2
Causal Concepts

2.1 Natural History Of Disease

Stages of Disease

The **natural history of disease** refers to the progression of a disease in an individual over time. This includes relevant phenomena from before initiation of the disease (the **stage of susceptibility**) until its resolution.

Figure 2.1 is a schematic of the stages of disease. In the period following exposure to the causal factor, the individual enters a **stage of subclinical disease** (also called the **preclinical phase**). For infectious agents, this corresponds to the **incubation period** during which the agent multiplies within the body but has not yet produced discernible signs or symptoms. For noninfectious diseases, this corresponds to the **induction period** between a causal action and disease initiation.

The **stage of clinical disease** begins with a patient's first symptoms and ends with resolution of the disease. Be aware that the onset of symptoms marks the beginning of this stage, not the time of diagnosis. The time-lag between the onset of symptoms and diagnosis of disease can be considerable. **Resolution** of the disease may come by means of recovery or death. When recovery is incomplete the individual may be left with a disability.

Figure 2.1. *Stages in the natural history of disease and levels of prevention.* [Figure0201.eps]

Incubation periods of infectious diseases vary considerably. Some infectious diseases are

characterized by short incubation periods (e.g., cholera has a brief 24- to 48-hour incubation period). Others are characterized by intermediate incubation periods (e.g., chickenpox has a typical incubation period of 2 to 3 weeks). Still others are characterized by extended incubation periods (e.g., the median incubation period of acquired immunodeficiency syndrome (AIDS) is often measured in decades). Table 2.1 lists incubation periods for selected infectious diseases. Note that even for a given infectious disease, the incubation period may vary considerably. For example, the incubation period for human immunodeficiency virus (HIV) and AIDS ranges from 3 to more than 20 years.

TABLE 2.1. Incubation Periods for Selected infectious Diseases

Disease	Typical Incubation Period
Acquired immune deficiency syndrome	Infection to appearance of antibodies: 1–3 months; median time to diagnosis: approx. 10 years; treatment lengthens the incubation period
Amebiasis	2–4 weeks
Chickenpox	13–17 days
Common cold	2 days
Hepatitis B	60–90 days
Influenza	1–5 days
Legionellosis	5–6 days
Malaria (*Plasmodium vivax and P. ovale*)	14 days
Malaria (*P. malariae*)	30 days
Malaria (*P. falciparum*)	12 days
Measles	7–18 days
Mumps	12–25 days
Poliomyelitis, acute paralytic	7–14 days
Plague	2–6 days
Rabies	2–8 weeks (depends on severity of wound)
Salmonellosis	12–36 hours
Schistosomiasis	2–6 weeks
Staphylococcal food poisoning	2–4 hours
Tetanus	3–21 days

Source: Benensen (1990).

Induction periods for noninfectious disease exhibit a range as well. For example, the induction period for leukemia following exposure to fallout from the atomic bomb blast in Hiroshima ranged from 2 to more than 12 years (Cobb et al., 1959). As another example, Figure 2.2 illustrates the empirical induction periods for bladder tumors in industrial dyestuff workers (Case et al., 1954). Variability in incubation is due to differences in host resistance, pathogenicity of the agent, the exposure dose, and the prevalence and availability of cofactors responsible for disease.

Figure 2.2. *Number of years after starting work and onset of urinary bladder tumors in industrial dyestuff workers (Case et al., 1954).* [Figure0202.eps]

Understanding the natural history of a disease is essential when studying its epidemiology. For example, the epidemiology of HIV/AIDS can only be understood after identifying its multifarious stages (Fig. 2.3). Exposure to HIV is followed by an acute response that may be accompanied by unrecognized flulike symptoms. During this acute viremic phase, prospective cases do not exhibit detectable antibodies in their serum, yet may still transmit the agent. During a lengthy induction, CD4+ lymphocyte counts decline while the patient is still be free from symptoms. The risk of developing AIDS is low during these initial years, but increases over time as the immune response is progressively destroyed, after which AIDS then may express itself in different forms (e.g., opportunistic infections, encephalitis, Kaposi's sarcoma, dementia, wasting syndrome).

Figure 2.3. *Natural history and progression of HIV / AIDS (Cotton, 1995).* [Figure0203.eps]

A slightly more sophisticated view of the natural history of disease divides the subclinical stage of disease into an induction period and a latent period (Figure 2.4). **Induction** occurs in the interval between the causal action up until the point at which disease occurrence becomes inevitable. A **latent period** follows after disease becomes inevitable but before clinical signs arise. During this latent phase, various causal factors may promote or retard the progression of disease. The induction and promotion stages combined are referred to as the **empirical induction period** (Rothman, 1981).

Figure 2.4. *Induction period, latent period, and empirical induction period.* [Figure0204.eps]

Stages of Prevention

Disease prevention efforts are classified according to the stage of disease at which they occur (Fig. 2.1). **Primary prevention** is directed toward the stage of susceptibility. The goal of primary prevention is to prevent the disease from occurring in the first place. Examples of primary prevention include needle-exchange programs to prevent the spread of HIV, vaccination programs, and smoking prevention programs.

Secondary prevention is directed toward the subclinical stage of disease, after which the individual is exposed to the causal factor. That goal of secondary prevention is to prevent the disease from emerging or delay its emergence by extending the induction period. It also aims to reduce the severity of the disease once it emerges. Treating asymptomatic HIV-positive patients with antiretroviral agents to delay the onset of AIDS is a form of secondary prevention.

Tertiary prevention is directed toward the clinical stage of disease. The aim of tertiary prevention is to prevent or minimize the progression of the disease or its sequelae. For example, screening and treating diabetics for diabetic retinopathy to avert progression to blindness is a form of tertiary prevention.

2.2 Variability In The Expression Of Disease

Spectrum of Disease

Diseases often display a broad range of manifestations and severities. This is referred to as the **spectrum of disease**. Both infectious and noninfectious diseases exhibit spectrums. When

considering infectious diseases, there is a **gradient of infection**. As an example, HIV infection ranges from inapparent, to mild (e.g., AIDS-related complex), to severe (e.g., wasting syndrome). As another example, coronary artery disease exists in various forms of severity, from asymptomatic atherosclerosis, to transient myocardial ischemia, to myocardial infarction and death.

The Epidemiologic Iceberg

Like an iceberg, the bulk of a health problem in a population may be hidden from view. This has been referred to as the **epidemiologic iceberg** (Last, 1963). This phenomenon applies to chronic diseases, infectious diseases, and all other forms of ill-health. Uncovering disease that might otherwise be "below sea level" by screening and better detection often allows for better control of health problems. Consider that for every successful suicide attempt there are dozens of unsuccessful attempts and a still larger number of people with depressive illness that might be severe enough to have them wish to end their lives. With appropriate treatment, individuals with suicidal tendencies would be less likely to have suicidal ideation and be less likely to attempt suicide. As another example: reported cases of AIDS represents only the tip of HIV infections. With proper antiretroviral therapy, clinical illness may be delayed and transmission averted.

Dog bite injuries provides another example. In the early 1992 and 1994, there were 20 deaths due to dog bites annually. However, if we had relied solely on death certificate information, many additional serious dog bite injuries would have gone undetected. For each fatal dog bite there were 670 dog bite hospitalizations, 16,000 emergency department visits for dog bites, 21,000 medical visits to other clinics, and 187,000 nontreated bites (Weiss et al., 1998; Fig. 2.5). With recognition of this problem, more effective animal control and surveillance programs can be put into place to prevent future dog bite injuries.

Figure 2.5. *Epidemiologic iceberg: annual number of dog bite injuries in the United States, 1992 – 1994. (Based on Weiss et al., 1998.)* [Figure0205.eps]

2.3 Causal Concepts

Definition of Cause

Effective disease control and prevention depends on understanding the causes of the illness. In general terms, a **cause** is something that produces an effect or brings about a result. At a deeper level, a cause is

> . . . an object, followed by another, and where all the objects similar to the first are followed by objects similar to the second. Or in other words where, if the first object had not been, the second never had existed. (Hume, 1772, Section VII)

This statement has two essential elements. First, the *cause* must precede its effect. Second, the effect would not have occurred if the *cause* did not precede it, all other things being equal ("where all the objects similar to the first"). This definition is **counterfactual**, because it is an idea that can not be proven in fact. The counterfactual causal argument goes something like this: "if the person who developed disease *Y* had not been exposed to factor *X*, then disease *Y* would not have occurred. Therefore, *X* is a cause."

In addition, the modern definition of cause incorporates an important element of time:

> A cause of a disease event is an event, condition or characteristic that preceded a disease without which the disease event either would not have occurred at all or would not have occurred until some later time. (Rothman & Greenland, 1998, p. 8)

On a population basis, we expect that an increase in the level of a causal factor in inhabitants will be accompanied by an increase in the incidence of disease in that population, *caeteris parabus* (all other things being equal). We also expect that if the causal factor can be eliminated or diminished, the frequency of disease or its severity will decline.

Component Cause (Causal Pies)

Most diseases are caused by the cumulative effect of multiple causal components acting ("interacting") together. Thus, a **causal interaction** occurs when two or causal factors act together to bring about an effect. Causal interactions applies to both infectious and noninfectious diseases and explains, for example, why two people exposed to the same cold virus will not necessarily experience the same outcome: one person may develop a cold while the other person may experience no ill effects.

Rothman's (1976) causal pies helps clarify the contribution of causal components in disease etiology. Figure 2.6 displays two causal mechanism for a disease. Let us assume these are the only two mechanisms that cause this ailment. Wedges of each pie represent components of each causal mechanism, corresponding to risk factors we hope to identify and diminish in the population. Each pie represents a **sufficient causal mechanism**, defined as a set of factors that in combination makes disease occurrence inevitable. Each casual component (wedge) plays an essential role in a given causal mechanism (pie), and a specific disease may result from a number of different causal mechanisms.

A cause is said to be **necessary** when it is a component cause member of every sufficient mechanism. In other words, the component cause is necessary if the disease cannot occur in its absence. (In Figure 2.6, Component *A* is a necessary cause, since it is evident in both possible disease mechanisms, and the disease cannot occur in its absence.) For example, the tubercular bacillus *Mycobacterium tuberculosis* is a necessary cause of tuberculosis. However, it is not sufficient by itself to cause disease: it is common for a person to harbor the *Mycobacterium* in their body while remaining disease-free. Some individuals are not susceptible to tuberculosis; they are resistant. In addition, there are complementary factor that encourage disease to manifest. Examples of complementary factors for the manifestation of tuberculosis, for instance, include familial exposure, immunosuppression, genetic susceptibility, poor nutrition, overcrowding, and high environmental loads of the agent.

Causal components that do not occur in every sufficient mechanism yet are still essential for some of the causal mechanisms are said to be **contributing component causes**. For example, cigarette smoking is a contributing but not necessary cause of lung cancer, since it contributes to the cause of the (vast majority) lung cancer, but is not necessary in every case. (Approximately 5 to 10% of lung cancer cases occur in non-smokers). Likewise, high serum cholesterol, while neither necessary nor sufficient as a cause of coronary heart disease, is an indispensable component of many such causal processes. In Figure 2.6, *B*, *C*, and *D* are nonnecessary

contributing causal components.

Figure 2.6. *Two causal mechanisms.* [Figure0206.eps]

Component causes that completes a given causal mechanism (pie) are said to be **causal complements**. In Figure 2.6, for example, the causal complements of factor *A* in Mechanism 1 is (*B* + *C*). In mechanism 2, the causal complement of factor *A* is *D*. Factors that work together to form sufficient causal mechanism are said to **interact causally**.[1]

Causal interactions have direct health relevance. For example, when a person develops an infectious disease, the causal agent must interact with the causal complement known as "susceptibility" to cause the disease. When considering hip fractures in elderly patients, the necessary element of trauma interacts with the causal complement of osteoporosis to cause the hip fracture. In similar veins, smoking interacts with genetic susceptibility and other environmental factors in causing lung cancer, and dietary excesses interact with lack of exercise, genetic susceptibility, atherosclerosis and various clotting factors to cause a heart attacks. Causal factors rarely act alone.

Causal pies demonstrate that **individual risk** is an all-or-none phenomenon. In a given individual, either a causal mechanism is or is not completed. This makes it impossible to directly estimate individual risk. In contrast, the notion of **average risk** is a different matter. Average risk can be estimated directly as the proportion of individuals regarded as a member of a recognizable group the develops a particular condition. For example, if one in ten smokers develop lung cancer over their lifetime, we can say that this population has a lifetime risk for this outcome of one in ten.

The effects of a given cause in a population depend on the **prevalence of causal complements** in that population. The effect of phenylketanines, for instance, depends not only on the prevalence of an inborn error of metabolism marked by the absence of phenylalanine hydroxylase, but depends also on the environmental prevalence of foods high in phenylalanine. Similarly, the effects of falls in the elderly depends not only on the opportunity for falling, but also on the prevalence of osteoporosis. The population-wide effects of a pathological factor cannot be predicted without knowledge of the prevalence of its causal complements in the population.

Hogben's (1933) example of **yellow shank disease in chickens** provides an memorable example of how population effects of a given causal agent cannot be separated from the prevalence of its causal complements. The trait of yellow shank in poultry is a condition expressed only in certain genetic strains of fowl when fed yellow corn. A farmer with a susceptible flock who switches from white corn to yellow corn will perceive the disease to due to caused by yellow corn. A farmer who feeds only yellow corn to a flock with multiple strains of chickens, some of which are susceptible to the yellow shank condition, will perceive the condition to be caused by genetics. In fact, the effects of yellow corn cannot be separated from the genetic makeup of the flock, and the effect of the genetic makeup of the flock cannot be separated from the presence of

[1] The concept of a *causal* interaction is not to be confused with that of a *statistical* interaction, despite the similarity of these terms.

yellow corn in the environment. To ask whether yellow shank disease is environmental or genetic is like asking whether the sound of a faraway drum is caused by the drum or the drummer—one does not act without the other. This what we mean by *causal interaction*.

Causal Web

The **causal web** is a metaphor that emphasizes the interconnectedness of direct and indirect cause of disease and ill-health. **Direct causes** are proximal to the pathogenic mechanism. **Indirect causes** are distal or "upstream" from the disease causing mechanism. Figure 2.7 depicts the well-established causal web for myocardial infarction (heart attack). The direct cause (pathogenic mechanism) of myocardial infarction is coronary artery blockage and subsequent death of the heart muscle. This model starts upstream from this direct cause by considering social and environmental factors that lead to hyperlipidemia, obesity, a sedentary lifestyle, arteriosclerosis, coronary stenosis, etc., ultimately leading to the coronary blockage.

Figure 2.7. *Causal-web model for myocardial infarction.* [Figure0207.eps]

Levels of cause in a causal web may be classified as:

- **Macro-level** (indirect cause: social, economic, and cultural determinants)
- **Individual-level** (intermediate cause: personal, behavioral, and physiological determinants)
- **Micro-level** (direct cause: organ system, tissue, cellular, and molecular determinants)

Consider, for example, the cause of early childhood mortality in non-industrialized countries. In this example, the macrolevel encompasses broad social, economic, and cultural conditions that lead to a paucity of food, shelter, and sanitation. Individual-level causes include child-care practices that expose children to pathogens, malnutrition, and dehydration. Microlevel causes include the immediate pathophysiologic interaction between malnutrition and the pathogenic respiratory and gastrointestinal agents that ultimately lead to death (Millard, 1994).

The relative contribution of various levels of cause in epidemiology and public health have been the subject of considerable and sometimes contentious debate, with advocates for each level of claiming particular and profound benefits for their way of addressing problems. In practice, however, advocating one or another level may hinder achieving the most practical solution for preventing a given disease. Maintaining fragmented methods of research into the various levels of cause can only obstruct our understanding and ultimately delay effective prevention measures (Savitz, 1997).

Agent, Host, and Environment

Causal components can be classified as agent, host, or environmental factors (Fig. 2.8). **Agents** are biological, physical, and chemical factors whose presence, absence, or relative amount (too much or too little) are necessary for disease to occur (Table 2.2). **Host factors** include personal characteristics and behaviors, genetic predispositions, and immunologic and other susceptibility-related factors that influence the likelihood or severity of disease. Host factors can be physiological, anatomical, genetic, behavioral, occupational, or constitutional. **Environmental**

factors are external conditions other than the agent that contribute to the disease process. Environmental factors can be physical, biologic, social, economic, or political in nature.

Figure 2.8. *Agent, host, and environment triad.* [Figure0208.eps]

TABLE 2.2. Types of Disease-Causing Agents

Biological	Chemical	Physical
Helminths (parasitic worms)	Nutritive (deficiencies and excesses)	Heat
Protozoan		Light
Fungi	Poisons	Radiation
Bacteria	Drugs	Noise
Rickettsia	Allergens	Vibration
Viral		Objects
Prion		

The **sexual transmission of HIV** in a population can be viewed in terms of agent, host, and environmental determinants (Fig. 2.9). Agent factors that influence HIV transmission include the prevalence of the agent in the environment and the phenotype of the agent. Examples of host factors include the coexistence of reproductive tract infections (especially genital ulcers), availability of antiretroviral therapies that decrease the HIV load in the population, sexual behaviors, and contraceptive methods. Environmental factors include the rate of sexual partner exchange, presence of unregulated commercial sex facilities, presence of "crack houses," sexual norms, and so on (Royce et al., 1997).

Figure 2.9. *Agent, host, and environmental factors associated with the sexual transmission of HIV.* [Figure0209.eps]

Over time, an **epidemiologic homeostasis** may form as agent, host, and environmental factors reach equilibrium. Thus, an **ecology of disease** is formed. When an element contributing to the epidemiologic equilibrium is disturbed, the population may experience an increase or decrease in disease occurrence. For example, an epidemic may arise from any of the following:

- Introduction of a new agent into the population
- Increases in the ability of an agent to survive in the environment
- Increases in an agent's ability to infect the host (**infectivity**)
- Increases in the ability of the agent to cause disease once inside the host (**pathogenicity**)
- Increases in the severity of the disease caused by the agent once it has established itself in the host (**virulence**)
- Increases in the proportion of susceptibles in the population
- Environmental changes that favor growth
- Environmental changes that favor transmission of the agent
- Environmental changes that compromise host resistance

Causal forces can strengthen, weaken, or cancel-out each other, tipping the epidemiologic balance in favor of the host or in favor of the disease causing agent (Figure 2.10).

Figure 2.10. *Agent, host, and environmental homeostasis and imbalance.* [Figure0211.eps]

Homeostatic principals of agent, host, and environmental balance apply to infectious and noninfectious agents alike. As an example, consider the ecologic balance between agent, host,

and environmental factors associated with **sulfur oxide air pollution and morbidity** (U.S. Department of Health, Education, and Welfare, 1967). In this example, high atmospheric levels of sulfur oxide pollution are traced to industrial pollution. Meteorologic conditions (e.g., climatic inversions) that favor retention of pollutants in the ecosphere have demonstrable effects on increasing morbidity and mortality, with the adverse effects of pollution concentrated in individuals with pre-existing cardiac and respiratory disease (Munn, 1970, p. 95). Thus, morbidity and mortality are linked to interdependencies between agent (e.g., sulfur dioxide pollution), host (compromised cardiopulmonary function), and environmental (meteorologic) conditions.

2.4 Causal Inference

The measures which are intended to prevent disease should be founded on a correct knowledge of its cause. For want of this knowledge, the efforts which have been made to oppose cholera have often had a contrary effect.— John Snow (1855, p. 136)

Introduction

Causal inference is the process of deriving cause-and-effect conclusions by reasoning from knowledge and factual evidence. Before delving into specific methods of inference, it will be helpful to keep in mind that epidemiologic concepts of cause are neither simple nor singular. Rarely do causes act alone! Instead, multiple causes act together, and every cause is viewed in relation to its causal complements.

It is also helpful to acknowledge that there is no such thing as ultimate proof in empirical sciences (and epidemiology is indeed an empirical science). “A statement in natural science can be made strong or even overwhelming... It is doubtful, however, if such proportions can ever be regarded as proved.” (Cornfield, 1954, p. 19). Thus, causal inferences in epidemiology require an enormous amount of skill. Studies need to isolate various influences, and alternative explanations must be advanced and tested, all while bringing together various lines of evidence. No mechanical rules can be laid down. Delicate judgments are required. There is ample opportunity for error, and much room for legitimate disagreement. Although this is not an easy process, it must be recognized that most of what we know about human health and disease comes from observations of human conditions.

Types of Decisions

The goal of causal inference is to create a framework for taking action in the face of varying levels of uncertainty. In adopting a pragmatic framework, it is helpful to distinguish between two types of decisions: (a) those having to do with scientific hypotheses and (b) those requiring immediate action. These two processes differ. Inferences about scientific hypotheses are intentionally skeptical with alternative explanations and theories raised without restriction, even after reaching tentative conclusions. In contrast to the stringent level of skepticism required to address scientific hypotheses, public health and regulatory decisions cannot always afford the luxury of unrestrained scientific skepticism. A framework for making choices with the best evidence currently at hand is occasionally required, for to decide not to make a decision may itself represent a costly choice.

Wynder (1994) notes that discoveries of many preventive measures predate discoveries of the mechanisms responsible for disease, often by many years (Table 2.3). In the same vein, there is evidence that the "war on cancer" initiated in the last quarter of the 20th century had been misdirected toward understanding carcinogenic mechanisms and discovering new treatments, when in fact applied preventive research might have met with better results (Bailar & Gornick, 1997). Thus, a utilitarian perspective provides for two complementary types of inference: those having to do with activities requiring immediate attention, and those having to do with scientific knowledge. Both processes must remain open to self-correction, although the former is more lenient in allowing for tentative connclusions based on incomplete understandings.

TABLE 2.3. Discovery Dates of a Measure to Prevent a Disease Compared with the Date of Identification of the Causative or Preventive Agent

Disease	Discoverer Of Preventive Measure	Year of Discovery of Preventive Measure	Year of Discovery of Agent	Causative Agent	Discoverer of Agent
Scurvy	J. Lind	1753	1928	Ascorbic acid deficiency	A. Szent-Gyorgi
Pellagra	G. Casal	1755	1924	Niacin deficiency	J. Goldberger
Scrotal cancer	P. Pott	1755	1933	Benzo[a]pyrene (chimney soot)	J. W. Cook
Smallpox	E. Jenner	1798	1958	*Orthopoxvirus*	F. Fenner
Puerperal fever	J. Semmelweis	1847	1879	*Streptococcus*	L. Pasteur
Cholera	J. Snow	1849	1893	*Vibrio cholerae*	R. Koch
Bladder cancer	L. Rehn	1895	1938	2-Napththylamine (aniline dye)	W. C. Harper
Yellow fever	W. Reed et al.	1901	1928	*Flavivirus*	A. Stokes
Oral Cancer	A. Abbe	1915	1974	N′-nitrosonornicotine (chewing tobacco)	D. Hoffmann

Source: Wynder (1994, p. 548).

Philosophical Considerations (Optional)

Although a detailed discussion of the doctrines involved in scientific lines of inquiry are beyond the scope of this text, two key points will be emphasized. These are:

1. Scientists rely on the same method of reasoning common to all types of problem solving.

2. Induction and refutation have roles in epidemiologic practice.

1. Scientists Rely on the Same Method of Reasoning Common to All Types of Problem Solving. Although one may hear mention of "the scientific method," it is not a method in the usual sense, since there are no orderly procedures and no rules of progression. Scientists rely on the same types of reasoning common to all types of problem solving. "Scientific knowledge can

only be an extension of common-sense knowledge" (Popper, 1959, p. xxi); "the scientific method, as far as it is a method, is nothing more than doing one's damnedest with one's mind, no holds barred" (Bridgeman cited in Wallis & Roberts, 1962, p. 13). Astronomer Carl Sagan (1996) advises: "We should not imagine that science is something erudite ...The keypoint of science is criticism, debate, open inquiry, the willingness to systematize knowledge, to withhold belief until the evidence is compelling, and to listen seriously to criticism." Einstein said, "if you want to know the essence of the scientific method, don't listen to what a scientist may tell you, watch what he does." In the end, "science is only the Latin word meaning 'knowledge'."

As a first-level introduction to problem solving, let's identify the following tools used during inquiry:

- **Observation**, in which the investigator observes what is happening, collects information, and studies facts relevant to the problem.
- **Hypothesis**, in which the investigator puts forth educated hunches or explanations for observed findings and facts.
- **Prediction**, in which anticipatory deductions based on hypotheses are put forward in testable ways.
- **Verification**, in which data are collected to test predictions.

Using these tools, inferences are established and tested as part of a continual and evolving process. As conclusions unfold, they are reinforced through replication.

2. Induction and Refutation Have Roles in Epidemiology. Induction is the process of inferring a general law or principle from particular observations. **Refutation** is the process of putting forward and critically testing hypotheses through a process of falsification. Brief descriptions of induction and refutation follow.

Induction seeks to uncover the "fabric of nature" through observation of facts. The underling assumption of induction is that phenomena that fall into regular patterns suggest more general statements about nature. The physicist and curious character Richard Feynman compared this process to watching a chess match without knowledge of the rules (Glashow, 1999):

> We can imagine that this complicated array of moving things that constitute the world is something like a great chess game played by the gods, and that we are observers of the game. We do not know what the rules of the game are; all we are allowed to do is to watch the playing. Of course, if we watch long enough, we may eventually catch onto a few of the rules. The rules of the game are what we mean by fundamental [laws of nature].

Induction, however, is highly prone to error, however, because the sequences of past events is no guarantor of future occurrences. This is called The Problem of Induction. The philosopher Bertrand Russell explained the Problem of Induction in this memorable way:

> The man who has fed the chicken every day throughout its life at last wrings its neck instead, showing that more refined views as to the uniformity of nature would have been useful to the chicken.

The more formal argument was made by **David Hume** when he wrote "even after the observation of the frequent or constant conjunction of objects, we have no reason to draw any inference concerning any object beyond those of which we have had experience" (1739–40, Book I, Part III, Section XII).

The Problem of Induction is related to the logical fallacy of *post hoc ergo propter hoc* (Latin for "after this therefore on account of this"). In a strictly logical sense, there is no reason to believe that what had been observed in the past will continue to occur in the future.

In recognizing the Problem of Induction, the influential 20th-century philosopher Karl Popper (1902–1994) placed central importance on the scientific doctrine of refutation. In contrast to induction, refutation explicates the "disproving" of hypothetical statements as an essential component of scientific inference. Popper noted that statements about nature could not be proved in the affirmative but could be refuted through rigorous attempts to disprove falsifiable statements. By this method, failure to refute a hypothesis provides the best possible support of its verity. Because the absence of disproof is a demonstration of support for a hypothesis, the value of a given hypothesis depends on the degree to which it is "disprovable." ('It has been said that a theory is scientific if it is falsifiable.') As the fictitious character Sherlock Holmes may have once remarked, "when you have eliminated the impossible, whatever remains, however improbable, must be the truth."

The basis of scientific falsification has been explained as follows. Suppose two professors observe a flock of white swans around a campus pond. Being thoughtful academic types, they begin to wonder about the color of swans. The non-refutationist induces that all swans are white, this being the basis of all previous observations. In contrast, the refutationist notes the observation and goes in search of non-white swans. If he finds one non-white swan, the white swan hypothesis is revoked. Thus, there is a fundamental asymmetry of proof. No number of observations of white swans proves "the white swan theory," whereas a strong refutation can disprove it.

While Popper's philosophy has had enormous practical benefits, it has at times been misapplied (Susser, 1988). The absence of disproof is not proof, and like induction, falsification is limited by the senses. As might happen when a scientist returns with what is believed to be a nonwhite swan, he is often met with the response "That's not a swan!" Even Popper recognized the limitations of his system of logic in the practice of science, admitting "probability statements are ...in some sense verifiable..." (Susser, 1988, p. 193).

Thus,

> The true spirit of science is positive. The building of theory is art; it depends on imaginative synthesis, most often by inductive sifting, sometimes by a leap of the mind. The execution of tests (either falsification or verification) is craft; it depends on ingenuity and technique. The refutation of the theory of spontaneous generation was sealed by Louis Pasteur's verification of the positive role bacteria in fermentation (1862). Much earlier Spallanzini, and the Schulze, Schwann and others, had refuted the theory when they showed that under controlled conditions fermentation did not occur. Falsification was less successful here than verification because supporters of the theory could advance an endless series of alternative explanations. It is Pasteur's work that is remembered... (Susser, 1988, pp. 195–196).

Report Of The Advisory Committee To The U.S. Surgeon General, 1964

Important debates over how best to infer causality from epidemiologic data intensified in the period following World War II. Many of these debates centered around the role of cigarettes in the development of lung cancer. In 1964, the Surgeon General of the United States convened a panel of scientists to advise him on this issue. This panel wrote a landmark report that established standards to address this and other issues related to the use of epidemiologic data

(U.S. Department of Health, Education, and Welfare, 1964). Acceptance of these standards and constructs has provided a framework for epidemiologic debates ever since. Some of the key constructs established by this report are:

- When coupled with [clinical, pathological, and experimental] data, results from the epidemiologic studies can provide the basis upon which judgments of causality may be made.
- In carrying out studies through the use of this epidemiologic method, many factors, variables, and results of investigations must be considered to determine first whether an association actually exists between an attribute or agent and disease.
- If it [is] shown that an association exists, then the question is asked: "Does the association have a causal significance?"
- Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability.
- To judge or evaluate causal significance... a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment. These criteria include:
    a. The consistency of the association
    b. The strength of the association
    c. The specificity of the association
    d. The temporal relationship of the association
    e. The coherence of the association

Today, many of these points may seem tepid. At the time, however, they provided an important link in helping to change the way in which the world thought about nonexperimental epidemiologic data. Although the above causal criteria were not a de novo innovation of the committee, having been developed gradually over time by many different epidemiologists and scientists, the value of these criteria of judgment cannot be overlooked (Wynder, 1997). The criteria first propounded by the Surgeon General's Advisory Committee on Smoking and Health were later expanded and refined by British scientist A. Bradford Hill in a classic 1965 work (Hamill, 1997). These criteria are briefly discussed in the section that follows.

Hill's Framework

In 1965, Sir Bradford Hill wrote a landmark article the presented a framework for considering whether observed associations may be considered evidence of cause. In this framework, Hill addressed 9 factors to consider when weighing the observed association. There are:

Consideration 1 (**strength**) holds that strong associations provide firmer evidence of causality than do weak ones, and that the most direct measure of the strength of an association is found in the form of the ratio of two incidences in the form of a risk ratio or its equivalent. According to this consideration, the larger the risk ratio, the stronger the evidence for causality. Hill (1965) explains it this way:

> To take a more modern and more general example upon which I have now reflected for over fifteen years,

> prospective inquiries into smoking have shown that the death rate from cancer of the lung in cigarette smokers is nine to ten times the rate in non-smokers and the rate in heavy cigarette smokers is twenty to thirty times as great. On the other hand the death rate from coronary thrombosis in smokers is not more than twice, possibly less, the death rate in non-smokers. Though there is good evidence to support causation it is surely much easier in this case to think of some features of life that may go hand-in-hand with smoking—features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of experience, nature of diet or other factors. But to explain the pronounced excess in cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such feature should be easily detectable. If we cannot detect it or reasonably infer a specific one, then in such circumstances I think we are reasonably entitled to reject the vague contention of the armchair critic 'you can't provide it, there may be such a feature. (pp. 295–296)

The basis of the "strength" recommendation lies is the difficulty in "explaining away" a strong association as compared to a weak one. To explain a strong association as artifactual, an undiscovered risk factor (confounder) with an association at least as strong as the proposed risk factor would have to exist. Overlooking such a risk factor would be unlikely when dealing with a large elevation in risk, especially if the disease was well understood. In contrast, explaining a small association in terms of confounding factors is more conceivable.

Hill (1965) is quick to point out that the converse argument—that weak associations provide evidence that the association is noncausal—is untrue. As he puts it:

> We must not be too ready to dismiss a cause-and-effect hypothesis merely on the grounds that the observed association appears slight. There are many occasions in medicine when this is in truth so. (p. 296)

Consideration 2 (**consistency**) suggests that it is important to show consistent findings in studies using diverse methods of study in different populations under a variety of circumstances. The greater the number of consistent studies, the stronger the causal evidence. For example, the data in 2.3 demonstrate highly consistent results between seven early cohort studies on smoking and lung cancer mortality. Note, however that consistency alone does not necessarily prove causation if, in fact, the consistent studies suffer from similar biases.

TABLE 2.3. Cohort Studies of Smoking and Lung Cancer Mortality

Authors	Doll & Hill (1856)	Hammond & Horn (1958)	Dorn (1958, 1959)	Dunn et al. (1960)	Dunn et al. (1964)	Best et al. (1961)	Hammond (1964)
Cohorts	British doctors	White men in nine state	U.S. Veterans	California occupational groups	California American Legion members	Canadian pensioners and dependents	Men in 25 states
Number of people	34,000	188,000	248,000	67,000	60,000	78,000+	448,000
Age range	35–75+	50–59	30–75+	35–69	35–75+	35–75+	35–89
Months followed	120	44	78	About 48	About 24	72	About 22
Lung cancer deaths in	129	448	535	139	98	221	414

study							
Lung cancer deaths, nonsmokers	3	25	56	3	12	8	16
Current Cigarettes Smoked per Day	Standardized Mortality Ratios (Lung Cancer)						
None	Referent	Referent	Referent	Referent	Referent	Referent	Referent
<10	4.4	5.8	5.2	(5)[a] 8.3	(≤20)[a] 4.2	8.4	
10–20	10.8	7.3	9.4	(10)[a] 9.0		13.5	(current smoker)a
21–39		15.9	18.1	(20)[a] 19.4			
	(21+)[a] 43.7			(30)[a] 25.1	(20+)[a] 7.4	15.1	9.6
40+		24.7	23.3	(40)[a] 28.7			

Source: U.S. Department of Health, Education, and Welfare (1964, pp. 83, 164).
[a]Indicates daily number of cigarettes smoked in which classes have been split or combined.

Consideration 3 (**specificity**) holds that a causal factor that leads to a particular outcome provides stronger evidence than one that is connected to many. This criterion, however, should not be over-emphasized, noting that specificity is difficult to establish without complete biological knowledge. For example, smoking's propensity to contribute to many outcomes (cardiovascular disease, cancer, chronic lung disease, musculoskeletal disease, neurologic disease) cannot be used as an argument against its causal contribution to each, when in fact, there are specific biological mechanism for each effect. Hill uses the example of milk being a non-specific cause of scarlet fever, diphtheria, tuberculosis, undulant fever, sore throat, dysentery and typhoid fever, acting as a vehicle for each specific bacterial agent.

Consideration 4 (**temporality**) requires that exposure to the causal factor precede the onset of disease. The importance of this may seem self-evident, but its demonstration is not always clear-cut. The problem in sorting out the proper temporal sequence of events is especially troublesome when studying conditions with long latency and insidious clinical onset. Consider the association between lead ingestion in children and impaired neuropsychological development. Lead encephalopathy is a clinical syndrome caused by ingestion of lead. It is a significant cause of preventable neurological illness, with the greatest risk in young children exposed to decaying fragments of lead-based paint. However, even though lead is a relatively common environmental contaminant capable of producing neurologic disease in humans, why some children seem susceptible to lead encephalopathy while others are not is unclear. It is plausible that children with behavioral problems and pica (a depraved or perverted appetite manifested by a hunger for substances not fit for consumption) are more likely to ingest lead-based paints. Pica is also associated with lower socioeconomic status and deficient care-giving, and this, too, can explain the association. Thus, the uncertain and insidious onset of encephalitic symptoms and the complex interrelationship among environmental contamination with lead, pica, socioeconomic status, and behavioral disorders in children make it difficult to sort out the correct temporal relationships among these factors (Fig. 2.11).

Figure 2.11. *Possible temporal sequences that could explain the association between lead encephalopathy and impaired psychological development in children.* [Figure0211.eps]

Consideration 5 (**biologic gradient**) holds that an increase in the level, intensity, duration, or total exposure to an agent leads to progressive increases in risk. This is in keeping with the general toxicologic principle of quantal dose–response relationships in populations. In a quantal dose–response relationship, the percentage of the population affected increases as the dose is raised. In an epidemiologic dose–response relationship, the incidence of disease increases as the level of the risk factor is raised. Examples of well-established epidemiologic dose–response relationships are the dose–response relationship between smoking and lung cancer (Fig. 2.12, Table 2.3); serum cholesterol levels, systolic blood pressure, and coronary heart disease (Fig. 2.13); and oral contraceptive estrogen dose and venous thromboembolism (Fig. 2.14).

Figure 2.12. *Age-adjusted death rates due to bronchogenic carcinoma exclusive of adenocarcinoma by current amount of cigarette smoking. (Based on data in Hammond & Horn, 1958).*

Figure 2.13. *Six-year cumulative incidence of coronary heart disease according to serum cholesterol and systolic blood pressures, men 45 to 62 years old. (Based on data in Kannel et al., 1961)*

Figure 2.14. *Oral contraceptive dose and rate of idiopathic deep venous thromboembolic disease. (Based on data in: (a) Stadel, 1981, p. 614; (b) Gerstman etal., 1991, p. 34.)*

TABLE 2.3. Cohort Studies of Smoking and Lung Cancer Mortality

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Number of people	34,000	188,000	248,000	67,000	60,000	78,000+	448,000
Age range	35–75+	50–59	30–75+	35–69	35–75+	35–75+	35–89
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Lung cancer deaths in study	129	448	535	139	98	221	414
Lung cancer deaths, nonsmokers	3	25	56	3	12	8	16
Current Cigarettes Smoked per Day	Standardized Mortality Ratios (Lung Cancer)						

None	Referent	Referent	Referent	Referent	Referent	Referent	Referent
<10	4.4	5.8	5.2	(5) [a] 8.3	(≤20)[a]4.2	8.4	
10–20	10.8	7.3	9.4	(10)[a] 9.0		13.5	(current smoker)[a]
21–39		15.9	18.1	(20)[a]19.4			
	(21+)[a] 43.7			(30)[a] 25.1	(20+)[a] 7.4	15.1	9.6
40+		24.7	23.3	(40)[a] 28.7			

Source: U.S. Department of Health, Education, and Welfare (1964, pp. 83, 164).
[a]Indicates daily number of cigarettes smoked in which classes have been split or combined.

Epidemiologic dose–response relationships come in different forms (e.g., linear, lognormal, "U" shaped, inverted "U" shaped), depending on the underlying pathophysiologic mechanism causing the elevations in risk. The type of dose–response relationship can have public health and regulatory implications. For instance, if there is a threshold response below which no further harm is done, further reduction in exposure is unwarranted; however, if risks are linearly related to cumulative dose throughout all potential levels of exposure, cumulative exposures must be minimized.

Consideration 6 (**plausibility**) holds that the association should be plausible with known biologic facts about the pathophysiology of the disease. Statistical solutions are unjustified without an understanding of the reasoning behind associations. Consider the fact that most people die in bed. This undeniable statistical association has little causal meaning given common sense. However, it has become all too commonplace see various associations promoted as causal just with only a tenuous biological or sociological basis. With this said, we must not be too ready to dismiss associations as noncausal simply because plausible explanation is as yet unavailable. Biological plausibility is contingent on the current state of knowledge, and the current state of knowledge can be inadequate in explaining associations that might in fact be causal.

Consideration 7 (**coherence**) holds that available evidence concerning the natural history, biology, and epidemiology of the disease should "stick together" (cohere) to form a cohesive whole. That is, the proposed causal relationship should not conflict or contradict information from experimental (human and animal), laboratory (*in vivo* and *in vitro*), clinical, pathological, and epidemiologic (both descriptive and analytic) sources of knowledge. For example, in considering smoking and lung cancer, the rise of smoking in Western countries during the early and mid-20th century was accompanied by a corresponding increase in lung cancer mortality, as one would expect given our current knowledge. This effect was more pronounced in men than in women, paralleling gender differences in the propensity to smoke. More recently, declines in the age-adjusted death rates for lung cancer in men parallel recent declines in the prevalence of, smoking (National Center for Health Statistics, 1995, p. 3). Moreover, animal experiments support the presence of carcinogenic factors in cigarette smoke, and histopathology evidence demonstrates the cytotoxic effect of smoking on the bronchial epithelium of smokers. These and other observations form a coherent whole in supporting the smoking and lung cancer causal hypothesis.

Consideration 8 (**experimentation**) requires experimental epidemiologic studies, natural experiments, in vitro laboratory experiments, and animal models in support of a causal hypothesis. The strength of experimental epidemiologic studies (i.e., clinical trials and community trials) lies in the investigator's ability to randomize the experimental intervention directly, thus negating the influence of extraneous factors in their potential to confound results. Experimental epidemiologic data, therefore, can provide strong evidence in support of a causal hypothesis. However, as discussed in Chapter 10, epidemiologic experimentation is often impractical or unethical, thus precluding its use.

Testing of causal theories in the lab can provide important support for causal arguments. This may occur in the form of *in vitro* experiments or in vivo experiments in animal models and human subjects. *In vitro* experimentation (literally meaning "within a glass" experimentation) involves study within a "test tube" environment. Animal models provide the opportunity to study pathological phenomena in living systems. This approach, sometimes called comparative medical research, may involve inducing a disease in laboratory species or studying a spontaneous disease of animals in nature.

When available, experimental evidence provides strong evidence in support of causal theories. However, as with most of these criteria, its absence does not necessarily weaken the causal argument, especially if pragmatic and ethical concerns preclude their use.

Consideration 9 (**analogy**) implies a similarity between things that are otherwise different. Analogy is one of the weaker forms of evidence, but it can be useful in providing insights into the cause of a disease, especially during early phases of investigation. An example of analogic thinking in epidemiology is that if one pharmaceutical drug (such as thalidomide) causes severe birth defects, so might others. Another example of analogic thinking is discussed by Fraser (1987):

> When testing of serum specimens from the patients in Sierra Leone confirmed the diagnosis of Lassa fever, an investigation was organized to determine how the disease was spreading and— if it was not from one person to another—what the ultimate source might be. Because Lassa virus under the electron microscope resembles lymphocytic choriomeningitis virus and other arenaviruses (which also cause chronic infections in particular rodents), the investigators reasoned, by analogy with the spread of lymphocytic choriomeningitis virus, that some West African rodent may be susceptible of Lassa virus infection and may infect humans through contaminated urine. (p. 311)

Thus, similar structures of otherwise dissimilar viruses led to clues about the source and transmission of the Lassa fever agent. As with all the criteria, this type of reasoning is incapable of providing hard-and-fast proof of cause and effect. In fact, no single criterion can be required as a necessary condition or indispensable need. Instead, a compilation of fact, judgment, experimental support, and perhaps even good fortune is required. It may take some time for uncertainties to be resolved. However, for the sake of saving lives, there is often the need to take action in the face of incomplete scientific knowledge. Hill reminds us of this responsibility with these parting word from his 1965 article:

> All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. This does not confer upon us a freedom to ignore the knowledge we already have, or to postpone action that it appears to demand at a given time. . .Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8.30 next day. (p. 12)

EXERCISES

2.1 Select a specific disease or type of injury that interests you or with which you have some experience or knowledge. For example, if you are a pediatrician, you might select otitis media or some other common childhood disease. If you are a respiratory therapist, you might select asthma or COPD. If you or a relative has diabetes, you may select this ailment. Then go to a medical reference (e.g., *http://www.merck.com/pubs/mmanual/*) and research the natural history and epidemiology of this condition. Address each of the following:

(A) Describe the spectrum of this disease and its range of clinical manifestations.

(B) Identify host, agent, and environmental causal factors for this disease. Address both direct and indirect causes, and relate these causal factors in the form of a causal web.

(C) List primary methods of prevention for this disease. Why, specifically, do you believe that these are primary methods of prevention, and not, say, secondary methods of prevention?

(D) List secondary methods of prevention. Justify why you believe these are secondary and not primary or tertiary forms of prevention.

(E) List tertiary forms of prevention. Justify why you believe these are tertiary and not primary or secondary forms of prevention.

(F) Which of the above forms of prevention listed in parts (D) and (E) do you believe to be most effective. Justify your response.

2.2 Match the descriptions of each of Hill's considerations with one of these brief descriptive label: Strength; Consistency; Specificity; Temporality; Biological gradient; Plausibility; Coherence; Experimentation; Analogy.

Descriptions of causal considerations:

(A) This criterion holds that all available clinical, experimental, and observational evidence should "stick together" in the argument for causation.

(B) This criterion holds that an increase in the level, intensity, duration, or total level of exposure leads to progressive increases in the magnitude of risk.

(C) This criterion holds that an association is explainable in terms of known biological fact.

(D) This criterion requires that exposure to the causal factor precedes the onset of disease by reasonable amount of time.

(E) This criterion requires supporting evidence from community and clinical trials, in vitro laboratory experiments, and animal models.

(F) This criterion is based on similarities from otherwise dissimilar sources.

(G) This criterion holds that the cause should lead to only one disease and that the disease should result from only this single cause.

(H) This criterion holds that diverse methods of study carried out in different populations under a variety of circumstances by different investigators provide similar results.

(I) This criterion holds that strong associations provide firmer evidence of causality than do weak ones.

2.3 The association between oral contraceptives and cardiovascular disease has been the subject of considerable debate. Indicate which of Hill's causal considerations are addressed by each of the statements below. Use these labels in tagging the appropriate consideration: Strength; Consistency; Specificity; Temporality; Biological gradient; Plausibility; Coherence; Experimentation; Analogy.

(A) The risk of cardiovascular disease increases with increasing the estrogen dose of the oral contraceptive formulation.

(B) Studies have shown that oral contraceptives cause endothelial proliferation, decrease the rate of venous blood flow, and increase the coagulability of blood by altering platelet function, coagulation factors, and fibrinolytic activity.

(C) The relative risk of oral contraceptive use and mortality from all circulatory disease in the 1970s was approximately 4.

(D) Most studies completed to date have demonstrated a positive association between oral contraceptive use and cardiovascular disease risk.

(E) Other steroidal sex hormones, such as testosterone, have known effect on cardiovascular disease risk.

(F) Altered parameters of hemostasis are measurable soon after oral contraceptives are begun. These alterations return to baseline within a month of discontinuing oral contraceptives.

2.4 Hill's criterion for "consistency" holds that the exposure will always lead to the disease. If the statement is false, state why it is false and supply the information that would make the statement true.

(A) True (B) False

2.5 A survey finds that patients who suffer from chronic back pain are more likely to be depressed than a series of age- and sex-matched controls. Can it be concluded that stress causes back pain. After selecting your response, state why you do or do not believe the conclusion is reasonable.

(A) Yes (B) No

REFERENCES

Bailar III, J. C., & Gornick, H. L. (1997). Cancer undefeated. New England Journal of Medicine, 336, 1569–1574.

Benenson, A. S. (Ed.). (1990). *Control of Communicable Diseases In Man* (15th ed.). Washington, DC: American Public Health Association.

Best, E. W. R., Josie, G. H., & Walker, C. B. A. (1961). Canadian study of mortality in relation to smoking habits, a preliminary report. Canadian Journal of Public Health, 52, 99–106.

Case, R. A. M., Hosker, M. E., McDonald, D. B., & Pearson, J. T. (1954). Tumors of the urinary bladder in workman engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. *British Journal of Industrial Medicine, 11*, 75–104.

Cobb, S., Miller, M., & Wald, N. (1959). On the estimation of the incubation period in malignant disease. *Journal of Chronic Diseases, 9*, 385–393.

Cornfield, J. (1954). Statistical relationships and proof in medicine. American Statistician, 8, 11–13.

Cotton, D. J. (1995). The natural history of HIV infection: implications for clinical trials. In D. M. Finkelstein & D. A. Schoenfeld (Eds.), *AIDS Clinical Trials*: Wiley-Liss.

Doll, R., & Hill, A. B. (1956). Lung cancer and other causes of death in relation to smoking. British Medical Journal, 2, 1071–1081.

Dorland's Illustrated Medical Dictionary. (1994) (28 ed.). Philadelphia: W.B. Saunders.

Dorn, H. F. (1958). The mortality of smokers and non-smokers. Proc. Soc. Stat. Sect. Am. Statist. Assoc., 34–71. [As cited in U.S. Department of Health, Education, and Welfare, 1964.]

Dorn, H. F. (1959). Tobacco consumption and mortality from cancer and other diseases. Public Health Reports, 74, 581–593.

Dunn, J. E., Jr., Linden, G., & Breslow, L. (1960). Lung cancer mortality experience of men in certain occupations in California. American Journal of Public Health, 50, 1475–1487.

Dunn, J. E., Jr., Linden, G., & Breslow, L. (1964). California State Department of Public Health. Special report to the Surgeon General's Advisory Committee on Smoking and Health. [Data published in U.S. Department of Health, Education and Welfare, 1964.]

Fraser, D. W. (1987). Epidemiology as a liberal art. New England Journal of Medicine, 316, 309–314.

Gerstman, B. B., Piper, J. M., Tomita, D. K., Ferguson, W. J., Stadel, B. V., & Lundin, F. E. (1991). Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. American Journal of Epidemiology, 133, 32–37.

Glashow, S. L. (1999). Can science save the world? Centro Congressi Cariplo. Available:

http://www.hypothesis.it/nobel/nobel99/eng/pro/pro_2_1_1.htm [2002, Aug 8].

Hamill, P. V. V. (1997). Re: "Invited commentary: Response to Science article, 'Epidemiology faces its limits.' " American Journal of Epidemiology, 146, 527.

Hammond, E. C. (1964). Prospective study of 1,085,000 men and women in 25 of the United States aged 35–89. Special report to the Surgeon General's Advisory Committee on Smoking and Health. [Data published in U.S. Department of Health, Education and Welfare, 1964.]

Hammond, E. C., & Horn, D. (1958). Smoking and death rates—report of forty-four months of follow-up of 187,783 men. Part I. Total mortality. Part II. Death rates by cause. JAMA, 166, 1159–1172, 1294–1308.

Hill, A. B. (1965). The environmental and disease: Association or causation? Proceedings of the Royal Society of Medicine, 58, 295–300.

Hogben, L. (1933). *Nature and nurture.* London: Williams and Norgate.

Hume, D. (1739–40). A Treatise of Human Nature. McMaster University Archive. Available: http://www.ets.uidaho.edu/mickelsen/ToC/hume%20treatise%20ToC.htm [2002, June 2].

Hume, D. (1772). *An enquiry concerning human understanding* (1993 Web reprint of the Harvard Classic published in 1910). Available: *http://eserver.org/18th/hume-enquiry.html*.

Kannel, W. B., Dawber, T. R., Kagan, A., Revotskie, N., & Stokes, J. (1961). Factors of risk in the development of coronary heart disease—six year follow-up experience. Annals of Internal Medicine, 55, 33–50.

Last, J. M. (1963). The iceberg: 'completing the clinical picture' in general practice. *The Lancet*, 6 July, 28–31.

Millard, A. V. (1994). A causal model of high rates of child mortality. *Social Science & Medicine, 38*, 253–268.

Munn, R. E. (1970). *Air quality for sulfur oxides.* New York: Academic Press.

National Center for Health Statistics (1995). Health, United States, 1994. Hyattsville, MD: Public Health Service.

Popper, K. (1959). The logic of scientific discovery. London: Routledge Classics.

Rothman, K. J. (1976). Causes. *American Journal of Epidemiology, 104*, 587–592.

Rothman, K. J. (1981). Induction and latent periods. *American Journal of Epidemiology*, 114(2), 253-259.

Rothman, K. J., & Greenland, S. (1998). *Modern E pidemiology* (2nd ed.). Philadelphia: Lippincott-Raven.

Royce, R. A., Sena, A., Cates, W., Jr., & Cohen, M. S. (1997). Sexual transmission of HIV. *New England Journal of Medicine, 336*, 1072–1078.

Sagan, C. (1996, Dec. 20). Carl Sagan Obituary. Bob Evans (Host). Morning Edition. Washington D.C.: National Public Radio.

Savitz, D. A. (1997). The alternative to epidemiologic theory: Whatever works. *Epidemiology, 8,* 210–212.

Snow, J. (1856). On the mode of communication of cholera. London: John Churchill. Reprinted in Snow on Cholera. (1936). New York: The Commonwealth Fund.

Stadel, B. V (1981). Oral contraceptives and cardiovascular disease. New England Journal of Medicine, 305, 612–618, 672–677.

Susser, M. (1988). Falsification, Verification and causal inference in epidemiology: Reconsideration in the light of Sir Karl Popper's philosophy. In K. J. Rothman (Ed.), Causal Inference (pp. 33–57). Chestnut Hill, MA: Epidemiology Resources, Inc. [Rejoinder: Rational science versus a system of logic. In K. J. Rothman (Ed.), Causal Inference (pp. 189–199)].

U.S. Department of Health, Education, and Welfare. (1964). Smoking and health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. USPHS Publication No. 1103. Washington: U.S. Government Printing Office. [Also published by D. Van Nostrand Company, Princeton, New Jersey.]

Wallis, W. A., & Roberts, H. V (1962). The nature of statistics. New York: Free Press.

Weiss, H. B., Friedman, D. I., & Coben, J. H. (1998). Incidence of dog bite injuries treated in emergency departments. *JAMA, 279,* 51–53.

Wynder, E. L. (1994). Invited commentary: Studies in mechanism and prevention. Striking a proper balance. American Journal of Epidemiology, 139, 547–549.

Wynder, E. L. (1997). The author replies. American Journal of Epidemiology, 146, 527–528.