

CHAPTER 2



Environmental Epidemiology

LEARNING OBJECTIVES

By the end of this chapter the reader will be able to:

- Define the term *environmental epidemiology*
 - Describe three major historical events in environmental epidemiology
 - Provide examples of epidemiologic tools used in environmental health
 - Identify types of associations found between environmental hazards and health outcomes
 - List study designs used in environmental epidemiology
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INTRODUCTION

In this chapter you will learn that epidemiology is one of the fundamental disciplines used in the study of environmental health. For example, epidemiology is one of the research tools that seeks answers to the following types of environmental questions, some of which are adapted from a report by the National Institutes of Environmental Health Sciences:¹

- What is the impact of air pollution on children's lung function?
- Is there a relationship between exposure to agents in the environment and degenerative brain diseases such as Alzheimer's disease?
- What environmental exposures might act in combination with genetic factors to cause breast cancer?
- What are the health effects of consuming seafood contaminated with mercury?
- Is it safe to eat tuna, because it could contain chemical pollutants that were dissolved in the ocean?

- What are the long-term consequences of beach pollution?
- Does secondhand cigarette smoke cause lung cancer in nonsmokers?
- Are death rates higher in geographic regions that have higher air pollution levels in comparison with regions that have lower levels?
- There is considerable concern today about the chronic health hazards of radiation. Would you consider chemicals to be an equal hazard?
- How large an increase in cancer incidence (occurrence) would be necessary before a chemical could be identified as a problem?
- Several years ago, people were concerned that daughters exposed to diethylstilbestrol (DES) would develop cancer. What are the chances that this disease will develop in 10 or 20 years in a DES-exposed daughter who does not have cancer now?

Epidemiology is the method of choice to answer questions such as the foregoing ones. Refer to the following text box for a further discussion of this issue.

Commencing with a definition of the term *environmental epidemiology*, this chapter reviews the scope of this discipline and defines several of the special quantitative measures used to study the occurrence of environmental health problems in populations. Next, the chapter traces the key historical developments in environmental epidemiology. Some of these historical developments include concerns of the ancient Greeks about diseases caused by the environment, the observations of Sir Percival Pott on scrotal cancer among chimney sweeps in

How Do You Study Environmental Health?

How do scientists study the effects of environmental factors—such as man-made and natural substances, and radiation—on human health? Headlines such as, “People in polluted cities have more breathing difficulties” are familiar to most of us. They are likely to be about a study of the occurrence of diseases in people who have been exposed to a natural or man-made factor in the environment. That kind of work is called epidemiology. It is the best known, best understood, and most accepted tool of the environmental health sciences. It is the type of research that most health regulations are based on. The linking of cigarette smoke to lung cancer (and then to many other conditions) was carried out, in large part, by epidemiology. To show that link, which seems so obvious today, researchers not only had to compare smokers with nonsmokers over many years, they had to rule out many other exposures these people might have had.

Source: Modified and reprinted from National Institutes of Health, National Institute of Environmental Health Sciences. How do you study environmental health? NIEHS Fact Sheet #2, 8/96. Available at: <http://www.medhelp.cc/NIHlib/GF-298.html>. Accessed February 11, 2010.

England, the work of John Snow on cholera, and later work on the role of toxic substances in the etiology of cancer. Closely linked to quantitative measures used by environmental epidemiology are the major study designs: experimental, quasi-experimental, and observational (cross-sectional, ecologic, case-control, and cohort). A special concern of the discipline is causality—whether research findings represent cause-and-effect associations. Environmental epidemiology is a complex field that in some cases provides keen insights into environmentally caused diseases and in others provides unclear results that must be followed up by other types of studies.

DEFINITION OF ENVIRONMENTAL EPIDEMIOLOGY

Epidemiology is concerned with the study of the distribution and determinants of health and diseases, morbidity, injuries, disability, and mortality in populations.² Epidemiologic studies are applied to the control of health problems in populations. Epidemiology is one of the core disciplines used to examine the associations between environmental hazards and health outcomes. The term *environmental epidemiology* refers to the study of diseases and health conditions (occurring in the population) that are linked to environmental factors.^{3,4} The exposures, which most of the time are outside the control of the individual, usually may be considered involuntary and stem from ambient and occupational environments.⁵ According to this conception of environmental epidemiology, standard epidemiologic methods are used to study the association between environmental factors (exposures) and health outcomes. Examples of topics studied include air and water pollution, the occupational environment with its pos-

sible use of physical and chemical agents, and the psychosocial environment.⁶

As noted previously, for an environmentally associated health outcome to be considered a topic of environmental epidemiology, exposure factors must lie outside the individual's immediate control. Hazards associated with smoking can be explored as an exposure dimension that is either under or not under the control of the individual. As an example of the former, studies of the health effects of smoking among individuals who smoke would not be a usual concern of environmental epidemiology. However, exposure of populations to secondhand cigarette smoke would be a concern because nonsmokers and vulnerable groups such as children cannot control whether they are exposed to environmental tobacco smoke.

Thus, traditionally, environmental epidemiology has tended to focus on health effects linked to degradation of the air we breathe, the water we drink, and the food we eat.⁷ With the advances achieved during the 20th century in environmental sanitation and control of disease-causing biological organisms, attention to chemical and physical impacts upon the environment has increased. Some of the agents and environmental factors being focused on are lead toxicity, particulates from diesel exhaust, and exposures to pesticides and halogenated compounds. The last category includes **polychlorinated biphenyls (PCBs)**, which through biological processes can become increasingly concentrated in foodstuffs, can pose hazards as potential carcinogens, and can impact the reproductive system. More recent concerns of environmental health include the reemerging infectious diseases (see Chapter 5) and the effects of climate changes due to global warming.

Although the relationship between environmental exposures and their unknown hazards remains a concern of environmental epidemiology, the field has evolved to include a broader approach: identification of previously unrecognized exposures to known hazardous agents and the quantification of such risks; estimation of the amount of exposures that individuals have to environmental hazards; assessment of risks associated with exposures (discussed in Chapter 3); and evaluation of procedures to prevent exposures.⁴ Similarly, in the related field of occupational health, the goals of epidemiologic research encompass the description of exposure–response gradients, discovery of how occupational hazards may cause harmful effects, characterization of vulnerable workers, and input into programs for the prevention of occupationally related diseases.⁸

CONTRIBUTIONS OF EPIDEMIOLOGY TO ENVIRONMENTAL HEALTH

Epidemiology aids the environmental health field through:

- Concern with populations
- Use of observational data
- Methodology for study designs
- Descriptive and analytic studies

Epidemiology is important to the study of environmental health problems because (1) many exposures and health effects associated with the environment occur at the population level; (2) the epidemiologic methods of natural experiments and observational techniques are appropriate; (3) the study designs used in epidemiologic research can be applied directly to the study of environmental health issues; and (4) epidemiology aids in the development of hypotheses and the study of causal relationships.

Concern with Populations

In contrast with clinical medicine's traditional focus on the individual, a unique characteristic of epidemiology is that it studies the entire population and hence is sometimes called population medicine. For example, epidemiologic studies of lung disease may examine the occurrence of lung cancer mortality across counties or among regional geographic subdivisions known as census tracts. Investigators may want to determine whether lung cancer mortality is higher in areas with higher concentrations of “smokestack” industries in comparison with areas that have lower levels of air pollution or are relatively free from air pollution. The alternative approach of the clinician would be to concentrate on the diagnosis and treatment of lung cancer among specific individuals.

Use of Observational Data

In examining the occurrence of health and disease in human populations, researchers often are prohibited from using experimental methods because of ethical issues such as potential dangers to subjects. Studies of the population's health present a challenge that is partially met by epidemiology because epidemiology is primarily an observational science that takes advantage of naturally occurring situations in order to study the occurrence of disease.

Methodology for Study Designs

In the realm of environmental health, epidemiologic research generally aims to portray the frequency of disease occurrence in the population or to link disease outcomes to specific exposures.⁹ In order to research environmentally caused disease in the population, the field of environmental epidemiology uses characteristic study designs: cross-sectional, ecologic, case-control, and cohort. For example, these methods are useful in and linked closely to the field of risk assessment (discussed in Chapter 3). Smith writes, “The epidemiologic input to environmental risk assessment involves the interpretation of epidemiological studies and their application to estimating the potential health risks to populations from known or estimated environmental exposures.”¹⁰(p124)

Two Classes of Epidemiologic Studies: Descriptive and Analytic

The term **descriptive epidemiology** refers to the depiction of the occurrence of disease in populations according to classification by person, place, and time variables. Examples of person variables are demographic characteristics such as sex, age, and race/ethnicity. Place variables denote geographic locations including a specific country or countries, areas within countries, and places where localized patterns of disease may occur. Some time variables are a decade, a year, a month, a week, or a day. Descriptive studies, regarded as a fundamental approach by epidemiologists, aim to delineate the patterns and manner in which disease occurs in populations.¹¹

An example of a pattern derived from descriptive studies is disease clustering, which refers to “A closely grouped series of events or cases of a disease or other health-related phenomena with well-defined distribution patterns in relation to time or place or both. The term is normally used to describe aggregation of relatively uncommon events or diseases, e.g., leukemia, multiple sclerosis.”¹²

Clustering may suggest common exposure of the population to an environmental hazard; it also may be purely spuri-

The Texas Sharpshooter Effect

A traveler passing through a small town in Texas noted a remarkable display of sharpshooting. On almost every barn he passed there was a target with a single bullet hole that uncannily passed through the center of the bull's-eye. He was so intrigued by this that he stopped at a nearby gas station to ask about the sharpshooter. With a chuckle, the attendant told him that the shooting was the work of Old Joe. Old Joe would first shoot at the side of a barn and then paint targets centered over his bullet holes so that each shot appeared to pass through the center of the target. . . . In a random distribution of cases of cancer over a geographic area, some cases will appear to occur very close together just on the basis of random variation. The occurrence of a group of cases of a disease close together in time and place at the time of their diagnosis is called a cluster.

Source: Reprinted from S Grufferman. Methodologic approaches to studying environmental factors in childhood cancer. *Environ Health Perspect.* 1998;106(suppl 3):882.

ous—due to the operation of chance. One cause of spurious clustering is called the Texas Sharpshooter Effect, discussed in the text box.

In the field of occupational health—which in many respects is emblematic of the general field of environmental health—“*Descriptive studies* provide information for setting priorities, identifying hazards, and formulating hypotheses for new occupational risk.”^{13(p944)} A historical example (discussed later in this chapter) is William Farr’s work showing that Cornwall metal miners had higher mortality from all causes than the general population.¹³

Analytic epidemiology examines causal (etiologic) hypotheses regarding the association between exposures and health conditions. “Etiologic studies are planned examinations of causality and the natural history of disease. These studies have required increasingly sophisticated analytic methods as the importance of low-level exposures is explored and greater refinement in exposure-effect relationships is sought.”^{13(p945)} The field of analytic epidemiology proposes and evaluates causal models that employ both outcome variables and exposure variables.

The exposure variables in epidemiologic research include contact with toxic substances, potential carcinogens, or air pollution. In other cases, exposure may be to biological agents or to forms of energy such as ionizing and nonionizing radiation, noise, and extremes of temperature. For an environmental epidemiologic research study to be valid, the level of exposure in a population must be assessed validly.

The outcome variable in epidemiologic studies is usually a specific disease, cause of mortality, or health condition. Accurate clinical assessments of an outcome such as lung cancer are vitally important to the quality of epidemiologic research.

One approach of analytic epidemiology is to take advantage of naturally occurring situations or events in order to test causal hypotheses. These naturally occurring events are referred to as **natural experiments**, defined as “Naturally occurring circumstances in which subsets of the population have different levels of exposure to a supposed causal factor, in a situation resembling an actual experiment where human subjects would be randomly allocated to groups.”¹² An example is the work of John Snow, discussed later in this chapter. Many past or ongoing natural experiments are relevant to environmental epidemiology. For example, in some regions of the United States, health legislation prohibits smoking in public areas in order to prevent exposure to secondhand smoke. At the same time, this activity may be considered a natural experiment that impacts human health and that can be studied by environmental epidemiologists.

Measures of Disease Frequency Used in Epidemiology

A number of quantitative terms, useful in environmental epidemiology, have been developed to characterize the occurrence of disease, morbidity, and mortality in populations. Particularly noteworthy are the two terms **prevalence** and **incidence**, which can be stated as frequencies or raw numbers of cases. In order to make comparisons among populations that differ in size, statisticians divide the number of cases by the population size. Several examples follow.

The term *prevalence* refers to the number of existing cases of or deaths from a disease or health condition in a population at some designated time. More specifically, **point prevalence** refers to all cases of or deaths from a disease or health condition that exist at a particular point in time relative to a specific population from which the cases are derived. Prevalence measures are used to describe the scope and distribution of health outcomes in the population. By revealing a snapshot of disease occurrence in the population, prevalence data contribute to the accomplishment of two of the primary functions of descriptive epidemiology: to assess variations

in the occurrence of disease in populations and to aid in the development of etiologic hypotheses.

Comparisons among populations that differ in size cannot be accomplished directly by using frequency or prevalence data. In order to make such comparisons, prevalence (usually referring to point prevalence) may be expressed as a proportion formed by dividing the number of cases that occur in a population by the size of the population in which the cases occur.

$$\text{Point prevalence} = \frac{\text{Number of persons ill}}{\text{Total number in the group}} \text{ at a point in time}$$

The term *incidence* refers to the occurrence of new disease or mortality within a defined period of observation (e.g., a week, month, year, or other time period) in a specified population. Those members of the population who are capable of developing the disease or condition being studied are known as the **population at risk**.

The **incidence rate** denotes a rate formed by dividing the number of new cases that occur during a time period by the number of individuals in the population at risk. (Several variations of incidence rates exist, but a discussion of all of them is beyond the scope of this chapter.) Statistically speaking, the incidence rate is a rate because of the specification of a time period during which the new cases occur.

$$\text{Incidence rate} = \frac{\text{Number of new cases}}{\text{Total population at risk}} \text{ over a time period} \\ \times \text{multiplier (e.g., 100,000)}$$

Incidence measures are central to the study of causal mechanisms with regard to how exposures affect health outcomes. Incidence measures are used to describe the risks associated with certain exposures; they can be used to estimate in a population “the probability of someone in that population developing the disease during a specified period, conditional on not dying first from another disease.”^{9(p23)}

One additional measure covered in this section is known as the case fatality rate (CFR). (Note that Chapter 5 will refer to the CFR.) The CFR, which provides a measure of the lethality of a disease, is defined as the number of deaths due to a specific disease within a specified time period divided by the number of cases of that disease during the same time period multiplied by 100. The formula is expressed as follows:

$$\text{CFR}(\%) = \frac{\text{Number of deaths due to disease "X"}}{\text{Number of cases of disease "X"}} \times 100 \text{ during a time period}$$

The numerator and denominator refer to the same time period. For example, suppose that 45 cases of hantavirus infection occurred in a western US state during a year of interest. Of these cases, 22 were fatal. The CFR would be:

$$\text{CFR}(\%) = \frac{22}{45} \times 100 = 48.9\%$$

BRIEF HISTORY OF ENVIRONMENTAL EPIDEMIOLOGY

Hippocrates

Environmental epidemiology has a long history that dates back 2,000 or more years.¹⁴ For example, in about 400 BC the ancient Greek authority Hippocrates expounded on the role of environmental factors such as water quality and the air in causing diseases.¹⁴ He produced the well-known book *On Airs, Waters, and Places*. Experts in the field posit that these writings form the historical cornerstone of environmental epidemiology. Hippocrates' work and the writings of many of the ancients did not delineate specific known agents involved in the causality of health problems, but referred more generically to air, water, and food. In this respect, early epidemiology shares with contemporary epidemiology the frequent lack of complete knowledge of the specific agents of environmentally associated diseases.

Sir Percival Pott

Sir Percival Pott, a London surgeon, was significant to the history of environmental epidemiology because he is thought to be the first individual to describe an environmental cause of cancer. (See Figure 2-1.)

In 1775, Pott made the astute observation that chimney sweeps had a high incidence of scrotal cancer (in comparison with male workers in other occupations).¹ He argued that chimney sweeps were prone to this malady as a consequence of their contact with soot.¹⁵ (See Figure 2-2.)

In a book entitled *Chirurgical Observations Relative to the Cataract, the Polypus of the Nose, the Cancer of the Scrotum, the Different Kinds of Ruptures, and the Mortification of the Toes and Feet*, published in London in 1775, Pott developed a chapter called “A Short Treatise of the Chimney Sweeper's Cancer.” This brief work of only 725 words is noteworthy because

it provided the first clear description of an environmental cause of cancer, suggested a way to prevent the disease, and led indirectly to the synthesis of the first known pure carcinogen and the isolation of the first carcinogenic chemical to

FIGURE 2-1 Percival Pott, F.R.S., 1714–1788.

PERCIVALL POTT Esq^r

*Engraved by Heath, from a Picture
of Sir Joshua Reynolds.*

Published March 16th 1790, by J. Johnson, St. Paul's Church Yard.

Source: © Wellcome Library, London.

be obtained from a natural product. No wonder therefore that Pott's observation has come to be regarded as the foundation stone on w[h]ich the knowledge of cancer prevention has been built!¹⁵(p521)

In Pott's own words,

[E]very body . . . is acquainted with the disorders to which painters, plumbers, glaziers, and the workers in white lead are liable; but there is a disease as peculiar to a certain set of people which has not, at least to my knowledge, been publicly noticed; I mean the chimney-sweepers' cancer. . . . The fate of these people seems

singularly hard; in their early infancy, they are most frequently treated with great brutality, and almost starved with cold and hunger; they are thrust up narrow, and sometimes hot chimnies, where they are bruised, burned, and almost suffocated; and when they get to puberty, become peculiar [sic] liable to a noisome, painful and fatal disease. Of this last circumstance there is not the least doubt though perhaps it may not have been sufficiently attended to, to make it generally known. Other people have cancers of the same part; and so have others besides lead-workers, the Poictou colic, and the consequent paralysis; but it is nevertheless a disease to which they are particularly liable; and so are chimney-sweepers to the cancer of the scrotum and testicles. The disease, in these people . . . seems to derive its origin from a lodgment of soot in the rugae of the scrotum.¹⁵(pp521–522)

FIGURE 2-2 A chimney sweep.

Source: © Annamaria Szilagyi/Shutterstock, Inc.

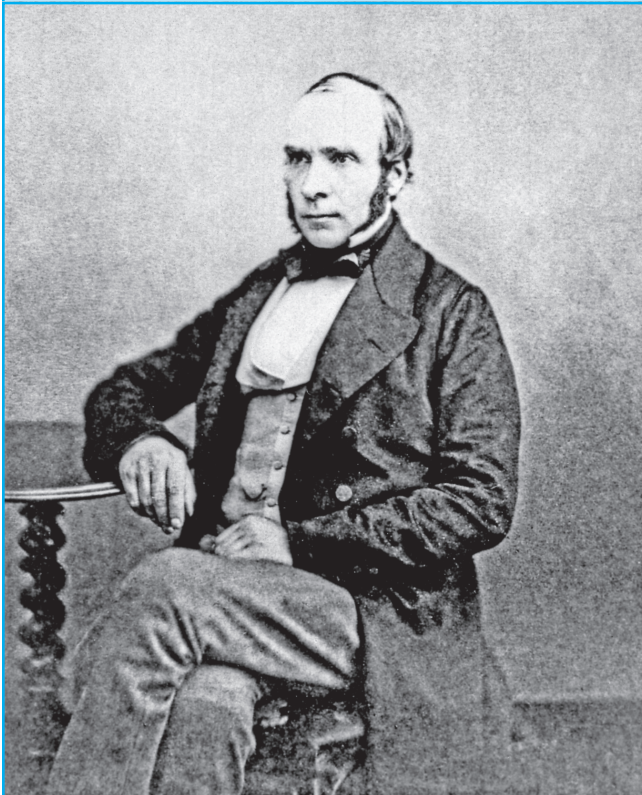
Following his conclusions about the relationship between scrotal cancer and chimney sweeping, Pott established an occupational hygiene control measure—the recommendation that chimney sweeps bathe once a week.

John Snow

During the mid-1800s, English anesthesiologist John Snow (see Figure 2-3) linked a cholera outbreak in London to contaminated water from the Thames River. His methodology for investigating the cholera outbreak of 1849 was known as a “natural experiment,” a methodology used currently in the study of environmental health problems. Refer to the text box for more information.

In addition to utilizing the method of natural experiment, John Snow provided expert witness testimony on behalf of industry with respect to environmental exposures to potential disease agents.¹⁷ Snow attempted to extrapolate from the health effects of exposures to high doses of environmental substances what the effects of low doses would be. On January 23, 1855, the Nuisances Removal and Diseases Prevention

FIGURE 2-3 John Snow.



Source: © National Library of Medicine.

The Natural Experiment

The natural experiment: Two water companies, the Lambeth Company and the Southwark and Vauxhall Company, provided water in such a manner that adjacent houses could receive water from two different sources. In 1852, one of the companies, the Lambeth Company, relocated its water sources to a section of the Thames River that was less contaminated. During a later cholera outbreak in 1854, Snow observed that a higher proportion of residents who used the water from the Southwark and Vauxhall Company developed cholera than did residents who used water from the Lambeth Company. The correspondence between changes in the quality of the water supply and changes in the occurrence of cholera became known as a natural experiment. The Lambeth Company provided cleaner water than the Southwark and Vauxhall Company. “The mortality in the houses supplied by the Southwark and Vauxhall Company was therefore between eight and nine times as great as in the houses supplied by the Lambeth Company.”^{16(p86)}

Amendments bill was introduced in the British Parliament. This bill was a reform of Victorian public health legislation that followed the 1854 cholera outbreak described in the foregoing paragraph.¹⁷ The intent of the bill was to control release into the atmosphere of fumes from operations such as gas works, silk-boiling works, and bone-boiling factories. Snow contended that these odors were not a disease hazard in the community.¹⁸ The thesis of Snow’s argument was that deleterious health effects from the low levels of exposure experienced in the community were unlikely, given the knowledge about higher-level exposures among those who worked in the factories. Snow argued that the workers in the factories were not suffering any ill health effects or dying from the exposure. Therefore, it was unlikely that the much lower exposures experienced by the members of the larger community would affect the latter’s health.

STRATEGIES OF ENVIRONMENTAL EPIDEMIOLOGY

Study designs used in environmental epidemiology are similar to those developed for general epidemiologic research. Study designs can be arranged on a continuum ranging from hy-

John Snow's Investigation of a Cholera Outbreak in London, Circa 1849

A section of London, designated the Broad Street neighborhood (now part of the Soho district), became the focus of Snow's detective work. Two water companies, the Lambeth Company and the Southwark and Vauxhall Company, provided water in such a manner that adjacent houses could receive water from two different sources. One of the companies, the Lambeth Company, relocated its water sources to a section of the Thames River that was less contaminated. During a later cholera outbreak in 1854, Snow observed that a higher proportion of residents who used the water from the Southwark and Vauxhall Company developed cholera than did residents who used water from the Lambeth Company. Snow's efforts to show a correspondence between changes in the water supply and occurrence of cholera became known as a natural experiment.

Here is Snow's graphic description of the cholera outbreak that occurred in 1849.

The most terrible outbreak of cholera which ever occurred in this kingdom, is probably that which took place in Broad Street, Golden Square, and the adjoining streets, a few weeks ago. . . . The mortality in this limited area probably equals any that was ever caused in this country, even by the plague; and it was much more sudden, as the greater number of cases terminated in a few hours. . . . Many houses were closed altogether, owing to the death of the proprietors; and, in a great number of instances, the tradesmen who remained had sent away their families: so that in less than six days from the commencement of the outbreak, the most afflicted streets were deserted by more than three-quarters of their inhabitants.¹⁶(p38)

Snow's pioneering approach illustrated the use of both descriptive and analytic epidemiology. One of his first activities was to plot the cholera deaths in relation to a pump that he hypothesized was the cause of the cholera outbreak. Each death was shown on the map (Figure 2-4) as a short line. An arrow in the figure points to the location of the Broad Street pump. "As soon as I became acquainted with the situation and the extent of this irruption of cholera, I suspected some contamination of the water of the much-frequented street-pump in Broad Street, near the end of Cambridge Street; . . . On proceeding to the spot, I found that nearly all the deaths had taken place within a short distance of the pump."¹⁶(pp38–39) The handle of the pump was later removed—a public health measure to control the outbreak. In Snow's time, many European cities took water for domestic use directly from rivers, which often were contaminated with microorganisms.

Source: Snow J. *Snow on Cholera*. Cambridge, MA: Harvard University Press; 1965.

hypothesis-generating designs that provide limited information to complex hypothesis-testing designs.⁸ Purely observational study designs include case series, cross-sectional, ecologic, case-control, and cohort studies. Nonobservational and partly observational designs that are used include experimental and quasi-experimental designs.

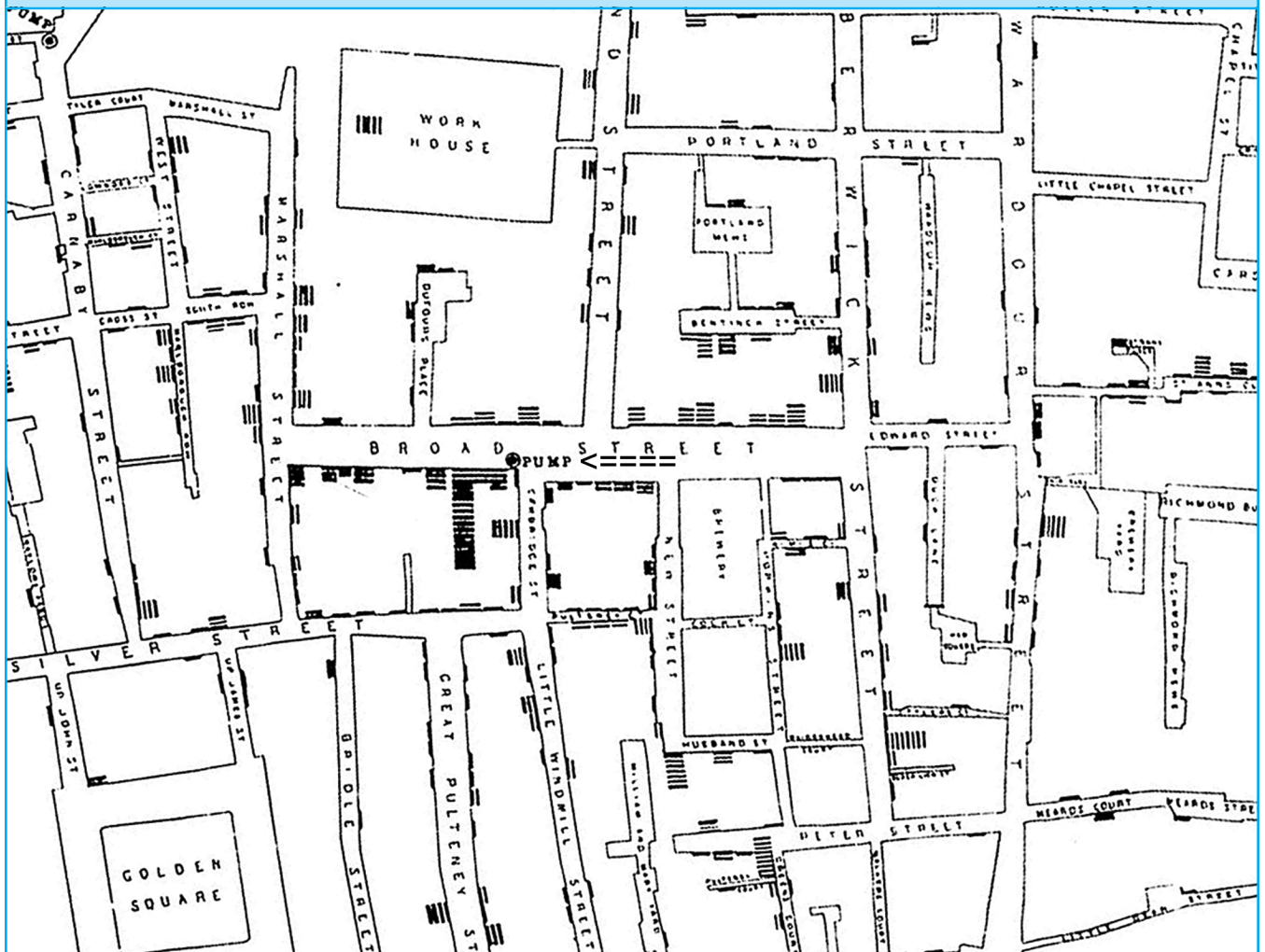
For the particular problem being investigated, some designs are better than others, depending upon what is to be achieved, the availability of study populations, the disease or health outcome studied, and the need to uncover disease etiology.⁸ Examples of the subset of observational designs that are used for hypothesis generation include cross-sectional studies, case series, some types of ecologic correlations, and proportionate mortality comparisons.⁸ The subset of observational designs that are used for hypothesis testing includes cohort and case-control studies. One of the distinguishing

characteristics of study designs is whether they involve the individual or group as the unit of analysis. With the exception of ecologic studies, all the designs presented in this chapter use the individual as the unit of analysis.

Experimental Studies

Consider the use of experimental studies in environmental health research; in epidemiology, experimental studies are implemented as intervention studies. An **intervention study** is "[a]n investigation involving intentional change in some aspect of the status of the subjects, e.g., introduction of a preventive or therapeutic regimen, or an intervention designed to test a hypothesized relationship. . . ."¹²

Two experimental methods are randomized controlled trials and quasi-experiments. A simple example of the former is a classic experimental design in which there is manipulation

FIGURE 2-4 Map of cholera cases in the Broad Street area. Each case is indicated by a short line.

Source: Reprinted from Snow J. *Snow on Cholera*. Harvard University Press; © 1965.

of an exposure variable and random assignment of subjects to either a treatment group or a control group. Some uses of randomized controlled trials are to test the efficacy of new medications, medical regimens, and vaccines. A specific application is the use of an experimental trial to test the efficacy of fluoridation of drinking water in preventing tooth decay.⁹ In this scenario, communities would be selected at random for the addition of fluoride to the public water supply; those with and those without fluoridated water would be compared with respect to the frequency of dental caries among their residents.

Fluoridation of water also could be conducted as a quasi-experimental study, in which there is manipulation of an exposure variable, but subjects are not randomly allocated to

the study conditions. During the 1940s and 1950s, two comparable New York cities (one having received fluoride for about a decade and the other having received none) were contrasted for the occurrence of tooth decay and related dental problems among children. In the community that added fluoride to the water supply, the frequency of such problems decreased by about one half.⁹ This example was a quasi-experiment because the “subjects” (cities) were assigned arbitrarily and not randomly.

For several reasons, the use of experimental methods in environmental epidemiology is difficult to achieve; consequently, observational methods are usually more feasible to implement. Rothman points out:

Randomized assignment of individuals into groups with different environmental exposures generally is impractical, if not unethical; community intervention trials for environmental exposures have been conducted, although seldom (if ever) with random assignment. Furthermore, the benefits of randomization are heavily diluted when the number of randomly assigned units is small, as when communities rather than individuals are randomized. Thus, environmental epidemiology consists nearly exclusively of non-experimental epidemiology. Ideally, such studies use individuals as the unit of measurement; but often environmental data are available only for groups of individuals, and investigators turn to so-called ecologic studies to learn what they can.^{6(p20)}

Consequently, in order to study the effects of environmental exposures when dealing with human populations, researchers must use observational methods, and, in fact, the majority of research on health outcomes associated with the environment uses observational methods.¹⁹

Case Series

A **case series study** is one in which information about patients who share a disease in common is gathered over time. Although this type of study is among the weakest for making causal assertions, a case series can be useful for developing hypotheses for further study. Usually information from a case series study is considered to be preliminary and a starting point for more complex investigations. However, some astute clinicians have used information from series of cases to make important observations. An example comes from the work of Herbst and Scully, who were the first to describe the association between exposure to diethylstilbestrol (DES) during mothers' pregnancies and risk of clear-cell cervicovaginal cancer among six female adolescents and young adults.²⁰

Cross-Sectional Studies

A **cross-sectional study** is defined as one

that examines the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at one particular time. The presence or absence of disease and the presence or absence of the other variables . . . are determined in each member of the study population

or in a representative sample at one particular time.¹²

Thus, a cross-sectional study is a type of prevalence study in which the distribution of disease and exposure are determined, although it is not imperative for the study to include both exposure and disease. A cross-sectional study may focus only on the latter.² Cross-sectional designs make a one-time assessment of the prevalence of disease in a sample that in most situations has been sampled randomly from the parent population of interest.⁹ Cross-sectional studies may be used to formulate hypotheses that can be followed up in analytic studies.

Here is an example of a cross-sectional study: As part of an asthma reduction program conducted in Passaic, New Jersey, during the 1998 through 1999 school year, investigators conducted a survey of a community in which all third graders were targeted.²¹ The study children and their parents were given self-report symptom questionnaires. A total of 976 children and 818 parents returned the questionnaire. A respiratory therapist collected spirometry (lung function) readings from 615 children (approximately 58% of the target population). The study demonstrated that about half the children experienced self-reported asthma-related symptoms. However, because self-reports were not associated closely with the results of the spirometry tests, the investigators concluded that the self-reported data from children were not good predictors of asthma risk. From the spirometry results, about 22% of the children had abnormal results, with significant differences occurring by race and ethnicity. More abnormal evaluations were found for blacks and Asians in comparison with other groups. Table 2-1 reports the results of the spirometry evaluation.

Ecologic Studies

Ecologic studies are different from most other types of epidemiologic research in regard to the unit of analysis. An **ecologic study** (also called an ecological study) is "a study in which the units of analysis are populations or groups of people, rather than individuals."¹² For example, the occurrence of an outcome of interest (e.g., a disease, mortality, health effect) might be assessed over different geographic areas—states, census tracts, or counties. To illustrate, one could study the "relationship between the distribution of income and mortality rates in states or counties."¹² The assumption is made that outcome rates would be comparable in exposed and nonexposed groups if the exposure did not take place in the exposed group. In the foregoing example, if the outcome were mortality from

TABLE 2-1 Population Distribution, by Race/Ethnicity, and Percentage of Each Subgroup with Physician-Interpreted Abnormal Spirometry Readings (n = 455)

| | Population Distribution > | Abnormal Spirometry, % |
|----------------------|---------------------------|------------------------|
| Dominican | 22.6 | 28.2 |
| Mexican | 19.8 | 10.0 |
| Puerto Rican | 19.3 | 8.0 |
| Mixed other Hispanic | 9.7 | 4.5 |
| Peruvian | 4.0 | 11.1 |
| Colombian | 2.6 | 8.3 |
| Black | 11.2 | 39.2 |
| White | 4.0 | 27.8 |
| Asian | 3.7 | 47.1 |
| Mixed non-Hispanic | 3.1 | 14.3 |

Source: Adapted and reprinted with permission from NCG Freeman, D Schneider, and P McGarvey. School-based screening for asthma in third-grade urban children: the Passaic asthma reduction effort survey. *Am J Public Health*. 2002;92:45.

cancer, researchers might hypothesize that persons living in lower-income areas have greater exposure to environmental carcinogens than those who live in higher-income areas, producing differences in cancer mortality.

Ecologic analyses have been used to correlate air pollution with adverse health effects such as mortality. Instead of correlating individual exposure to air pollution with mortality, the researcher measures the association between average exposure to air pollution within a census tract and the average mortality in that census tract. Other types of geographic subdivisions besides census tracts may be used as well. This type of study attempts to demonstrate that mortality is higher in more polluted census tracts than in less polluted census tracts.

A major problem of the ecologic technique for the study of air pollution (and for virtually all ecologic studies) stems from uncontrolled factors. Examples relevant to air pollution include individual levels of smoking and smoking habits, occupational exposure to respiratory hazards and air pollution, differences in social class and other demographic factors, genetic background, and length of residence in the area.⁸ Nonetheless, ecologic studies may open the next generation of investigations; the interesting observations gathered in ecologic studies may provide the impetus for more carefully designed studies. The next wave of studies that build on ecologic studies then may attempt to take advantage of more rigorous analytic study designs.

Ecologic studies have examined the association between water quality and both stroke and coronary diseases. A group of studies has demonstrated that hardness of the domestic water supply is associated inversely with risk of cerebrovascular mortality and cardiovascular diseases. However, a Japanese investigation did not support a relationship between water hardness and cerebrovascular diseases. In the latter ecologic study, the unit of analysis was municipalities (population subdivisions in Japan that consisted of from 6,000 to 3 million inhabitants). In analyzing the 1995 death rates from strokes in relationship to the values of water hardness, the researchers did not find statistically significant associations across municipalities.²²

Other ecologic studies have examined the possible association between use of agricultural pesticides and childhood cancer incidence. For example, a total of 7,143 incident cases of invasive cancer diagnosed among children younger than age 15 were reported to the California Cancer Registry during the years 1988–1994. In this ecologic study, the unit of analysis was census blocks, with average annual pesticide exposure estimated per square mile. The study showed no overall association between pesticide exposure determined by this method and childhood cancer incidence rates. However, a significant increase of childhood leukemia rates was linked to census block groups that had the highest use of one form of pesticide, called propargite.²³

Case-Control Studies

In a **case-control study**, subjects who participate in the study are defined on the basis of the presence or absence of an outcome of interest. The cases are those who have the outcome or disease of interest, and the controls are those who do not. In a case-control study, cases and controls generally are matched according to criteria such as sex, age, race, or other variables. Exposure to a factor is determined retrospectively, meaning that exposure has already occurred in the past. One method to determine past exposure is for the investigator to interview cases and controls regarding their exposure history. An advantage of case-control studies is that they can examine many potential exposures. For example, subjects may be queried about one or more exposures that they may have had in the past; in some variations of this approach, it may be possible to conduct direct measurements of the environment for various types of exposures. A disadvantage of case-control studies is that, in most circumstances, they can examine only one or a few outcomes.⁸

Researchers have a variety of sources available for the selection of cases and controls. For example, they may use pa-

TABLE 2-2 Table for a Case-Control Study

| | | Disease Status—Outcome of Interest | |
|-----------------|-------|------------------------------------|---------------|
| | | Yes (Cases) | No (Controls) |
| Exposure Status | Yes | A | B |
| | No | C | D |
| | Total | A + C | B + D |

tients from hospitals, specialized clinics, or medical practices. Sometimes, advertisements in media solicit cases. Cases may be selected from disease registries such as cancer registries. Controls can be either healthy persons or those affected by a disease that is etiologically unrelated to the outcome of interest. For example, investigators may identify as controls patients from hospitals or clinics; however, these control patients must not have been affected by the outcome of interest. In other studies, controls may be friends or relatives of the cases or be from the community.

The measure of association between exposure and outcome used in case-control studies is known as the **odds ratio (OR)**. A particular form of OR, the exposure-odds ratio, refers to “the ratio of odds in favor of exposure among the cases [A/C] to the odds in favor of exposure among the non-cases [the controls, B/D].”¹² Table 2-2 illustrates the method for labeling cells in a case-control study. This table is called a 2 × 2 table.

The OR is defined as $\frac{A/C}{B/D}$, which can be expressed as $\frac{AD}{BC}$

An odds ratio of more than 1 suggests a positive association between the exposure and disease or other outcome (provided that the results are statistically significant—a concept that will not be discussed here).

Calculation example: Suppose we have the following data from a case-control study: A = 9, B = 4, C = 95, D = 88. The OR is calculated as follows:

$$OR = \frac{AD}{BC} = \frac{(9)(88)}{(4)(95)} = 2.08$$

In this sample calculation, the OR is greater than 1, suggesting that the odds of the disease are higher among the exposed persons than among the nonexposed persons.

Case-control studies are very common in environmental epidemiologic research. For example, environmental health researchers have been concerned about the possible health effects of exposure to electromagnetic fields (EMFs). A case-control study among female residents of Long Island, New

York, examined the possible association between exposure to EMFs and breast cancer.²⁴ Eligible subjects were those who were younger than 75 years of age and who had lived in the study area for 15 years or longer. Cases (n = 576) consisted of women diagnosed with in situ or invasive breast cancer. Controls (n = 585) were selected from the same community by random digit dialing procedures. Several types of measurement of EMFs were taken in the subjects’ homes and by mapping overhead power lines. The investigators reported that the odds ratio between EMF exposure and breast cancer was not statistically significantly different from 1; thus, the results suggested that there was no association between breast cancer and residential EMF exposure.

In comparison with cross-sectional study designs, case-control studies may provide more complete exposure data, especially when the exposure information is collected from the friends and relatives of cases who died of a particular cause. Nevertheless, some unmeasured exposure variables as well as methodological biases (a term discussed later in this chapter) may remain in case-control studies. For example, in studies of health and air pollution, exposure levels are difficult to quantify precisely. Also, it may be difficult to measure unknown and unobserved factors, including smoking habits and occupational exposures to air pollution, which affect the lungs.⁸

Cohort Studies

A **cohort study** design classifies subjects according to their exposure to a factor of interest and then observes them over time to document the occurrence of new cases (incidence) of disease or other health events. Cohort studies are a type of longitudinal design, meaning that subjects are followed over an extended period of time. Using cohort studies, epidemiologists are able to evaluate many different outcomes (causes of death) but few exposures.⁸

Cohort studies may be either prospective or retrospective. At the inception of a prospective cohort study, participating individuals must be certified as being free from the outcome of interest. As these individuals are followed into the future, the occurrence of new cases of the disease is noted. A retrospective cohort study (historical cohort study) is “conducted by reconstructing data about persons at a time or times in the past. This method uses existing records about the health or other relevant aspects of a population as it was at some time in the past and determines the current (or subsequent) status of members of this population with respect to the condition of interest.”¹² An example of a retrospective cohort study would be one that examined mortality among an occupational cohort such as shipyard workers who were employed

at a specific naval yard during a defined time interval (e.g., during World War II).

The measure of association used in cohort studies is called **relative risk (RR)**, the ratio of the incidence rate of a disease or health outcome in an exposed group to the incidence rate of the disease or condition in a nonexposed group. As noted previously, an incidence rate may be interpreted as the risk of occurrence of an outcome that is associated with a particular exposure. The RR provides a ratio of two risks—the risk associated with an exposure in comparison with the risk associated with nonexposure.

Mathematically, the term *relative risk* is defined as $A/(A + B)$ (the rate [incidence] of the disease or condition in the exposed group) divided by $C/(C + D)$ (the rate [incidence] of the disease or condition in the nonexposed group). A 2×2 table for the elements used in the calculation of a relative risk is shown in Table 2-3.

$$RR = \frac{\frac{A}{A + B}}{\frac{C}{C + D}}$$

Calculation example: Suppose that we are researching whether exposure to solvents is associated with risk of liver cancer. From a cohort study of industrial workers, we find that three persons who worked with solvents developed liver cancer (cell A of Table 2-3) and 104 did not (cell B). Two cases of liver cancer occurred among nonexposed workers (cell C) in the same type of industry. The remaining 601 nonexposed workers (cell D) did not develop liver cancer. The RR is:

$$RR = \frac{\frac{3}{3 + 104}}{\frac{2}{2 + 601}} = 8.45$$

We may interpret relative risk in a manner that is similar to that of the odds ratio. For example, a relative risk greater than 1 (and statistically significant) indicates that the risk of disease is greater in the exposed group than in the nonexposed

group. In other words, there is a positive association between exposure and the outcome under study. In the calculation example, the risk of developing liver cancer is eight times greater among workers who were exposed to solvents than among those who were not exposed to solvents.

Sometimes a relative risk calculation yields a value that is less than 1. If the relative risk is less than 1 (and statistically significant), the risk is lower among the exposed group. This level of risk (i.e., less than 1) sometimes is called a protective effect.

Accurate disease verification is necessary to optimize measures of relative risk; disease misclassification affects estimates of relative risk. The type of disease and method of diagnosis affect accuracy of diagnosis.⁸ To illustrate, death certificates are used frequently as a source of information about the diagnosis of a disease. Information from death certificates regarding cancer as the underlying cause of death is believed to be more accurate than the information for other diagnoses such as those for nonmalignant conditions. Nevertheless, the accuracy of diagnoses of cancer as a cause of death varies according to the particular form of cancer.

Cohort studies are applied widely in environmental health. For example, they have been used to examine the effects of environmental and work-related exposures to potentially toxic agents. One concern of cohort studies has been exposure of female workers to occupationally related reproductive hazards and adverse pregnancy outcomes.²⁵

A second example is an Australian study that examined the health impacts of occupational exposure to insecticides.²⁶ The investigators selected a cohort of 1,999 outdoor workers known to be employed as field officers or laboratory staff for the New South Wales Board of Tick Control between 1935 and 1996. Only male subjects were selected for the study. A control cohort consisted of 1,984 men who worked as outdoor field officers at any time since 1935. Occupational monitoring programs demonstrated that members of the exposure cohort had worked with pesticides, including DDT. The investigators carefully evaluated exposure status and health outcomes such as mortality from various chronic diseases and cancer. They reported an association between exposure to pesticides and adverse health effects, particularly for asthma, diabetes, and some forms of cancer including pancreatic cancer.

Study Endpoints Used in Environmental Epidemiologic Research

In evaluating the health effects of occupational exposures to toxic agents, researchers may study various endpoints, including measures derived from self-report questionnaires, results of direct physical examinations, and mortality experience in a

TABLE 2-3 Table for a Cohort Study

| | | Disease Status | | |
|-----------------|-----|----------------|----|-------|
| | | Yes | No | Total |
| Exposure Status | Yes | A | B | A+B |
| | No | C | D | C+D |

population. The endpoints also may be keyed to any of a number of stages in the natural progression of disease (e.g., presymptomatic, symptomatic, or permanent dysfunction).²⁷

In some studies, self-reported symptom rates are used as a measure of the effects of low-level chemical exposure. Occupational health investigators can design and administer self-report questionnaires inexpensively. Self-reports to questionnaires, however, may not always be reliable, and although they correlate often with clinical diagnoses they also may differ markedly.⁶

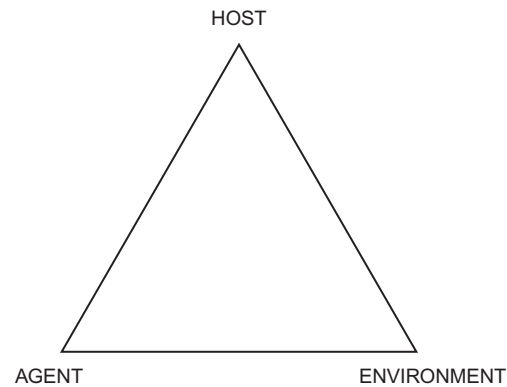
Physiologic or clinical examinations are other means to evaluate adverse health effects. For example, in a study of respiratory diseases, pulmonary function tests, such as forced expiratory volume, may be an appropriate indicator. Although clinical examinations may provide “harder” evidence of health effects than self-reports, such examinations may be expensive or impractical to conduct in the case of workers who have left employment.

In other studies, mortality is the outcome of interest; research on mortality frequently uses a retrospective cohort study design.⁷ Mortality experience in an employment cohort can be compared with the expected mortality in the general population (national, regional, state, or county) by using the standardized mortality ratio (SMR), which is defined as “The ratio of the number of deaths observed in the study group or population to the number that would be expected if the study population had the same specific rates as the standard population. Often multiplied by 100.”¹² Typically the SMR is denoted by a percentage; when the percentage is greater than 100%, the SMR in the study population is elevated above that found in the comparison population. Conversely, when the SMR is less than 100%, the mortality experience in the study population is lower than that of the comparison population.

One also can contrast the mortality experience of exposed workers with the mortality rate of nonexposed workers in the same industry. For example, production workers might be compared with drivers or office workers. Another option is to identify a second industry or occupation that is comparable in terms of skill level, educational requirements, or geographic location but in which the exposure of interest is not present.

The use of mortality as a study endpoint has several advantages, including the fact that it may be relevant to agents that have a subtle effect over a long time period. Although any fatal chronic disease may be investigated, mortality from cancer often is studied as an outcome variable in occupational exposures. According to Monson, “Cancer specifically tends to be a fatal illness; its presence is usually indicated on the death certificate. Also, cancer is a fairly specific disease and

FIGURE 2-5 The epidemiologic triangle.



Source: Reprinted with permission from RH Friis, TA Sellers. *Epidemiology for Public Health Practice*. 4th ed. Sudbury, MA: Jones and Bartlett Publishers; 2009:439.

is less subject to random misclassification than, say, one of the cardiovascular diseases.”^{28(p106)}

CAUSALITY IN EPIDEMIOLOGIC STUDIES

One of the fundamental models of causality used in epidemiologic studies is the **epidemiologic triangle**, which includes three major factors: agent, host, and environment. Although this model has been applied to the field of infectious disease epidemiology, it also provides a framework for organizing the causality of other types of environmental problems. Refer to Figure 2-5 for an illustration.

The term *environment* is defined as the domain in which disease-causing agents may exist, survive, or originate; it consists of “[a]ll that which is external to the individual human host.”¹² The **host** is “[a] person or other living animal, including birds and arthropods, that affords subsistence or lodgment to an infectious agent under natural conditions.”¹² A human host is a person who is afflicted with a disease; or, from the epidemiologic perspective, the term host denotes an affected group or population. An **agent** (of disease) refers to

a factor—such as a microorganism, chemical substance, or form of radiation—whose presence, excessive presence, or (in deficiency diseases) relative absence is essential for the occurrence of a disease. A disease may have a single agent, a number of independent alternative agents (at least one of which must be present),

or a complex of two or more factors whose combined presence is essential for the development of the disease.¹²

In environmental health, agent factors can include (but are not limited to) particulate matter from pollution, toxic chemicals and pesticides, and microbes. Examples of agent factors covered in this text are:

- Microbial agents responsible for zoonotic diseases
- Microbial agents linked to foodborne illness
- Toxic chemicals including pesticides
- Toxic metals
- Airborne particulates and gases
- Radiation: ionizing and nonionizing

These agents are relevant to many of the environmental problems discussed in this text, including hazardous waste disposal, zoonotic illnesses, foodborne illnesses, accidents, occupational illnesses, and adverse health outcomes associated with water and air pollution.

Criteria of Causality

The epidemiologic triangle provides a framework for viewing hypothesized relationships among agent, host, and environmental factors in causation of disease. One of the central concerns of environmental health epidemiology is to be able to assert that a causal association exists between an agent factor and a disease in the host. Hill pointed out that in the realm of occupational health, extreme conditions in the physical environment or exposure to known toxic chemicals should be invariably injurious.²⁹ More commonly the situation occurs in which weaker associations have been observed between certain aspects of the environment and the occurrence of health events. An example would be the development of lung diseases among persons exposed to dusts (e.g., miners who work in dusty, unventilated mines). Hill raised the question of how one moves from such an observed association to the verdict of causation (e.g., exposure to coal dust *causes* coal miner's pneumoconiosis). A second example is the perplexing question of the extent to which studies reveal a causal association between a specific environmental exposure and a particular form of cancer.²⁰

Hill proposed a situation in which there is a clear association between two variables and in which statistical tests have suggested that this association is not due to chance. For example, data have revealed that smoking is associated with lung cancer in humans and that chance can be ruled out as being responsible for this observed association. The 1964 US government report *Smoking and Health* stated that

Table 2-4 Hill's Criteria of Causality

| | |
|-------------|---------------------|
| Strength | Biological gradient |
| Consistency | Plausibility |
| Specificity | Coherence |
| Temporality | |

the evaluation of a causal association does not depend solely upon evidence from a probabilistic statement derived from statistics, but is a matter of judgment that depends upon several criteria.³⁰ Similarly, Hill listed nine causal criteria that need to be taken into account in the assessment of a causal association between factor A and disease B. For the purposes of this text, we will consider seven of the criteria, which are included in Table 2-4.

Strength

Strong associations give support to a causal relationship between factor and disease. Hill provided the example of the very large increase in scrotal cancer (by a factor of 200 times) among chimney sweeps in comparison with workers who were not exposed occupationally to tars and mineral oils. Another example arises from the steeply elevated lung cancer mortality rates among heavy cigarette smokers in comparison with nonsmokers (20 to 30 times higher). Hill also cautioned that we should not be too ready to dismiss causal associations when the strength of the association is small, because there are many examples of causal relationships that are characterized by weak associations. One example would be exposure to an infectious agent such as meningococcus that produces relatively few clinical cases of meningococcal meningitis.

Consistency

According to Hill, a consistent association is one that has been observed repeatedly “by different persons, in different places, circumstances and times. . . .”^{29(p296)} An example of consistency comes from research on the relationship between smoking and lung cancer, a relationship that was found repeatedly in many retrospective and prospective studies.

Specificity

A specific association is one that is constrained to a particular disease–exposure relationship. In a specific association, a given disease results from a given exposure and not from other types of exposures. Hill gave the example of an association that “is limited to specific workers and to particular sites and types of disease and there is no association between

the work and other modes of dying. . . .”^{29(p297)} Returning to the smoking–lung cancer example, one may argue that the association is not specific, because “the death rate among smokers is higher than the death rate of non-smokers from many causes of death. . . .”^{29(p297)} Nevertheless, Hill argued that one-to-one causation is unusual, because many diseases have more than one causal factor.

Temporality

This criterion specifies that we must observe the cause before the effect; Hill stated that we cannot put the cart before the horse. For example, if we assert that air pollution causes lung cancer, we first must exclude persons who have lung cancer from our study; then we must follow those who are exposed to air pollution to determine whether lung cancer develops.

Biological Gradient

A biological gradient also is known as a dose–response curve (discussed in Chapter 3), which shows a linear trend in the association between exposure and disease. An example arises from the linear association between the number of cigarettes smoked and the lung cancer death rate.

Plausibility

This criterion states that an association must be biologically plausible from the standpoint of contemporary biological knowledge. The association between exposure to tars and oils and the development of scrotal cancer is plausible in view of current knowledge about carcinogenesis. However, this knowledge was not available when Pott made his observations during the 18th century.

Coherence

This criterion suggests that “the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease. . . .”^{29(p298)} Examples related to cigarette smoking and lung cancer come from the rise in the number of lung cancer deaths associated with an increase in smoking, as well as lung cancer mortality differences between men (who smoke more and have higher lung cancer mortality rates) and women (who smoke less and have lower rates).

BIAS IN ENVIRONMENTAL EPIDEMIOLOGIC STUDIES

Epidemiologic studies may be impacted by **bias**, which is defined as the “[s]ystematic deviation of results or inferences from the truth. Processes leading to such deviation. An error in the conception and design of a study—or in the collection,

analysis, interpretation, reporting, publication, or review of data—leading to results or conclusions that are systematically (as opposed to randomly) different from the truth.”¹² There are many types of bias; particularly important for environmental epidemiology are those that impact study procedures. Examples of such bias are related to how the study was designed, the method of data collection, interpretation and review of findings, and procedures used in data analysis. For example, in measurements of exposures and outcomes, faulty measurement devices may introduce biases into study designs.

A complete discussion of all the kinds of bias is beyond the scope of the text; however, we will consider two types of bias, *recall bias* and *selection bias*. The former is particularly relevant to case-control studies. Recall bias refers to the fact that cases may remember an exposure more clearly than controls.¹⁹ The consequence of recall bias is to reduce the reliability of exposure information gathered from control groups.

Selection bias is defined as “Distortions that result from procedures used to select subjects and from factors that influence participation in the study.”¹² The effect of selection bias may be to cause systematic differences in characteristics between participants and nonparticipants in research. An example of selection bias is the **healthy worker effect**, which may reduce the validity of exposure data when employed persons are chosen as research subjects in studies of occupational health. Monson states that the healthy worker effect refers to the “observation that employed populations tend to have a lower mortality experience than the general population.”^{28(p114)} The healthy worker effect may have an impact on occupational mortality studies in several ways. People whose life expectancy is shortened by disease are less likely to be employed than healthy persons. One consequence of this phenomenon would be a reduced (or attenuated) measure of effect for an exposure that increases morbidity or mortality; that is, because the general population includes both employed and unemployed individuals, the mortality rate of that population may be somewhat elevated in comparison with a population in which everyone is healthy enough to work. As a result, any excess mortality associated with a given occupational exposure is more difficult to detect when the healthy worker effect is operative. The healthy worker effect is likely to be stronger for nonmalignant causes of mortality, which usually produce worker attrition during an earlier career phase, than for malignant causes of mortality, which typically have longer latency periods and occur later in life. In addition, healthier workers may have greater total exposure to occupational hazards than those who leave the workforce at an earlier age because of illness.

Another example of study bias is **confounding**, which denotes “the distortion of a measure of the effect of an exposure on an outcome due to the association of the exposure with other factors that influence the occurrence of the outcome.”¹² Confounding factors are associated with disease risk and produce a different distribution of outcomes in the exposure groups than in the comparison groups. The existence of confounding factors that occur in the exposed group may lead to invalid conclusions from a study.

An example of confounding arises from the possible association between exposure of workers to occupational dusts and development of lung cancer. One of the types of dust encountered in the workplace is silica (e.g., from sand used in sandblasting). In a retrospective cohort study, one might compare the workers’ mortality rates for lung cancer with those of the general population (by using SMRs). Suppose we find that the SMR for lung cancer of workers exposed to silica is greater than 100% (i.e., exceeds the rate of the nonexposed population). One conclusion is that the workers have a higher risk of lung cancer than the nonexposed population. However, the issue of confounding also should be considered: Employees exposed to silica are usually blue-collar workers who, as a rule, have higher smoking rates than the general population (that might be used as a comparison population). When smoking rates are taken into account, the strength of the association between silica exposure and lung cancer is reduced—suggesting that smoking is a confounder that needs to be considered in the association.³¹

LIMITATIONS AND DEFICIENCIES OF ENVIRONMENTAL EPIDEMIOLOGY

According to Buffler, the three major requirements for the successful epidemiologic investigation of environmental exposures are: “(1) direct and accurate estimates of the exposures experienced by individual members of the study population, (2) direct and accurate determination of the disease status of individual members of the study population, and (3) appropriate statistical summarization and analysis of the individual data pertaining to disease and exposure.”¹⁴(p131) To the extent that these requirements are not met, limitations are introduced into epidemiologic studies. Other limiting factors include the long latency periods and infrequent occurrence that characterize many environmentally associated diseases. (Refer to Table 2-5.)

Long Latency Periods

A consideration that limits one’s ability to derive causal inferences from epidemiologic studies is the long **latency** period phenomenon.⁹ The term *latency period* refers to the time

TABLE 2-5 Limitations Faced by Epidemiologists in Studying Relationships between Exposure and Disease Outcomes in Relation to Community Environmental Pollution

Limitations in detecting disease

1. Long and variable latency periods between exposure and disease diagnosis
2. Etiologic nonspecificity of disease clinical features
3. Small population size coupled with low disease frequency
4. Observer bias in reporting illness occurrence

Limitations in measuring exposure

1. Dependence on indirect, surrogate estimates of exposure and dose (distance from pollution site, etc.)
2. Uncertainty regarding pathways of exposure
3. Probable low-dose levels in most settings
4. Frequent inability to develop useful dose–response data

Source: Reprinted with permission from CW Heath Jr. Uses of epidemiologic information in pollution episode management. *Arch Environ Health*. 1988;43:76.

interval between initial exposure to a disease-causing agent (e.g., environmental risk factor or exposure) and the appearance of a disease or its manifestations in the host.¹² Note that the occurrence of disease can be conceptualized in a number of different ways depending on the measure used, such as screening tests and observation of clinical signs and symptoms. Environmentally caused diseases, for example, cancer, have latency periods that span many years. These long latency periods reduce the epidemiologist’s ability to ascertain definitively the outcomes of exposure.⁹ Examples are asbestos-related diseases, which in many cases do not appear until many years after initial exposure.³²

Low Incidence and Prevalence

Another limiting factor of studies concerns the infrequent occurrence of certain diseases that are the target of environmental epidemiologic studies.⁹ An example is the occurrence of childhood cancers, which have been examined in relation to environmental factors such as toxic chemicals.¹¹ The incidence of cancers among children is only one-twentieth that of adults—143.9 per million and 126.9 per million for white males and females aged 0 to 14 years, respectively, and 330.4 and 277.0 per 100,000 white males and females of all ages, respectively. When diseases are uncommon, one’s ability to make precise estimates of exposure–disease associations is reduced. The researcher also may be dependent upon less powerful research designs—descriptive and case-control studies.

Difficulties in Exposure Assessment

Several authorities have stressed the requirement for accurate assessment of exposures in epidemiologic studies of environmental health. Rothman points out that “Atop the list of methodologic problems is the problem of exposure assessment, a problem that extends through all of epidemiologic research but is a towering obstacle in environmental epidemiology.”^{6(p19)} Gardner points out that “Epidemiological methods of investigation are incomplete without good quality exposure data to parallel information on health. The need for monitoring environmental and biological exposure is paramount to the successful interpretation of results and implementation of any required preventive programs.”^{33(p108)}

For high levels of exposures to toxic agents that produce clear and immediate effects, causation is clear-cut.³⁴ Examples are the release of toxic gases in Bhopal, India, in 1984, and the 1986 Chernobyl nuclear reactor disaster in the former Soviet Union. Moreover, although earlier generations of studies led to the control of intense environmental exposures that were strongly correlated with disease outcomes, the focus of contemporary research has shifted. Modern studies examine low levels of exposure that potentially are associated with low levels of risk.¹⁴

Low-level environmental exposures challenge epidemiologic researchers who when dealing with them have difficulty applying standard laboratory methods used to determine exposure levels. Consequently, researchers are unable to establish definitively whether exposure to a particular agent has occurred. In the ambient environment, not only may several exposures be mixed, but also the levels of exposures may be uncertain.³⁴

Examples of exposure measurements used in environmental epidemiology include the following: samples of toxic fumes in a manufacturing plant, ozone readings in the community, and distances of housing tracts from high-tension power lines that emit electromagnetic radiation. All of these measures are prone to error because they are indirect measures of exposure and do not provide direct information on

the amount of exposure that an individual may actually receive.⁶ As noted, a common method for approximating exposure is the use of proxies (substitutes for direct measures). An example of such a measure is the previously noted distance of a housing tract from the source of an environmental hazard. These proxy or surrogate measures are usually too diffuse to establish exposure definitively.

Nonspecific Effects

A specific health outcome is one that is usually associated with a particular exposure, and only that exposure. When an outcome is nonspecific, it can be associated with several or many different environmental exposures. The majority of diseases and conditions thought to be related to environmental exposures are influenced by many factors.³² Consequently, any particular environmental exposure probably will not be associated with a specific outcome. Further complicating the picture of exposure determination is the fact that we are exposed to hundreds of chemicals in the environment; these chemicals often are mixed, clouding our knowledge of the level of exposure that took place. Exposures to any of these chemicals could produce outcomes that are similar to one another.

CONCLUSION

Environmental epidemiology is one of the fields that research fundamental questions regarding the role of environmental exposures in human health. The discipline traces its history from the time of Hippocrates and from early studies of occupational cancer during the late 18th century. Also historically significant were Snow’s investigations of cholera during the mid-19th century. Epidemiology, with its emphasis on observation as well as focus on populations, contributes important methodological tools—particularly with respect to study design.

Several of the key characteristics, weaknesses, and strengths of environmental epidemiology are shown in Table 2-6. One strength is the ability to deal with “real world”

TABLE 2-6 Characteristics, Weaknesses, and Strengths of Environmental Epidemiology

| Characteristics | Weaknesses | Strengths |
|--------------------------------|------------------------------------|---|
| Deals with nondisease effects | Sample size is insufficient | Engages the real world |
| Involves numerous variables | Important variables “uncontrolled” | Unique perspective on disease/health |
| Tends to be community-specific | Exposure estimation invalid | Basis for action despite ignorance of mechanism |

Source: Reprinted with permission from JR Goldsmith. Keynote address: improving the prospects for environmental epidemiology. *Arch Environ Health*. 1988;43:71.

problems, for example community exposure to environmental contaminants; a second strength is the possibility of examining complex problems that involve multiple variables (e.g., exposure, demographic, and outcome variables); a third is the capability to impel environmental action, even though the level of exposure and etiologic mechanisms of health effects have not been ascertained definitively. The weaknesses include the fact that exposure levels in environmental epidemiology studies are difficult to measure precisely; also, there may be many uncontrolled variables that can bias the results.³⁵ In the words of Grandjean, “The quality of environmental epidemiology research can be considered from two perspectives, one representing methodological issues,

the other dealing with the usefulness of the work. These two views are connected, because a study of superior quality is likely to be of greater validity and therefore more useful. Still, an imperfect study can be of great relevance, and epidemiologists must therefore tackle the challenging balance between being an advocate for particular policies and being a skeptical ivory-tower scientist.”^{36(p158)} Nevertheless, these weaknesses do not negate the fact that environmental epidemiology has made, and will continue to make, important contributions to the environmental health field. For more information about epidemiology, consult Friis and Sellers² or one of the other introductory texts that is available.



Study Questions and Exercises

1. Define the following terms:
 - a. Epidemiology
 - b. Environmental epidemiology
 - c. Descriptive epidemiology
 - d. Natural experiments
 - e. Prevalence
 - f. Incidence
 - g. Case fatality rate
 - h. Odds ratio
 - i. Relative risk
2. What is meant by a cause in environmental epidemiology? Apply Hill's criteria of causality to an example of an association between a specific environmental exposure and health outcome.
3. Explain the reason why studies of the health effects of smoking among individuals who smoke would not be a concern of environmental epidemiology. Explain the reason why exposure to secondhand cigarette smoke is a concern of this discipline.
4. Define the following terms and discuss how each affects the validity of epidemiologic study designs:
 - a. Bias
 - b. Confounding
 - c. Latency period
 - d. Exposure assessment
5. List the reasons why epidemiology is important to research studies of environmental health. What are some of the important limitations of the epidemiologic approach with respect to the study of environmental health problems?
6. Explain why epidemiology sometimes is called "population medicine." State how epidemiology contrasts with clinical medicine.
7. Explain the difference between descriptive and analytic epidemiology. Give examples of how both types of study design are utilized in the field of environmental health.
8. What does early epidemiology (e.g., Hippocrates) share in common with contemporary epidemiology in terms of examining the causality of health problems?
9. Describe the importance of the contributions of Sir Percival Pott to environmental health, particularly in the area of cancer prevention.
10. Explain the work of John Snow using the methodology of the natural experiment.
11. Name the study designs that are used for hypothesis testing and those that are used for generating hypotheses.
12. Explain why most studies conducted in the field of environmental epidemiology are nonexperimental.
13. Explain how ecologic analysis is used to study the health effects of air pollution. Give examples of uncontrolled factors that may affect ecologic study results.
14. Explain why cross-sectional studies are defined as prevalence studies. Give an example of a cross-sectional study.
15. Explain why cohort studies are an improvement over case-control studies with respect to measurement of exposure data.

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