposure	Lung cancer		Person-years of observation	Incidence rates*
	Yes	No		
Yes	640	3,360	55,200	1,159
No	200	9,800	150,000	133

*Rates per 100,000 person-years

Measures of Association:

Rate ratio = 8.7
Attributable risk = 1,026 per
  100,000 person-years

Attributable fraction (%) = 88.5%
Population attributable
  risk percent = 67.4%

One important application of the randomized controlled trial design is the evaluation of disease screening programs (see Box 4, page 30). The research question in this case is whether screening programs appreciably prolong the length and improve the quality of life for the program participants.

Intervention studies are usually classified by whether they focus on factors that cause disease or other health problems (**putative risk factor trials**), that prevent disease (**prophylactic clinical trials**), or that cure disease (**therapeutic clinical trials**). Intervention studies may be conducted with a community rather than the individual as the unit of analysis (**community trials**).

Putative risk factor trials are usually avoided for ethical reasons unless they entail reducing or eliminating exposure to substances thought to pose health risks. One such trial in the United States was the Multiple Risk Factor Intervention Trial (MRFIT), begun during the 1970s.[41] MRFIT's primary purpose was to find out whether people could lessen their risk of death from heart disease by ceasing cigarette smoking and lowering their blood pressure and cholesterol levels. After a seven-year follow-up period, MRFIT's results were inconclusive—probably because the members of the control group lowered their blood pressure, cholesterol levels, and rate of smoking about as much as the study group. Researchers did not know whether these health improvements in the control group reflected the advice of their physicians, media publicity, or some other factor.

The Physicians' Health Study (PHS), started in 1980, is an influential prophylactic clinical trial in the United States. Using some 22,000 American physicians as subjects, the PHS has shown that routine use of low-dose aspirin protects men against a first heart attack.[42]

A similar protective effect for aspirin was noted for women in a large observational cohort study, the Nurses' Health Study (NHS), begun in 1976.[43] Even though NHS investigators followed the health status of nearly 122,000 American nurses for six years, the NHS results were less persuasive than those of the much smaller PHS because of the inherent limitations of the observational cohort study design.

A randomized trial of whether aspirin can prevent a first heart attack among women is included in the Women's Health Study, started in 1992. The design of this study, similar to that of the PHS, enables researchers to evaluate more than one hypothesis.[44] Investigators in both the PHS and Women's Health Study, for example, are testing whether beta-carotene (vitamin A) reduces cancer risk as well as whether aspirin lowers the risk of heart disease. Unlike aspirin, epidemiologic evaluation of beta-carotene use has yet to show conclusive health benefits.

Therapeutic clinical trials are intervention studies undertaken to learn the most effective treatment for people who already have a disease. Therapeutic trials might assess the effectiveness of a new drug compared with a conventional drug in treating cardiac patients or the success of chemotherapy versus surgery for cancer patients.

Community trials are costly to conduct and, because they include relatively few units of study, their results can be inconclusive. Community trials were rarely conducted in the past, but have become more prevalent because they can provide important guidance for health and public policy. A community trial in Rhode Island suggested that community mobilization, bartender training, and police training and enforcement reduced alcohol-related injuries, at least in the short term.[45] In the 1940s, an intervention study was carried out in two New York towns: Newburgh and Kingston. The public water supply in Newburgh was treated with fluoride to test whether this would reduce tooth decay among children. Over time, the children living in Newburgh devel-

oped fewer cavities than children in Kingston, where the water supply was not treated with fluoride. The result of this and similar trials demonstrated that fluoride in public water supplies protects children's teeth from cavities.[46] While fluoridated drinking water is now commonplace because of such studies, the alcohol interventions in the Rhode Island trial need further evaluation to determine whether they are effective over the long term.

Case-Control Study

Case-control is the second major type of analytic study. In a case-control study, two groups are differentiated by disease status: the group of cases with disease and the group of controls without the disease. Researchers then reconstruct the exposure history of the two groups to determine which factors might explain why one group developed the disease. For example, if a case-control study addressed the question of whether drinking alcohol increases the risk of breast cancer for women, then the alcohol consumption history of women with breast cancer (the cases) would be compared with that of women without cancer (the controls). This approach is the opposite of the cohort approach, which begins with disease-free subjects and follows them forward over time. The strength of the association between the disease and risk factors in a case-control study is measured by the odds ratio or relative odds, explained in Box 5, page 32.

Sources of Error

Analytic studies are subject to errors that may plague health scientists in any phase of a study. These errors may be classified as bias, random variation, and random misclassification. Bias and random variation are the more serious types of error.

Bias

In the context of analytic studies, bias is defined as any trend in the design, data collection, analysis, or interpretation of a study that produces "conclu-

sions … systematically different from the truth."[47] Numerous types of bias are identified in the literature, but they can be reduced to three categories: selection bias, information bias, and confounding.

Selection bias is a research design problem that occurs when study and comparison groups differ systematically in a way that distorts the results. For valid or fair comparisons, the study and comparison groups should be homogeneous and differ only with regard to the factor being analyzed. That is, apples should be compared with apples, not with oranges. In a cohort study, for example, groups should differ only in their exposure to risk factors. In a case-control study, the groups should differ only in their disease or injury status.

Selection bias is most easily prevented in cohort study designs that have prospective data collection—especially clinical trials because they randomly assign group membership.

Information or observation bias can occur in the data-collection phase of both cohort and case-control studies. It happens in cohort studies when information on health outcomes is not collected uniformly for the study and comparison groups, and in case-control studies when information on exposure is not collected uniformly for cases and controls.

Investigators can help minimize information bias by not revealing the true intent of a study to either study subjects or data collectors—an approach called blinding. In a study designed to test whether radiation exposure was linked to breast cancer, data were gathered on all types of cancer; neither the subjects nor data collectors knew that the study specifically concerned breast cancer. If data collectors had known that the study was about breast cancer specifically, they might have been more zealous in looking for evidence of radiation exposure among the subjects with breast cancer than among the comparison group. This zeal could distort the results.[48] Information bias also can be reduced by using objective

Investigators can help minimize information bias with an approach called blinding.

data-collection instruments such as standardized questionnaires and forms. Standardized instruments encourage data collectors to be consistent in soliciting and recording information.

Confounding can occur when a disease risk factor, such as smoking, is both a cause of the disease under study, such as heart disease, and is associated with other risk factors for the disease, such as heavy alcohol consumption. Confounding can dampen or mask the true relationship between exposure to a risk factor and disease outcome. For example,

a 1990 dietary guideline issued by the U.S. government was misleading because it failed to account for the effects of confounding risk factors on body weight and health.[49] This guideline stated that a 25-year-old woman 5 feet 5 inches tall and under 120 pounds in weight could afford to gain 40 pounds up to age 70 without harming her health. This recommendation runs counter to research suggesting that such a large weight gain sharply increases the risk of heart disease, stroke, and other health problems. The individuals developing the dietary guideline had overlooked im-

Specificity measures the ability of the test to correctly ascertain true noncases of preclinical disease—the true negatives:

$$\text{Specificity (\%)} = \frac{d}{b + d} \times 100$$

There is usually a trade-off between these two measures. If a screening test is so sensitive that it detects almost every true case, the test is likely to produce a larger percentage of false positives than less sensitive tests. Conversely, if the test is so specific that nearly every case that tests negative is truly free of the disease, the test is likely to miss a larger percentage of true cases of disease than a less specific test.

Predictive values measure the likelihood that test results for individuals will prove consistent with their true disease status. **Positive predictive value (PPV)** is the probability that an individual with a positive screening result indeed has the disease:

$$\text{PPV (\%)} = \frac{a}{a + b} \times 100$$

Negative predictive value (NPV) is the probability that an individual with a negative screening result is actually free of the disease:

$$\text{NPV (\%)} = \frac{d}{c + d} \times 100$$

Overall test **accuracy** is measured by the proportion of tests in which individuals are correctly classified as to their true disease status:

$$\text{Accuracy (\%)} = \frac{a + d}{N} \times 100$$

At a minimum, screening programs need to be evaluated to determine whether they successfully reduce mortality from a target disease. Such evaluations can be seriously distorted by several types of bias that require special precautions by investigators. Because a disease may be detected earlier in a screening test than through a physician's diagnosis, the known survival time of a cancer patient taking part in a screening program is likely to be longer than for another patient with an identical condition because the cancer was diagnosed earlier—regardless of the treatment each patient received. This **lead-time bias** overestimates the impact of a screening program in prolonging the lives of its participants. **Length bias** refers to the possibility that slower progressing cases of a target disease, such as breast cancer, are more likely to be detected through screening than faster progressing cases. This bias can exaggerate the effectiveness of both a screening program and early treatment in promoting survival.

Selection bias can distort an outcome evaluation if the screening group is made up of volunteers who were generally healthier and more cooperative than a comparison group who are not volunteers. The volunteer group would be expected to have a more favorable outcome, which might erroneously be attributed to the screening program.

A randomized controlled trial may be conducted to evaluate a disease screening program.

Reference
1. Alan S. Morrison, *Screening in Chronic Disease,* 2d ed. (New York: Oxford University Press, 1992).

portant confounding factors. Probably the most serious confounder was cigarette smoking. Smokers tend to be thinner than nonsmokers, and smoking is associated with many health problems. Failing to control for smoking status may have allowed thinness to mimic an adverse health risk, making thin people appear to be less healthy than heavy people. Similarly, because anorexia and severe alcoholism relate to thinness, they could also confound the true association between body weight and ill health.

Confounding is ever present in research data. It can never be eliminated entirely as an explanation for an observed association. To minimize confounding, subjects in study and comparison groups may be matched on putative or suspected confounders, such as age and weight, or they can be selected randomly in the hope that confounding characteristics are evenly distributed between the two groups. During data analysis, various statistical techniques are used to test whether the results were affected by confounding variables.[50]

Box 5
Measures of Association for Case-Control Studies

In case-control studies, researchers use several measures to summarize the association between exposure to a risk factor and a disease or other health outcome. The most basic of these is the **odds ratio**, which measures the strength of the association between the exposure and health outcome. It approximates the rate ratio, explained in Box 3 (page 26), when a

A disease incidence rate can be computed in a case-control study only when an investigator can identify all new cases in a defined population. This is possible, for example, where a case-control study is "nested" within a cohort study. Case-control studies will be conducted as part of Health Watch, the Australian cohort study mentioned on page 25.

Two-by-Two Table for Case-Control Study

Prior	Current disease status	
exposure	Yes (case)	No (control)
Yes	a	b
No	c	d
Total	a + c	b + d
Proportion exposed	$\dfrac{a}{a + c}$	$\dfrac{b}{b + d}$

disease is rare in the general population or when the case-control study uses incidence cases rather than prevalence cases (see Box 1, page 18).

The odds ratio represents the ratio of the odds of cases being exposed to the odds of exposure among controls:

$$\text{Odds ratio} = \frac{a \times d}{b \times c}$$

Like the rate ratio, the odds ratio varies between zero and infinity. A value of 1 indicates there is no association between exposure and disease. The exposure is positively related to the disease if the ratio exceeds 1, and negatively related if less than 1.

Because incidence rates usually cannot be computed for case-control studies, investigators cannot calculate the attributable risk. However, the **attributable fraction (AF)** can be estimated. It is often expressed as a percentage:

$$\text{Attributable fraction} = \frac{\text{Odds ratio} - 1}{\text{Odds ratio}}$$

The **population attributable risk percent** also can be estimated if researchers have other evidence about the prevalence of exposure within a population. To estimate this, the proportion of controls exposed (P_e) must accurately represent the proportion

Random Variation

Random variation refers to chance differences between a study group and a comparison group on a particular measure. Random variation affects the external validity of a study—that is, the ability to generalize results of the study sample to a larger population. By contrast, bias affects internal validity—the ability to make fair comparisons between a study group and a comparison group.

Random variation can be illustrated using a hypothetical cohort study on coffee drinking and stomach ulcers. Suppose the study indicated erroneously that coffee drinking raises the risk of getting an ulcer. Assuming that the study's measurements were accurate and that sampling was random, the misleading results probably appeared because the study and comparison groups did not accurately represent their coffee-drinking and coffee-abstaining counterparts in the population. Random variation can be minimized by increasing the number of participants in the study and comparison groups (see also Box 6, page 34).

Case-Control Study of Kaposi's Sarcoma and Sexual Promiscuity, With Measures of Association

| Number of sex partners | Kaposi's sarcoma | |
(per month)	Yes	No
≥ 10	10	7
0-9	10	33
Total	20	40

Source: M. Marmor, et al. *The Lancet* 1 (May 15, 1982): 1082-87.

Measures of Association:

Odds ratio = 4.7   Attributable fraction (%) = 78.7%

of the population exposed to a particular disease risk:

$$\text{Population attributable risk percent} = AF \times P_e \times 100$$

An AIDS-related case-control study conducted early in the 1980s, before the discovery of the HIV virus, illustrates how the odds ratio and the estimated attributable fraction are interpreted in health research.[1] In this study, male homosexual Kaposi's sarcoma cases were matched to controls on gender, age, sexual preference, and race. The two groups were then compared by the level of sexual promiscuity. Promiscuity was indexed, respectively, by average number of sexual partners per month in the year prior to disease diagnosis for cases, and in an equivalent period for controls.

The odds ratio calculated in the Kaposi's sarcoma study indicates that cases were 4.7 times as likely as their controls to have averaged 10 or more sexual partners per month during the observation interval. Expressed as an estimated rate ratio, an alternative interpretation is that individuals averaging 10 or more sexual partners per month had 4.7 times the risk of becoming afflicted with Kaposi's sarcoma as those averaging fewer partners. Based on the estimated attributable fraction, almost four of every five Kaposi's sarcoma cases could be attributed to the exposure of 10 or more sexual partners per month. Kaposi's sarcoma, an opportunistic malignant tumor chiefly involving the skin, has appeared in excess because of suppression of the autoimmune system through HIV infection.

Reference

1. Michael Marmor, Linda Laubenstein, Daniel C. William, Alvin E. Friedman-Kien, R. David Byrum, Sam D'Onofrio, and Neil Dubin, "Risk Factors for Kaposi's Sarcoma in Homosexual Men," *The Lancet* 1 (May 15, 1982): 1083-87.

Random Misclassification

Random or nondifferential misclassification occurs when there is equal likelihood that subjects will be misallocated to the study or to the comparison group. Random misclassification occurs in a cohort study when persons who have been exposed to a disease risk are equally likely to be misallocated to the exposed or unexposed group. In case-control studies, misallocation relates to whether subjects have the disease under study. In either situation, the results underestimate the true association between exposure and disease. In other words, random misclassification makes it less likely that an investigator will find a relationship between a disease and a cause.

Refining Measures of Disease and Exposure

Analytic epidemiologic studies typically focus on dichotomous relationships. Subjects are usually categorized as being (1) exposed or (2) not exposed to a disease and as (1) having a disease or (2) not having a disease. These relationships between exposure status and disease status can be presented in simple two-by-two tables, as shown in Box 3, page 26, and Box 4, page 30. However, epidemiologists sometimes use more refined measures to show severity of disease or injury and degree of exposure. Cancer cases, for instance, can be ranked for severity using stages (commonly, stages I to IV). A scoring system, ranging from 1 to 75, has

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Box 6

Real vs. Chance Associations: P-Values and Confidence Intervals

Analytic studies are nearly always conducted using study samples that represent a larger population. Researchers rely on samples under the key assumption that they can make inferences about a larger population on the basis of information derived from a sample. The difference in rates (the attributable risk) between a study group and a comparison group computed from sample data is an estimate of the real difference in the rates of the population groups they represent.

Health scientists must confront the possibility that an observed difference between the incidence rates of the study groups and comparison groups is due to chance. The difference between the rates of prostate cancer of a group of smokers and a group of non-smokers may not reflect a true rate difference between smokers and non-smokers in the population.

Significance testing is a statistical approach that researchers can use to assess whether an observed difference in rates computed from a population sample represents a true difference in the population. Before accepting the possibility that the difference is real, researchers must eliminate the null

hypothesis, which states that there is no association between a risk exposure (such as smoking) and a health outcome (such as prostate cancer). The result can be expressed as a P-value, the probability that the difference is a chance occurrence.

A P-value of .05 (that is, the probability that a particular outcome occurred by chance is 5 in 100) is the conventional cutoff point in significance testing. If the P-value equals or exceeds .05, researchers accept the null hypothesis and dismiss any difference observed between the rates of the study and comparison groups as a chance occurrence. Researchers sometimes lower the cutoff point for statistical significance, say to .01. The lower cutoff provides a more conservative test of the null hypothesis and makes it more likely that an observed difference or association in sample data will be attributed to chance.

Significance tests, however, can yield varying results depending on the sample size. A difference in the incidence rates of study and comparison groups may not be statistically significant in a small study, but may attain significance if the sample is enlarged.

been developed to measure the severity of injuries.

Exposure to a specific disease risk factor may be measured more accurately as a continuous variable (for example, temperature) or in several ordinal (ranked) categories, such as none, moderate, or high. Exposure variables can be further differentiated and quantified in terms of available dose, administered dose, absorbed dose, and active dose.[51] **Dose**—or more accurately the active or biologically effective dose—can be defined as the "amount of a substance that remains at the biological target (such as the lungs or stomach) during some specified time interval."[52] By using refined measures, epidemiologists are more likely to detect a relationship, for example, between a specific dose of a treatment drug and an effect or response, such as slowing the progression of a disease.[53]

Dose-effect, or the health effect of a specific exposure—to arsenic, for example—can range from no clinically detectable signs and symptoms, to a mild headache, to coma, to death. Health effects can be further differentiated by kind of disease, such as cancer or arthritis, or type of injury, such as burn or laceration.

Dose-response measures the proportion of an exposed group or population that has been clinically diagnosed with a specific disease or injury at a given dosage. Dose-response has direct relevance to the issues of determining safe exposure

This varying effect of sample size is one reason that significance testing is a controversial issue in health research and has lost favor among epidemiologists.[1]

Because of the limitations of significance tests and P-values, researchers usually use an alternative statistical method, the construction of confidence intervals. The confidence interval provides an estimated range for the true population measure, and it shows the probability that this measure falls within a specified range. For example, in a recent Boston study, investigators estimated that there was a 95 percent probability that the true ratio of the rate of occupational injury for postal workers who used marijuana to that of postal workers who did not use marijuana varied between 1.04 and 3.90.[2] In other words, the marijuana users' risk of occupational injury was estimated to be between 4 percent and 290 percent greater than the risk among nonusers. A significance test may have shown that the difference in injury rates of the two groups was statistically significant at the .05 level, but this information is less useful than the range of values produced by the confidence interval approach.

Like the significance test, the confidence interval can be used to test the validity of the null hypothesis. The 95 percent confidence interval corresponds to the .05 P-value. If a rate ratio equal to 1.0 (implying no association between a risk factor and a health outcome) falls within the 95 percent interval, the null hypothesis is supported. If it does not, as in the study of the postal workers, this gives researchers the evidence to reject the null hypothesis. Methods for constructing confidence intervals and conducting significance tests can be found in any contemporary introductory biostatistics textbook.

References
1. Robert F. Woolson and Joel C. Kleinman, "Perspectives on Statistical Significance Testing," *Annual Reviews of Public Health* 10 (1989): 423-40.
2. Craig Zwerling, Nancy L. Sprince, James Ryan, and Michael P. Jones, "Occupational Injuries: Comparing the Rates of Male and Female Postal Workers," *American Journal of Epidemiology* 138, no. 1 (1993): 46-55.

limits and setting standards, and general relevance to safety standards in the home, work environment, and recreation areas.[54]

In its broadest conception, exposure covers all putative causes of, and risk factors for, a particular health outcome. Exposure may include bacteria, viruses, and toxins, as well as demographics, attitudes, and behavior. When there are multiple exposures, they should be examined for synergism; that is, to see if the joint health risks from these exposures exceed the sum of the separate risks.

Choosing an Analytic Research Design

How do epidemiologists decide whether to conduct a case-control or a cohort study to research a specific disease? Their choice will depend on the relative frequency of disease and the exposure they want to study, knowledge of possible causes, and the time and resources available for research.

Researchers often prefer cohort studies for investigating diseases that are relatively common, such as heart disease. Cohort studies are useful for studying diseases with an etiology that scientists already know something about, such as heart disease and some cancers. But they may also be used to follow a population exposed to a rare disease risk, such as the survivors of the atomic bomb dropped on Hiroshima in 1945.

In a cohort study, researchers often collect extensive information on the personal background and exposure history of subjects. These historical data can provide crucial information for developing and testing research hypotheses.

The cohort design has another crucial advantage over the basic case-control design—it permits researchers to separate the time of exposure to health risk factors from the onset of disease or other health outcomes. Furthermore, cohort studies allow researchers to investigate multiple health effects of an exposure. A hepa-

Researchers often prefer cohort studies for investigating diseases that are relatively common.

titis infection can be examined over the short, intermediate, and long term as a determinant of acute hepatitis, cirrhosis of the liver, and liver cancer, respectively.

Cohort studies have still other strengths. Cohort data allow researchers to calculate incidence rates and to compare rates among different exposure statuses. Multiple risk factors can be studied or controlled, and data quality can be monitored and maintained at a high standard.

Because they involve larger numbers of subjects, cohort studies have the disadvantage of requiring more resources and time than case-control studies. In addition, the nature and dose of exposure may change over the course of the investigation, which can complicate analysis. However, the cohort design is essential for evaluating disease interventions because it allows subjects to be randomly assigned to study and comparison groups.

Epidemiologists usually choose the case-control study design for research about very rare diseases, especially when scientists know little of their etiology. The case-control method was used to investigate a new neurologic disease first recognized among newborn French babies in the early 1970s.[55] Researchers discovered that the "disease" was actually hexachlorophene poisoning resulting from the use of talcum powder.

Compared with cohort studies, case-control studies can be conducted relatively quickly and cheaply and may involve relatively few subjects. With a small sample, researchers can more easily follow leads on exposure to multiple risk factors.

Case-control studies also have shortcomings. They are highly susceptible to information bias, and it is sometimes difficult to find an appropriate comparison group. Moreover, researchers cannot calculate incidence rates in a case-control study unless it is population-based. However, case-control studies often provide the first clues about the etiology of a disease—clues that can stimulate more definitive analytic research.

Assessing Causation

Causation can never really be proved. However, epidemiologists can ask a series of questions to assess the likelihood that a particular exposure causes a given health outcome.[56] The first and most important question is, did the exposure to the risk factor precede the onset of the disease? If it did not, the answers to the remaining questions are irrelevant because the exposure could not have caused the disease.

If researchers can verify that an individual or group was exposed to a health risk first, then developed the disease, they can then gauge the validity of any causal links between suspected risk factors and the disease by the answers to the following questions:

- Is there a strong association between risk exposure and disease outcome (for example, as measured by the rate ratio or odds ratio)?
- Is there a dose-response relationship?
- Has the association between exposure and outcome been demonstrated at different times and in different settings, using diverse statistical tests?
- Has the association been confirmed in animal experiments?
- Does elimination or reduction of the exposure (for example, cigarette smoking) lead to a decline in disease risk (for example, risk of lung cancer or heart disease)?
- Can exposure and outcome be specified? For example, evidence of a link between exposure to petroleum products and cancer is less informative than evidence of a dose-response relationship between exposure to a specific petroleum product (benzene) and a specific cancer (myeloid leukemia).
- Does the relationship between exposure and outcome seem consistent with established theory and knowledge?

The argument for causation becomes more convincing as investigators answer "yes" to more of these questions.

Epidemiologists and medical researchers work together to discover the who, what, where, and why of specific health problems.

Protocols, Ethics, and Integrity

Analytic studies demand careful planning. The protocol—the research blueprint or road map—is at the heart of effective planning and execution of analytic studies.[57] The protocol details the study purpose, objectives, choice of subjects, ethical issues, research design, data collection instruments and procedures, computerization, statistical methods, personnel needs, time lines, budget, and procedures for disseminating the findings.

Analytic studies often raise ethical questions, especially when the study involves medical interventions and their attendant risks. The risks to people participating in the study can be psychological as well as physical. To minimize risks to subjects, investigators try to guarantee their subjects free and informed consent, privacy, and confidentiality. Subjects also need to feel assured that the investigators are competent and do not have a conflict of interest.[58] To avoid a breach of confidentiality or other ethical problems, the protocols of any epidemiologic study involving direct human

participation are usually scrutinized by impartial institutional review boards (IRBs) or ethics committees.

Concern about biomedical ethics can be traced back to publicity surrounding the inhumane medical experiments on prisoners carried out by the Nazis during World War II. These experiments included deliberately exposing the prisoners to the communicable disease agents of malaria and spotted fever or to extremes of temperature and altitude.[59] Concerns about the ethics of these experiments were reflected in postwar documents such as the 1948 Declaration of Geneva and the 1964 Declaration of Helsinki. Recently, a number of leading professional epidemiologic organizations, including the Society for Epidemiologic Research and the International Epidemiological Association, have formulated their own ethical guidelines. In 1993 the Council for International Organizations of Medical Sciences, prompted by the need for trials to evaluate HIV/AIDS vaccines and drugs, released a revision of International Ethical Guidelines for Biomedical Research Involving Human Subjects.[60] These guidelines aim to prevent the exploitation of vulnerable research subjects, especially in less developed countries.

People who believe that the medical atrocities committed in Nazi Germany could not happen in democratic countries are advised to read the sobering account of the Tuskegee Syphilis Experiment.[61] In this nontherapeutic trial begun in 1932 in Alabama's Macon County, researchers followed the progression of tertiary (late stage) syphilis in more than 400 African American men to evaluate the complications of the disease if left untreated. Highly effective therapy, penicillin, was available by the 1940s, yet researchers failed to inform the men that they had syphilis and the men did not receive treatment. The predominantly white investigators worked under the auspices of the U.S. Public Health Service and in cooperation with federal, state, and local health officials, white private physicians, the

> *Concern about biomedical ethics can be traced back to inhumane medical experiments carried out by the Nazis.*

African American leadership of the Tuskegee Institute, and an African American nurse. The study continued until 1972, when the researchers' unethical practices were revealed, which created a well-publicized scandal. The Tuskegee study and a number of other studies where unethical conduct has been documented[62] underscore the necessity for creating and empowering IRBs to protect human subjects in epidemiologic research.

Even investigators who scrupulously adhere to high standards of ethical conduct and scientific integrity may produce incompetent research. Epidemiologic studies that are seriously flawed deserve to be labeled poor science regardless of the reason or motivation.[63] Poor science can be prevented or controlled through proper training and by peer review of research protocols and of scientific papers before publication. However, the fraud and deceit associated with deliberate disregard for the scientific method are clearly unethical behavior and may be harder to detect in the short run. Ultimately, the inability of other epidemiologists to replicate such results will discredit fraudulent research. The possible damage this fraud might render to the public image of epidemiologic research may be more difficult to overcome.

Reconciling Contradictions: Meta-Analysis

Sometimes analytic epidemiologic studies investigating an identical research question produce contradictory results.[64] In recent years, some studies have shown that eating oat bran improved an individual's health by lowering blood cholesterol levels; however, other studies did not confirm this finding. A study suggesting that drinking coffee increased the risk of pancreatic cancer was also refuted by subsequent research. Contradictory research results such as these can create confusion in the public agencies entrusted with issuing dietary guidelines or restricting harmful

substances. Physicians and other health professionals who advise patients are forced to make an educated guess about which researchers or research results they should follow.

Meta-analysis is a promising solution to the problems created by contradictory epidemiologic research. Meta-analysis was introduced in a rudimentary form by the statistician Karl Pearson in 1904, but only recently has evolved into a sophisticated quantitative technique with general scientific applications. This technique involves pooling analytic studies sharing the same research question to produce a summary conclusion.[65] When done correctly, meta-analysis can provide an objectivity and rigor that a qualitative review of these studies cannot.

Meta-analysis is especially useful for analyzing the results of the many randomized controlled trials investigating similar questions. Approximately 10,000 randomized controlled trials are being conducted in clinical settings worldwide. About 5,000 new trials begin each year.[66]

A meta-analysis conducted in the early 1990s entailed pooling 33 trials involving use of the drug streptokinase in patients hospitalized after a heart attack.[67] The cumulated evidence showed that the drug therapy reduced related deaths. This research also showed that time, money, expertise, and human lives could be saved through meta-analysis. In the meta-analysis of the streptokinase trials, for example, the effectiveness of the drug was well established after data from the first eight trials were cumulated and analyzed. In other words, the 25 subsequent trials were unnecessary.

Integrating Epidemiology

The 1990s have brought epidemiology into the public spotlight through a proliferation of media stories about epidemiologic studies of risk factors for chronic disease, communicable disease, and injury. Epidemiology's appearance in the spotlight has been accompanied by unprecedented criticism from epidemiologists and from those outside the field.[68] This, in turn, has fostered lively debates in health journals and at epidemiology conferences. There have been two primary stimulants. The first has been conflicting and frequently modest epidemiologic findings concerning putative chronic disease risks, especially those for cancer. The second has been the inability of epidemiology to predict and evaluate threats to human health from persisting and growing social inequality and massive global environmental shifts.

Risk factor epidemiology, the predominant form of epidemiology and the focus of this *Population Bulletin*, has been the target of the criticism. Using the individual as the unit of analysis, risk factor epidemiology occupies the middle ground in the scientific assessment of cause-effect relationships between exposures to health risks and health states. But it is an important point of departure for epidemiologists as they extend the causal search downstream from the individual level to the molecular level and upstream to the societal-environmental level. Scientists label these downstream and upstream domains of epidemiologic analysis **microepidemiology** and **macroepidemiology**, respectively.

Operating at the cellular and intracellular levels, microepidemiology encompasses the specialties of molecular epidemiology (also a specialty within toxicology) and genetic epidemiology.[69] Its debt to microbiology is profound. The laboratory scientists who perform microepidemiology are investigating biochemical disease mechanisms hitherto hidden in the black box of risk factor epidemiology. When the black box paradigm prevails, epidemiologists are left to infer or reject causal relationships from knowledge largely confined to the box's inputs and outputs.[70] Inputs comprise individual study subjects' sociodemographics and measures of

Risk factor epidemiology often functions in a social, economic, political, and cultural vacuum.

their potentially harmful or beneficial exposures. Outputs are measures of their health status; for example, cause-specific incidence and mortality rates.

While microepidemiology is essential for decoding disease processes, risk factor epidemiology helps narrow the search for disease agents. Moreover, it may yield strong circumstantial evidence (such as that linking tobacco smoking in the 1930s with lung cancer in the early 1950s) that can motivate effective and pervasive public health interventions. Modern risk factor epidemiology has revealed health hazards to humans from other exposures entering the body through the respiratory tract, gastrointestinal tract, or skin. These hazards include asbestos, ionizing radiation, and saturated fat.[71] Although risk factor epidemiology and microepidemiology can be at odds, they can operate cohesively and effectively. Examples of this cooperation are the discovery of a causal connection between HIV-infection and Kaposi's sarcoma, and another between genes and breast cancer.[72]

Besides the vagueness of the black box, a second serious deficiency of risk factor epidemiology is its tendency to function in a social, economic, political, and cultural vacuum.[73] What, when and how much people eat and exercise; their sexual and reproductive behavior; their household living arrangements; their modes of work, recreation, and transportation; and their education and health care practices all partially reflect contextual forces that transcend the personal choices they can make. These contextual forces include social-structural factors like racism, residential segregation, poverty, and types of political and economic systems. Responsibility for examining their population health effects falls within the emerging domain of macroepidemiology.

Advocates for macroepidemiology envision complex and dynamic causal webs whose health mysteries will be unlocked only through sophisticated theory construction and model building, with multilevel analyses of data on individuals and context.[74] Further complicating the big health picture is rapid population growth that has pushed world population to 6 billion, and the industrialization that continues to exact an enormous toll on such nonrenewable resources as fresh water, stratospheric ozone, oceans, forests, and arable land.[75] Rapid population growth and industrialization work together to severely diminish the Earth's biodiversity through the extinction of many plants and animals.[76] Unless we better protect our natural resources, there could be substantial reversals in the rising trend in life expectancy that transformed most national populations in the 20th century. These reversals would occur first in the most recent beneficiaries of this rising trend, the less developed countries.

Anthony J. McMichael, an epidemiologist who writes extensively on likely adverse health effects from climatic, ecological, and environmental changes, argues compellingly for macroepidemiology to be proactive.[77] Proactive macroepidemiology would contrast with risk factor epidemiology, which typically responds reactively to public and scientific concerns about the safety of various practices and products. To anticipate global hazards and facilitate disease and injury prevention, macroepidemiologists must use mathematical modeling, and incorporate new technologies like digital communications and geographic information systems (or GIS).

The spirited debates of the 1990s over the limitations of risk factor epidemiology have not seriously undermined the credibility and viability of epidemiology as a science. But, epidemiology will function optimally as the foundation science of public health and preventive and clinical medicine only if there is complete integration of microepidemiology, risk factor epidemiology, and macroepidemiology.

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Human Health and Global Environmental Change, Consortium for International Earth Science Information Network:
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Epidemiology Virtual Library, University of California, San Francisco:
http://www.epibiostat.ucsf.edu/epidem/epidem.html

National Library of Medicine's free MEDLINE search engine:
http://www.ncbi.nlm.nih.gov/PubMed/

Epidemiology Supercourse, University of Pittsburgh:
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