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Veterinary Epidemiology: Principles and Methods

Part 1: Basic Principles

Chapter 1: Epidemiologic Concepts

Originally published 1987 by Iowa State University Press / Ames

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CHAPTER 1

Epidemiologic Concepts

1.1 Meaning and Scope of Epidemiology

Epidemiology is a very old science, yet it did not flourish until after the "germ theory" of disease causation became established in the 1800s. Since that time, and until approximately 1960, epidemiology has been closely allied with microbiology in the battle against disease. Subsequent to 1960, epidemiology has become a more holistic discipline, and many factors in addition to the specific agent are investigated to determine their role as potential causes of disease (Schwabe 1982). Concurrently, the use of quantitative methods has become more widespread in epidemiologic research. In veterinary medicine the latter trend has been most pronounced in the last decade. As the emphasis both in veterinary education and practice shifts from the individual animal toward the population, the need for the veterinarian to have skills in quantitative methods will be accentuated. This text has been written in an attempt to assist veterinary students and veterinarians in developing quantitative epidemiologic skills that can be applied to population medicine. It contains a number of introductory epidemiological methods and examples of their application.

Epidemiology may be defined as the study of the patterns of disease that exist under field conditions. More specifically, epidemiology is the study of the frequency, distribution, and determinants of health and disease in populations. Thus, the epidemiology of a disease is the population analogue to the pathogenesis of disease in individuals, and in this context epidemiology is a fundamental science for medicine in populations.

To some, epidemiology is merely a set of methods; however, the use of these methods frequently leads the practitioner to a holistic, population-oriented way of thinking about health and disease that is quite different from the individual patient-oriented approach of clinical medicine. In many instances, the unit of concern in epidemiologic studies is not the individual but rather groups or categories of individuals such as the pen, herd, or flock. Despite this difference in unit of concern, epidemiology requires the same attention to detail and observer skills as clinical medicine and the other biologic sciences.

One method of exploring and understanding epidemiology is by elaborating the previous definition. First, it is noted that epidemiology is the study of the frequency and distribution of disease. Initial clues about the etiology of a disease are often provided by its distribution. That is, information about what animals are affected and where and when a disease occurs often is suggestive of the causes of disease. Subsequently, it will be necessary to formally identify some of the determinants (causes) of the disease, (i.e., to explain why the disease occurs with the objective being to reduce its severity or frequency of occurrence). These details may be obtained by formally contrasting the characteristics of healthy versus diseased individuals, or by contrasting the characteristics of groups having a relatively high frequency of the disease versus groups having either none or a low frequency of the disease of interest. (Studies of the latter type are called case-control studies, and along with other types of analytic observational studies, they are introduced in Chapter 2 and elaborated in Chapter 6.)

Determinants, those factors that influence health and disease, are commonly called causes of disease. In epidemiology the word determinant is used to describe any factor that when altered produces a change in the frequency or characteristics of disease. Therefore, as will be stressed throughout this text, few diseases have a single cause. Host factors (such as age, breed, and sex) frequently are determinants of disease. Many determinants are external to the individual animal, as opposed to the internal factors that relate to the pathogenesis of disease. Putative causes of disease may be referred to as exposure or risk factors (or as independent, predictor, or explanatory variables) because they are suspected of producing the outcome of interest. The presumed effect, usually either health (as measured by productivity) or disease occurrence, is called the outcome, response, or dependent variable. (Variable refers to a property, factor, or characteristic of an individual or group being measured, rather than meaning "changeable.") For example, in a study of the association between immune status (e.g., level of serum antibodies) and the occurrence of disease, immune status is the independent and health status the dependent variable. If the impact of disease on the level of production were being studied, production would be the dependent variable and the presence or absence of disease the independent variable.

Disease and health are not redundant in the above definition, since in all epidemiologic studies both "diseased" and "healthy" animals should be present. As one example of their dual value, contrasting the characteristics of diseased versus healthy animals can provide valuable clues about the causes of disease. Nonetheless, health and disease are relative terms and their definitions usually depend on the circumstances in which they are applied. Hence some working definitions are in order.

Disease may affect individuals in either a subclinical or clinical form. Clinical disease represents the state of dysfunction of the body detectable by one or more of a person's senses. In contrast, subclinical disease represents a functional and/or anatomical abnormality of the body detectable only by selected laboratory tests or diagnostic aids. Although subclinical disease usually is less serious for the individual than clinical disease, it may be more important for the population because of its frequency. As a general rule, regardless of the primary cause(s) of the disease, the number of animals subclinically diseased will be much larger than the number clinically diseased. In this regard, it is particularly important to make a distinction between infection and disease. Infection with most agents (including microorganisms and parasites) of so-called infectious diseases does not lead to clinical disease in the majority of infected animals. In many cases the infected animals appear to be healthy. For present purposes, an animal that is neither clinically nor subclinically diseased is by definition healthy. Most populations comprise varying proportions of healthy, subclinically diseased, and clinically diseased individuals, with the proportions being subject to change over time.

Although health in humans has been defined as a state of complete physical, mental, and spiritual well being, in veterinary medicine, productivity is often used as a surrogate measure of health. In domestic animal populations, whether a disease is present or not is usually less important than the frequency with which the disease occurs and its subsequent impact on productivity. In this context, whereas disease may limit productivity, disease per se may not be the most important limiting factor of production. Other factors (such as management decisions, improper housing, or inadequate feeding practices) may have a greater impact on production in many situations (Williamson 1980). The association of these factors with health status may be investigated in a manner similar to studying the impact of disease on production using the techniques described in this text.

Due partly to the premise that the herd or flock is more important than the individual, the unit of concern for the epidemiologist frequently is an aggregate or population of animals, not an individual (e.g., it is more important that the feedlot is healthy than that a particular animal is healthy). Even when the individual is the unit of concern (e.g., in a study of the effect of vaccination on the health status of individuals), epidemiologic techniques are limited to groups (categories of individuals) rather than to an individual. Epidemiologists do observe individuals within the groups, but the conclusions are based on the experience of the group. Despite this limitation, inferences derived from groups may be extrapolated under certain circumstances to individuals (see 1.5). ("Population" is used throughout this text in two senses—first, to describe the total number of animals in a group being studied who are biologically at risk of the event under study, and second, to refer to the larger number of individuals of a particular type or species about which inferences are being made, based on information from a sample.)

One dimension for conceptualizing the structure of populations is that they are composed of a number of levels of organization. For example, the levels of organization from smallest to largest may be conceptualized in the following manner: cells of similar structure or function form organs, organs form body systems, and individuals are composed of body systems. Litters, pens, or herds are composed of a number of individuals; a collection of herds in one geographic area would form a local industry; and the local industries together would make up a larger animal industry, such as the swine or dairy industry. Each higher level of organization has characteristics beyond those of the lower levels. Individuals have more properties or characteristics than the sum of all the body systems; likewise, herds of animals have more properties than the individuals that compose them.

The level of organization selected for a specific study (the sampling unit in observational studies and the experimental unit in field trials) is the unit of analysis for that study. The unit of analysis often is not the individual animal; for example, if pens of pigs are the sampling units in an observational study, the unit of analysis would be the pen. Recognition of the correct unit of analysis is important for a number of reasons in addition to those already described. The unit of analysis may constrain the causal inferences about individuals that can be drawn from a sample (see 5.6.1) and, in addition, the unit of analysis is the basis for determining the degrees of freedom used in statistical testing.

It should be obvious from the definition and the preceding discussion that the setting for most epidemiologic work is the field (farm, animal clinic, city, nation, etc.) rather than the laboratory. Thus, epidemiologic observations relate to and are derived from field situations, although the analysis of data based on these observations may be conducted in a laboratory environment. Suitably stored and analyzed data will give the epidemiologic laboratory the same essential role in population medicine as the clinical pathology or microbiologic laboratory in individual animal medicine. In another sense, epidemiology is the diagnostic tool for populations, analogous to the role of clinical medicine as the diagnostic tool for individuals.

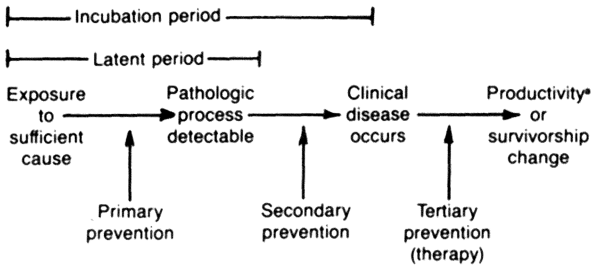
Finally, all animals, including humans, are possible subjects for epidemiologic study. Historically, epizootiology has been used to describe studies of disease in animal populations, and epidemiology for similar studies in human populations. Since a literal translation of "epidemiology" is the study (logos) of what is upon (epi) the population (demos) and because of the many similarities between human and animal medicine, there is little need to continue to use the term epizootiology. For those wishing to retain the distinction between studies of disease in animals and humans, the linguistic problems associated with this carried to the extreme would result in terms such as epiornithology, epiicthyology, and epiphytology to describe the study of diseases in populations of birds, fish, and plants respectively.

1.2 Purposes of Epidemiology

The major purpose of epidemiology is a pragmatic one; namely, to provide data on which a rational decision for the prevention and/or control of disease in animal populations can be based. In domestic animals this involves optimizing health (productivity) and not necessarily minimizing the occurrence of disease. Many medical disciplines have a similar general purpose. The special contribution of epidemiology is providing information describing the frequency and distribution of health and disease, identifying factors influencing the occurrence and severity of disease in the population of concern (in its natural setting), and quantitating the interrelationships between health and disease.

To fulfill these purposes, an epidemiologic study might be carried out to estimate the frequency of disease (e.g., the rate of infertility in dairy cows) or to identify factors that might cause the disease of concern (e.g., whether the type of ration is associated with the rate of respiratory disease in feedlot cattle). The former activity is known as descriptive epidemiology because its primary purpose is to describe what the syndrome is, who is affected, where the disease occurs, and when it occurs. The latter activity is called analytic epidemiology because the primary emphasis is on the collection and analysis of data to test a hypothesis; that is, to provide answers to why the disease occurred.

The relationship between development of disease and the operational purposes of epidemiology is shown in Figure 1.1. These operational purposes include primary, secondary, and tertiary prevention of disease. (This ordering not only represents a convenient way of differentiating among these purposes, but also reflects their inherent utility in the health care of populations. That is, society should emphasize primary rather than tertiary prevention as a means of improving health status. Health will improve only marginally by killing weeds and treating disease.) Primary prevention includes those activities directed toward preventing exposure to causal factors, particularly the complexes of factors that are sufficient to produce disease. Quarantine and vaccination are examples of primary prevention. Vaccination does not prevent exposure to the agent but can prevent a sufficient cause from forming by rendering the animal immune to the level of challenge by the agent under field conditions.



Note: Disease may be studied with the primary objective of increased understanding or pragmatically, with intervention as the objective. Good understanding is an aid to control, but it is neither necessary, nor sufficient, for successful intervention.

*Monitoring productivity changes may be used to indicate the presence of a pathologic process, in the absence of clinical disease. Also, productivity may itself be a component of a sufficient cause. A sufficient cause is one that always produces the disease (see 5.6.2).

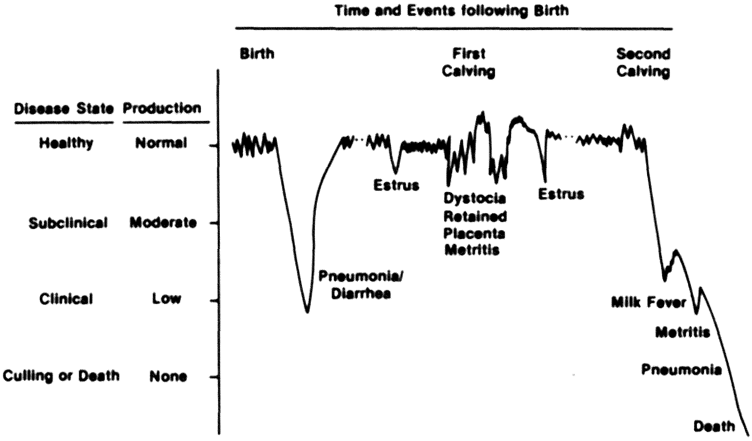
1.1. Relationship between development of disease and operational purposes of epidemiology.

Secondary prevention includes those activities designed to detect disease processes as early as possible before clinical disease occurs. The underlying and biologically reasonable principle is that early detection will allow treatment and hence increase the probability of restoring the individual to full health and reducing production losses. Despite the reasonableness of this argument, its basis should be formally evaluated whenever possible. Screening tests to detect brucellosis and tuberculosis, somatic cell counts to detect mastitis, regular examinations of the postpartum cow, and metabolic profiles are examples of tests used in secondary prevention.

Tertiary prevention is more commonly known as therapeutics. It has been noted that for economic reasons tertiary prevention, especially in domestic animals, is somewhat of a salvage operation. However, despite the best efforts to prevent disease, it will occur (it is hoped much less frequently), and many veterinarians will continue to be employed primarily in the therapeutic role. At present, much of the time spent during a veterinarian's education is devoted to understanding the pathogenesis of disease, diagnosing disease, and instituting an adequate therapeutic (including surgical) regime. Yet, epidemiologic skills can increase the clinician's abilities at tertiary prevention. The concepts of field trials (Chapter 7) are applicable to clinical trials and the evaluation of therapeutic regimes. In terms of diagnosing disease, various forms of decision analysis (see Chapter 9) are becoming more widely used as an aid to understanding the process of differential diagnosis as well as for evaluation of alternative therapeutic strategies. Epidemiologic studies are used infrequently to study the pathogenesis of disease; nonetheless, the results of epidemiologic studies often provide indirect but useful clues about the nature of the disease process.

As shown in Figure 1.1, the period between exposure to an agent (infection) and the occurrence of clinical disease is referred to as the incubation period. Infectious agents often have different incubation periods, and this knowledge can be of value when investigating or predicting disease outbreaks. The latent period for infectious diseases refers to the period between infection and shedding of the organism and is usually shorter than the incubation period. For noninfectious diseases, it is the period between exposure to the agent and the occurrence of detectable pathologic changes.

As previously mentioned, high production can be a cause of disease as well as being affected, usually adversely, by the occurrence of disease (Figure 1.1). Monitoring productivity at the herd and the individual animal level often provides the first clue that something is wrong biologically. Hence production monitoring should be an integral component of a health management program, a feature that will be elaborated in subsequent chapters. A simplified concept of production monitoring is shown in Figure 1.2. By monitoring production, disease may be detected at an early stage; hence production monitoring is a form of secondary prevention. For instance in Figure 1.2 production decreases could have been used to predict the subsequent occurrence of calfhood diseases and/or those occurring at the second calving. The diagram also implies that level of production could be used to detect subclinical diseases (e.g., mild metritis at the first calving) as well as the occurrence of other events such as estrus.



1.2. Hypothetical relationship between production monitoring and disease states and other events. Production level can be measured in calves by weight gain or feed efficiency and after first calving in milk production per day.

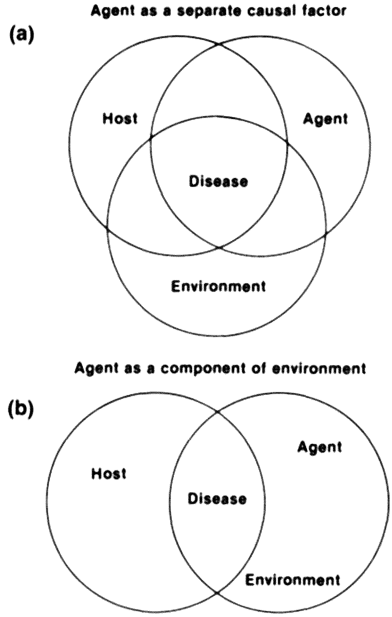
1.3 Basic Concepts

Most epidemiologic work is based on four principles or concepts about health and disease (see MacMahon and Pugh 1970, Chapter 1). The first and perhaps oldest concept is that disease occurrence is related to the environment of the species being studied. Here environment includes the physical, biological, and sociological (ethological) milieu of an individual. The origin of this concept is usually attributed to the Hippocratic writings in "On Airs Waters and Places," although the factual basis for this belief has been disputed (Roth 1976). To identify the specific environmental factors leading to disease occurrence, epidemiologists frequently compare environments where disease is prevalent to those where it is infrequent or absent.

Weather is a major component of the environment, and its role as a determinant of many parasitic diseases and vectorborne infections is well documented. For example, warm, wet weather provides optimal environment for most helminth parasites to survive outside the host. Dryness is usually harmful to their survival, while most survive cold weather quite well. Similarly, warm, wet conditions provide a very suitable environment for the survival and multiplication of insects that can serve as vectors of disease. However, less obvious effects (such as the impact of weather on morbidity and mortality) are poorly documented and understood. In a study designed to investigate the association between weather and survivorship of dairy calves in California, the results indicated that the number of births each day, the risk of death for calves born each day, and the day of death were all influenced by weather extremes (Martin et al. 1975).

Weather also could exert its effects on calf health in indirect ways. In hot climates, cows kept in an open paddock will seek shade during the day to reduce heat stress. However, most cows prefer to calve in more isolated, quiet areas and will usually leave the shaded areas and deliver their calf near the periphery of the paddock. Subsequent to parturition, the cow is torn between her mothering instincts such as licking and drying her calf and assisting it to nurse and her desire to return to the shaded area. Many cows choose the latter, and the calf is deserted and left in the hot sun. This can severely compromise the calf since the temperature regulating mechanisms of the newborn are subject to extremes in temperature, and the calf can lose large amounts of body fluids attempting to maintain its body temperature within reasonable limits. Thus lack of mothering, failure to obtain adequate amounts of colostrum, and stress of maintaining its body temperature can singly and jointly greatly increase the susceptibility of a calf to a number of infectious agents. Because of this, many calves succumb to enteritis, septicemia, and pneumonia, greatly reducing the likelihood of surviving the early postpartum period. Nonclimatic components of the environment, such as management and housing, also appear to exert a great effect on calf health in particular and on disease occurrence and productivity in general. Most of the evidence on this matter, however, is based largely on clinical impressions, and relatively few formal studies on the role of these factors have been conducted.

Although conceptually some prefer to have a separate category for agents in the host-environment-agent triad (see Fig. 1.3a), the preference here is to treat agents as a component of the environment (see Fig. 1.3b) and to evaluate their importance in perspective, relative to other environmental factors that influence the health status of animals. It may be noteworthy that host and agent factors receive much emphasis in veterinary education, most schools having departments formally structured to study these factors. Few medical or veterinary schools have departments whose faculty are devoted to the study of the environment or the relationship between the environment and host. This may lead to a failure to appreciate the multiple ways environmental factors exert their effects. It also may narrow the concepts of disease causation and methods of disease control. Knowledge of the involvement of specific infectious and/or toxic agents in a disease has been extremely helpful in controlling many diseases. At the



1.3. Relationship among host characteristics, environmental factors, agents, and disease.

same time, however, it has tended to lead to the overreliance on antimicrobials and vaccines as the primary means of disease control. In discussing this subject, White (1974) stresses the need for a more holistic ecological view of health and disease.

The second principle of epidemiologic work is to count the occurrence of natural events such as births, disease and death. Quantification per se is perhaps the most obvious aspect of modern day epidemiology and points out the need for veterinarians to have knowledge of basic demographic and statistical techniques. Using this approach, and despite the incompleteness and inaccuracies of the available data (the Bills of Mortality), it was demonstrated in the mid-1600s that many biological phenomena when taken in mass were quite predictable. John Graunt, who is credited with this observation, is often viewed as the father of demography and as such contributed greatly to both statistics and epidemiology. "It may be of interest . . . that the father of demography was not a trained statistician, nor a trained epidemiologist, but (a draper) a careful and original thinker who reasoned that if disease was more common in one area, in one sex, in one population, there had to be a reason which required exploration and which, upon identification, could lead to a reduction of illness. This, after all, is still the basic goal of the epidemiologist" (Wynder 1975).

This predictability of mass events is used implicitly and explicitly by veterinarians and is a cornerstone of epidemiologic field studies. Clinicians implicitly make use of this feature as an aid to diagnosis (e.g., by knowing that certain diseases—milk fever, left displaced abomasum, and reticuloperitonitis—occur much more frequently at or near parturition than at other times in a cow's life). Epidemiologists explicitly use this feature (e.g., castrated cats fed dry cat food and housed only indoors are much more likely to develop feline urologic syndrome than noncastrated cats fed moist foods and allowed exercise outdoors, or as another example, the morbidity curve in recently transported feedlot animals is much more predictable than which individual will develop disease). Implicitly, this feature stimulates the inquiring mind to seek reasons to explain why a disease occurs in certain circumstances and not others (e.g., why wildlife rabies appears to be more common in relatively urbanized areas than in more isolated rural areas).

It may be worthwhile to note that a medical or veterinary degree is not essential for a person to an epidemiologist (White 1974). Certainly, both historically and presently, many people not specifically trained in medicine contribute greatly to the field of disease prevention and control, if not specifically to epidemiology. The exact training and educational requirements to become a "card-carrying" epidemiologist have been the subject of much debate, mainly in response to the formation of a professional college to certify epidemiologists (Lilienfeld 1980; Stallones 1980). Veterinarians, because of their excellent biological training, have made great contributions to health maintenance and disease prevention. To an extent the statement that "every veterinarian is an epidemiologist" is true, yet this should not detract from the additional benefits to be obtained by formal training in epidemiology.

The third concept of epidemiologic work is to utilize nature's experiments whenever possible. Because the epidemiologist usually is involved in nature's experiments only as an observer, such studies are termed observational studies. As an example, in a study to assess the effect of different ventilation systems on pneumonia in swine, one could identify sufficient numbers of swine—some raised in barns ventilated by one system, some raised in barns ventilated by other systems, and some raised in barns with no formal system for exchange of air—and note the extent of pneumonia in pigs raised under these specific ventilation systems. If carefully planned and analyzed, field observations such as these can provide much useful information on the effectiveness of various types of ventilation systems, as well as the relationship of other factors to health and disease. In many such instances experimental studies are too impractical, and thus observational studies provide the only remaining scientific avenue of investigation. Yet, despite the practical utility and scientific validity of observational studies, many medical scientists dismiss or play down the results of such nonexperimental work. The logical basis for their dismissal is often unclear or nonexistent, and a detailed discussion concerning observational and experimental studies will be provided in subsequent chapters.

Sometimes it is possible to observe natural situations that simulate manipulative experimental conditions quite closely. A classic example of such a study is Dr. John Snow's investigation of cholera epidemics in England during the 1800s, some 30 years prior to the identification of the cholera bacillus (MacMahon and Pugh 1970; Susser 1973).

Dr. Snow noted the nature of the disease, a profuse diarrhea, and observed that although most members of a household became infected, the doctors and nurses who cared for them usually remained healthy. On this basis, he believed the disease was not directly contagious, but that contamination of the water supply by feces was a major method of disease transmission. (He had difficulty convincing his colleagues of this because miasma—bad air—was the major explanation of disease causation at that time.)

To test his hypothesis, Snow analyzed data from Bills of Mortality and was able to show a close association between the company supplying water and the level of cholera in different areas of London. The Southwark and Vauxhall and the Lambeth companies both obtained water downstream from the sewage outlet in the Thames River, and people in the areas served by these companies experienced higher mortality rates than people in other areas of London. After the 1849 epidemic, Lambeth moved its inlet upstream. Subsequently, in the 1853 cholera epidemic, people receiving water from this company had much lower levels of mortality from cholera than people in the same area who received water from Southwark and Vauxhall. Snow used this change of inlet location to study the occurrence of cholera in households. In one area of London this change resulted in the two companies supplying water to houses on the same streets, the residents in the area often not recognizing this fact. He cleverly developed a screening test to determine which company supplied water to each house when the occupants, relatives, or previous owners were unsure of the source of their water (downstream water had a high salt content). By doing this, Snow was able to show that people in houses supplied with water from Southwark and Vauxhall had a much higher rate of cholera than those supplied by Lambeth. By carefully documenting the water supply, the number of deaths, number of cholera cases, and number of people at risk in each household, Snow was able to convince the authorities that a clean water supply was indeed the key to preventing cholera epidemics. (Using households as the sampling unit rather than larger units defined by water supply was a significant improvement in Snow's ability to identify the cause of cholera in individuals. It is in fact a general principle that if the unit of concern is individuals, then individuals should be the sampling unit if one hopes to detect a direct cause of disease.)

The history of contagious bovine pleuropneumonia (CBPP) and its eradication from North America provide further insight into the usefulness of field observations, when attempting to understand and/or control disease (Law 1887; Jasper 1967; Schwabe 1984). CBPP (lung fever) was probably present in Asia for hundreds of years before the nineteenth century. It was probably spread throughout Europe by the movement of cattle as a sequel to the Napoleonic wars and was introduced into North America, Australia, and probably Africa by shipments of infected cattle.

The first recorded case of lung fever introduced into the United States was in a cow purchased from an English ship in 1843. Later shipments of cattle from Holland to America (1859) were also known to be infected. The disease had a long incubation period, approximately 4–7 weeks, and was usually progressive, with severe debility or death within a few weeks to months subsequent to clinical onset. Field observations suggested that animal to animal contact was the major route of transmission, although spread by fomites (human clothes or boots, infected barns, feed, and manure) was known to have occurred. Effective transmission usually required close and prolonged animal-to-animal contact, although numerous examples of its spread after brief contact are cited (Law 1887). (Interpretation of the historical information on this subject is difficult because other respiratory diseases may have been confused with CBPP.)

Initially, much debate centered on "spontaneous generation" versus "contagion" as an explanation for the pattern of disease occurrence. However, with careful documentation of cases and outbreaks (descriptive epidemiology), it became clear that imported or purchased cattle were the most logical source of the disease in almost every instance. Experiments were also conducted to demonstrate conclusively that the disease was contagious and did not arise spontaneously. It was noted, however, that the disease spread more rapidly and tended to be more severe during the summer than during the winter; this feature may have been of help in the eradication program. (The disease was more difficult to control in warmer climates such as Australia, a country that only recently became CBPP-free.) Early uncoordinated control efforts by individual veterinarians and farmers proved unsuccessful at slowing the spread of the disease, and by 1886 it had spread to Illinois, Kentucky, and Missouri. Consequently, the export of meat and meat products to England from the United States was terminated; the embargo lasting for almost 35 years, long after CBPP had been eradicated.

In 1856 the Bureau of Animal Industry was formed in the United States under the direction of Daniel Elmer Salmon, and in 1887 Congress provided sufficient funds to begin a large-scale organized eradication program. These activities included case-finding, slaughter of infected animals and/or herds, disinfection with lime and/or sulphur as well as fodder and manure disposal on infected farms, and quarantine, both for cattle entering the United States and for cattle movement within the continent. Through these activities CBPP was eradicated by 1892, at least 6 years before Nocard, a French veterinarian, cultured and identified the direct cause of the disease, a mycoplasma agent. This successful campaign was the first major triumph of organized veterinary medicine in North America. Today, the eradication of CBPP and the work of Snow on cholera serve to remind epidemiologists that control of disease is possible without a complete understanding of its etiology or pathogenesis provided that a sufficient amount of its natural history is known. Knowing the natural history of a disease often suggests weak links in the causal chain, that if broken can prevent the spread and/or persistence of the disease.

The fourth basic concept of epidemiology is that controlled field experiments should be performed whenever possible. However, they should be performed in the species of interest and in its natural environment. Such experiments, often called field trials, are analogous to laboratory experiments requiring the same design and performance rigor. In field trials the type, timing, and level of challenge are left to nature; the possible modifying effects of the natural environment are incorporated in the trial such that the results are directly applicable to practical situations. Thus, although a major part of epidemiologists' work involves observational studies, the necessity to conduct experiments under field conditions can not be overemphasized. For example, Snow's ultimate evidence incriminating contaminated water as the major factor in the cholera outbreaks was obtained from an experiment; his experiment involved removing the handle of the Broad Street pump at a major contaminated water source in this area of the city. This forced the people to walk to a more distant but clean water source. Subsequently, a dramatic decline in morbidity and mortality from cholera occurred in this area of London, while people in other areas supplied with contaminated water continued to experience high levels of sickness and death.

A number of new drugs, vaccines, and feed additives have been marketed for prophylactic and therapeutic purposes. At the same time, many programs, including the construction of new buildings, have been proposed to prevent or control disease. If these products or programs were as effective as originally claimed, there would be little need for the continuous supply of new programs and products. Changes in resistance patterns, emergence of new agents, and new demands from industry and society (e.g., protection against residues) may place demands on the biologic industries to supply better products. However, many biologics and disease control programs are not adequately tested to ensure that they are efficacious under field conditions at the time of marketing. Often, officials in charge of licensing biologics do not believe that field trials are practical or valid; hence most governmental licensing agencies do not require formal randomized field trials to be conducted prior to licensure. It is an unfortunate truism that efficacy under controlled laboratory conditions is often not validated under actual field conditions. A review of bovine respiratory disease vaccines discusses and highlights some of these problems (Martin 1983).

Today most progressive medical schools stress the need for controlled trials to ensure that medical practitioners do more good than harm when they administer biologics to their clients. As mentioned, some veterinarians and medical doctors advance the argument that testing biologics or disease prevention programs under "real-world" conditions is inappropriate because of the lack of control over challenge; others believe that any experimentation with clients' animals is unethical. In general, the epidemiologic stance on this matter is that it is necessary to evaluate biologics and disease control programs under the conditions that will be used in the field and to alter the management systems and/or develop new biologics as required. Field-trial design can make allowance for the probability of challenge, the likely effectiveness of the product being evaluated, etc. Failure to experiment may allow the widespread use of ineffective programs or potentially dangerous biologics, which might prove more costly biologically and economically than the original disease.

1.4 Nature of Epidemiologic Studies

Epidemiologic studies follow the general scientific method. Hypotheses are derived from clinical observations and descriptive studies (descriptive epidemiology and case reports) in combination with existing knowledge about the disease. (Recall that Snow's original hypothesis was based on his clinical observations, and his initial descriptive studies provided results consistent with his hypothesis.) These theories are then tested by a formal study, the results of which either validate or modify current knowledge. The process is repeated, each iteration of this cycle bringing the investigators closer to the solution of the problem.

At any point different disciplines may be at very different stages of this cycle (e.g., there may be much knowledge about the pathogenesis of a disease yet little knowledge about the natural history of that disease), and given the current burgeoning of knowledge, today's facts will probably change in the near future. It is partially for this reason that this text stresses concepts (organizing principles) and methods whose rate of change is much slower than that of facts. In this regard, Schwabe (1982) has summarized five scientific revolutions in veterinary medicine (the profession's response to the recognition by researchers and practitioners that the prevailing concepts were inadequate to solve prevailing problems) and the new developments these revolutions produced. In terms of disease causation, the concepts have evolved from supernatural forces, to natural forces (miasma), humoral imbalances, and man-created filth (sanitary awakening) to specific etiologic agents. Today most medical professionals accept the concept of multiple determinants (i.e., host, agent, and environmental factors).

The formal evaluation of hypotheses is central to the advancement of medicine. The three distinctly different approaches to hypothesis testing are observational studies, controlled experiments, and theoretical studies.

In observational studies, the epidemiologist observes but does not attempt to influence or directly control the independent or dependent variables under study. That is, the epidemiologist has no control over which animals are exposed to a specific factor (e.g., vaccination) and no control over the challenge of that factor (e.g., the presence or absence of specific organisms). (The presence of the investigator may indirectly influence the factors under study, however. This is true when studying management factors, particularly when the study is conducted over a prolonged period. Revealing initial results can similarly induce owners to change their management practices before the study is completed. These unintentional effects need to be considered when performing and interpreting the results of observational studies.)

Experiments may be laboratory- or field-centered and may be classified as true experiments if formal random allocation to treatment is used and quasi experiments if formal random allocation is not used. As previously mentioned, it is an epidemiologic tenet that field trials (controlled experiments) may be required to assess how well products and programs work under field conditions (e.g., how well a vaccination regime works under field conditions). In laboratory experiments the investigator exerts direct control over the treatment (e.g., vaccination) and challenge (exposure) of the animals under study. This control can greatly enhance the precision of the results obtained relative to observational methods and field experiments, but the conditions of the experiment may differ sufficiently from actual field conditions so as to greatly restrict the extrapolation of the results beyond the actual experimental setting. The more natural the experimental setting, the less likely this is to be a problem. Regardless of where the experiment is performed, in true experiments the investigator exerts control over the actual allocation of treatment to individuals using a formal random process. In quasi experiments the investigator personally assigns the treatment rather than using formal random allocation. True experiments are much more likely to yield valid results than quasi experiments, particularly if the investigator is seeking to prove a point rather than trying to solve a biologic problem.

For a variety of reasons there are few examples of well-conducted field trials in the veterinary medical literature. Many veterinarians understand basic principles of experimentation, but laboratory experiments often utilizing germ-free animals, single-agent disease models, or highly controlled trials in atypical environments have dominated research interest. Although the latter experiments provide much useful basic scientific information, they are not substitutes for well-performed field trials. It is hoped that the use of experimentation under field conditions will become more widespread.

An example may help to clarify the difference between observational studies and experiments. There has been renewed interest in assessing the efficacy of vaccines against respiratory disease in feedlot calves, particularly when vaccination is conducted 3–4 weeks prior to shipment of calves to feedlots (preimmunization or prevaccination). In a field trial of these vaccines, individual calves were randomly (a formal, not haphazard, process) assigned to receive or not receive specific vaccines. The calves were identified by ear tag and followed to the purchasing feedlot; the subsequent rates of treatment for respiratory disease were noted (Martin et al. 1983). At the same time, an observational study was conducted based on the extent of respiratory disease in prevaccinated calves sold as part of a program to encourage preconditioning (weaning, creep feeding, and vaccination) and prevaccination (vaccination only). The owners of the prevaccinated calves had decided to vaccinate their calves; the decision was not influenced by the investigator. Nonprevaccinated calves in the same feedlots, many from the same saleyard, served as controls (Church et al.

1981). What then is the key difference between these two studies? The main difference is the control offered by the process of randomization. In the field trial, randomization ensured that the vaccinated and unvaccinated groups were comparable and thus prevented other factors, known and unknown, from biasing the results. (Technically, randomization allows one to calculate the probability of dissimilarities in the groups after assignment; it does not guarantee that the groups will be similar.) In the observational study a large number of differences may have existed between the vaccinated and unvaccinated calves, and these could magnify or reduce the true effect of the vaccine(s). Thus the evidence from one observational study is much less convincing than evidence from one field experiment, but the observational study is much easier to perform. In this instance both the experimental and observational study results suggested little if any benefit from prevaccination. (Note in this analytic observational study that the unit of analysis was a group of calves, not an individual calf. The importance of this difference will be elaborated in Chapters 2 and 7.)

The theoretical approach to hypothesis testing has expanded with the advent of modern computers and represents a major new and expanding activity for epidemiologists. In studies of this type, some form of model is used in an attempt to mimic reality. If the model can simulate field conditions closely, it may be used to test a large number of hypotheses without having to do expensive and time-consuming field studies. Although the use of this approach has only recently gained attention and credence in veterinary medicine, appropriate models can greatly enhance our ability to test multiple theories in a short period. For example, a model of mastitis in dairy herds (Morris 1976) can be used to investigate biologic and economic results from various control strategies. Similarly, a model of *Fasciola hepatica* in sheep (Meek and Morris 1981) can be used to assess alternative treatment strategies for sheep under various stocking densities and paddock conditions. Even much simpler mathematical models, such as the Reed-Frost model of disease transmission in populations, are illustrative of the principles that underlie the spread of infectious diseases (Schwabe et al. 1977). This approach to the study of disease will be described later (Chapter 8), and although still in its infancy, computer modelling will likely become an integral part of decision making in veterinary medicine.

1.5 Sequence of Causal Reasoning

Since observational studies are central to epidemiologic work and their use is only now becoming widespread in veterinary medicine, it may be instructive to review the reasoning process associated with these studies. In observational studies the sequence of causal reasoning might be described as a three-stage process. First, it is necessary to ascertain whether the independent variable (the exposure factor) is statistically associated with the dependent variable (the outcome). Second, if the variables are associated statistically, there is a set of accepted criteria to assess whether the variables are likely to be causally associated. Finally, the nature and consequences of the causal association may be elaborated, using for example, path models, simulation models, or actual experimentation.

Thus the study of associations is central to observational studies. The way in which epidemiologists use "association", in contrast to its general use by veterinarians and biologists, is perhaps best explained with an example. Suppose *Haemophilus somnus* is isolated from 30% of lungs of cattle with pneumonia. Does this mean that isolating the organism and having pneumonia are associated? In common usage, the word association describes two events occurring together (physically, functionally, or temporally) in the same individual. Thus in everyday parlance they would appear to be associated. However, epidemiologically speaking, there is insufficient information to reach such a conclusion. For two events to be associated epidemiologically, they must occur together more or less frequently than would be expected from chance alone. For an epidemiologic association, *H. somnus* must be present more or less frequently in cattle with pneumonia than in cattle without pneumonia. Notice that a formal comparison group is always required to measure association. That is, nondiseased animals are compared to diseased animals, and unexposed animals serve as a comparison for exposed animals. Statistical tests to evaluate the likelihood that the observed association (i.e., the difference in frequency of the factor or disease) is due to sampling error (i.e., chance variation) will be described in subsequent chapters.

Associations describe the relationship for categories of individuals rather than for a particular individual. As an example, there is a valid association between castration and feline urologic syndrome, the categories being castration status and urologic disease status. The association does not say that a particular cat developed urologic syndrome because it was castrated, nor does it say that a particular cat did not develop urologic disease because it was not castrated. It could happen in an individual cat that castration prevented the disease, although the general tendency was in the opposite direction. However, the stronger the association (the group experience), the more likely it is that the association based on categories of individuals may apply to individual cats. Thus if 90% of agammaglobulinemic calves die within 28 days of birth and only 2% of calves with normal levels of gammaglobulin die in that period, it would very likely be true to say that an individual agammaglobulinemic calf died because of the lack of globulins. Arguments such as this that move from the general (the study result) to the specific (the individual) are termed deductive. Arguments that move from the specific (the study) to the general (the reference population) are called inductive. For either type of argument to be of value, the study results must be valid; hence this text stresses methods of design likely to enhance the validity of results.

The above scenario also illustrates the difficulty in establishing the cause(s) of an event in individual animals. If an aborted fetus is infected with bovine virus diarrhea virus (a putative cause of abortion), what is the likelihood that the fetus was aborted because of this viral infection? In other words, what is the probability that bovine virus diarrhea virus was the cause of abortion in this fetus? Further study of this text should provide the reader with a basis for attempting to answer this and similar questions.

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