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Epidemiologic Practice
Basic Principles

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There are three main circumstances in which the occupational physician may utilize epidemiologic methods or studies. These are:

- In the investigations of individual cases of injury or illness
- Initiating, conducting, and evaluating epidemiologic reports or research
- Investigations of epidemics

Since several excellent texts describe sophisticated epidemiologic methods that have evolved in the last 50 years, this chapter will provide certain basic and practical guidance that is oriented to these three areas of epidemiology serving as an introduction to the practice of epidemiology and its application in occupational medicine.

INVESTIGATION OF CASES

The conceptual framework for the investigation of individual cases of specific illnesses and injuries comes from the arena of clinical medicine. In 1913, Ernest Amory Codman, a Boston physician, proposed a system for the evaluation of the end results of surgery in order to improve the quality of clinical care.[34] For each surgical patient, Codman advised asking a series of questions:

1. What was the matter?
2. Did they find out beforehand?
3. Did the patient get entirely well?
4. If not, why not?
5. Was it the fault of the surgeon, the disease, or the patient?
6. What can we do to prevent similar failures in the future?

This general methodology has been adopted subsequently for the prevention of maternal mortality, anesthesia deaths, and the like.

In 1976, Rutstein[32] proposed a similar approach for patients with a broader array of conditions and with a broader goal—the evaluation of the quality of medical care. Rutstein and colleagues defined a *sentinel health event (SHE)* as a case of unnecessary disease, unnecessary disability, or death whose occurrence was a *warning signal* that the quality of preventive or medical care may need to be improved. In the 1980s, Rutstein worked with colleagues at the National Institute for Occupation Safety and Health (NIOSH) to devise a *SHE (Occupational)*.[33]

A *SHE(O)* is defined as an unnecessary disease, disability or untimely death which is occupationally related and whose occurrence may:

1. Provide the impetus for epidemiologic or industrial hygiene studies
2. Serve as a warning that materials substitution, engineering control, personal protection, or medical care may be required

Examples of SHE(O) include tuberculosis in health care workers, silicosis in sandblasters, and cataract in microwave technicians. The original list of SHE(O) has been updated by Mullan and Murthy.[27]

The essence of the SHE(O) approach is the recognition that occurrence of cases of specified diseases or injuries represents a failure of prevention. In the occupational setting, a reasonable and modifiable set of questions might include:

1. Was this case preventable?
2. Was there a failure of primary prevention (control of exposure or physical hazard), secondary prevention (screening and early detection) or tertiary prevention (medical care and rehabilitation)?
3. Are other co-workers similarly at risk?
4. What preventive efforts will this case stimulate?

The practicing occupational physician should consider three types of cases for investigations. The first class of cases should be derived directly from the lists of preventable, nonoccupational cases promulgated by Rutstein in 1976. This list focuses on nonoccupational diseases that occur in the general population and are amenable to preventive efforts valuable for everyone, not only workers. The occupational physician along with the owner/operator of enterprises will have to determine whether they have a role in the prevention of nonoccupational disease occurring among members of the work force. The second class of cases should be the list of occupational diagnoses designated as SHE(O)s by Mullan and Murthy. This list includes well-recognized, preventable occupational diseases. Occurrence of cases on either of these two lists provides an opportunity for prevention of occupational and nonoccupational diseases.

The published SHE(O) list is general and may not reflect in detail the potential exposures in a particular workplace. To most effectively utilize the "SHE approach," the occupational physi-

cian must have a thorough appreciation of the exposures to which the workers are exposed and the diseases that are well known to be associated with the exposures (see Chapters 9 and 52). In addition, if the SHE approach is to serve as an early warning system for a problem that is suspected but has not yet been documented, the occupational physician should work with an industrial hygienist and/or toxicologist to predict expected but not yet documented outcomes of exposure. In summary, the occupational physician should devise a SHE(O) list to suit the specific workplace and its potential risks and exposures.

There are many ways in which the SHE(O) approach can be instituted. Key to all of these approaches is for the physician to be cognizant first-hand of the known and suspected hazards of the workplace. The simplest and most intuitive approach is for the occupational physician to inquire whether each episode of illness or injury occurring in the work force represents a failure of prevention. More formal surveillance programs may be based upon a variety of data sources as well as a variety of mechanisms for investigation. Examples of data sources include absentee reports due to illness or injury, claims for workers' compensation, claims for medical benefits for health insurance, and review of death certificates submitted to obtain insurance benefits and the like.

On occasion, the occupational physician must investigate an epidemic. A useful paradigm for the investigation of epidemics has been developed over decades by the Centers for Disease Control.[8] Before embarking on the practical steps for investigating an epidemic, the investigator should reflect on the goals for the planned investigation. Four major actions are possible.

The etiology, that is, the specific agent (whether chemical, physical, viral, etc.) responsible for disease, may be known or not. The mode of transmission of the agent may or may not be well known. The etiology of disease may be known as well as the mode of transmission.

A thorough case investigation requires a multidisciplinary approach. Regardless of whether the investigation is conducted by a physician alone or by a multidisciplinary team of physician, industrial hygienist, nurse and toxicologist, the goal should be to identify the full range of possibilities for prevention. This includes attention to the adequacy of engineering and administrative procedures to control exposures or hazardous conditions, primary prevention and secondary prevention, which may include selected medical tests for early detection of disease and tertiary prevention which is appropriate medical care and rehabilitation.

On occasion, so many cases of a preventable disease or injury will occur either over a short enough time period in a well-defined place or in particular people that it is obvious that an epidemic is occurring (e.g., in the early 1990s, cholera in Peru, in 1993 cryptosporosis in city water supplies in Milwaukee and other cities). This is consistent with Last's definition of an epidemic: "The occurrence in a community or region of cases of an illness, specific health-related behavior, or other health-related events clearly in excess of normal expectancy . . . ."[18] This definition fits the classic communicable disease epidemic in which an excess of disease in a particular community begins at a particular time, takes its toll, then subsides either burning out after taking its toll or having been controlled by some intervention. Last's definition is more problematic when used to describe when the continued accumulation of cases over a long period of time appears quite consistent with expectancy but in excess of that desired. For example, there is a continuing nationwide epidemic of highway fatalities which we intuitively recognize as preventable only if drivers did not drink, vehicles did not fail, roads did not cross train rails, and so on. Some may prefer to call the occurrence of these problems that occur predictably—such as highway fatality, cancer, and chronic disease—endemics. Last defines an endemic disease as "the constant presence of a disease or infectious agent within a given geographic area or population group; may also refer to the usual prevalence of a given disease within such area or group."[18]

The outcropping of an obvious excess of disease or injury may occur by chance alone and not be attributable to any failure of prevention in the work force or community.

What is a disease "cluster"? A cluster is an unusual aggregation of health events, real or perceived. This aggregation occurs in a given time span and in a limited geographic area. Disease cases included in the cluster might share toxic substance exposure, interpersonal contact, or occupation. Earlier examples of clusters of cases include the epidemic of cholera in London in the 1850s; Legionnaires' disease at the Bellevue-Stratford Hotel in Philadelphia in 1976; and Pneumocystis carinii pneumonia among young, homosexual men in Los Angeles. Among the disease clusters reported, "neoplastic clusters" (leukemia) and multiple sclerosis are more often reported.[7]

How are clusters investigated? An investigator will:

- Characterize the cluster (e.g., location, disease types, history, and suspected toxic exposure)
- Verify actual disease occurrence using medical records, death certificates, or disease surveillance data (e.g., by State Cancer Reporting System)
- Assess toxic exposure potential using environmental monitoring data
- Compare cluster disease rates to geographic rates (community, county, and state)
- Determine the probability of a true cluster by:
  - Searching scientific literature for evidence of etiologic association between the cluster disease and any suspected toxic exposure
  - Considering the biologic plausibility that the toxic exposure may have resulted in the disease(s)
- Assess the cluster significance by evaluating disease rates, evidence of toxic exposure, and the possible relationship between the two
- Decide whether further epidemiologic study is needed

What are some of the limitations of a cluster study? Cause/effect or even association between a disease cluster and a possible toxic exposure is difficult to prove. Some of the limitations of cluster studies are:

- The number of disease cases in cluster is often too small to allow meaningful statistical analysis. Thus, the investigator is prevented from determining whether the disease rate is truly higher than expected.
- Even if the cluster area has a higher than expected disease rate, this may still be a chance event.
- Before it can be verified that a cause/effect relationship exists, a study must demonstrate that people who developed the disease had a (toxic) exposure at greater levels than those who did not. Cluster studies do not typically address toxic exposure dose.
- For cancer clusters, the latency period makes it difficult to link it to a toxic exposure. The latency period for cancer ranges from approximately 5 to 30 years. Therefore, if a study is an attempt to determine possible causes of cancers diagnosed in the present, it would have to consider toxic exposures that occurred 5 to 30 years ago (often difficult, or impossible, unless accurate records are available; a problem in the United States).

What factors support or refute a true disease cluster? First, if the cluster consists of many different diseases or cancer sites, it

almost certainly is not a true cluster and cannot be attributed to one toxic substance in the environment. Second, if the cluster is a cancer cluster and it includes rare cancers occurring among an unexpected group, it may, in fact, be a true cluster. A classic example is the discovery of liver angiosarcoma and vinyl chloride exposure (see Chapter 50).

The second situation is one in which the source or transmission of the causative agent is known but the etiology or causative agent is not. For example, the goal of an investigation of vitiligo was not the mode of transmission (skin exposure) but, rather, the identification of the causative agent. The goals in this instance were dual: control of the epidemic, and research into the chemical etiology of vitiligo (see Chapter 9 for details).[28]

The third situation is one in which the etiology is known but the source of transmission is not. For example, the tubercle bacillus is the known etiology of tuberculosis; in recent investigations of tuberculosis in hospital personnel, the relevant questions have been the means of exposure, direct contact with patients, or recirculation of air due to malfunctioning ventilation used to isolate infected patients. The goal of this investigation was not research into the etiology of tuberculosis but investigation of its transmission and adequate means of control of exposure.

In the fourth situation, the etiology of the disease is unknown, as is the source of means of transmission. For example, several studies have identified farmers to be at increased risk of non-Hodgkin's lymphoma. The goals of investigation are to identify the etiologic agent and the means and sources of exposure.

A modification of the steps recognized by the Centers for Disease Control are discussed below.[6] This series of steps in the investigation of an epidemic assumes that there is a system of surveillance, formal or informal, for learning of the occurrence of clusters of cases that raise suspicion that an epidemic is occurring. Ideally, prior to the first step is maintenance of a surveillance system that will alert the physician to the possible occurrence of an epidemic. Identification of the epidemic may be the key role played by the occupational physician. A case definition should be created. The case definition can be broad, designed to capture as many true cases as possible, accepting that the net will snare other cases and diagnoses that will later be determined as not verifiable cases or that are not related to the epidemic. Alternately, the definition can be narrowly drawn accepting a loss in *sensitivity* (the ability to detect all cases) but an increase in *specificity* (ability to exclude noncases from the case list). Depending upon the circumstances, there can be motivations to manipulate the case definition in either direction. The investigator should be cognizant that there are goals and consequences of broad and narrow case definitions and should also recognize that epidemiologic case definitions differ from clinical case definitions or case definitions used for administrative purposes, such as awarding workers' compensation. The investigator/epidemiologist should consider establishing categories of cases, including "noncase," "possible," "probable," and "confirmed cases," based upon the availability and content of information in relationship to the case definition.

1. Step 1 of the epidemic investigation is consideration of the goals of the epidemic investigation. Are the goals to institute control measures and contain the epidemic, to describe the etiology of the epidemic, or to identify the means of transmission of the etiologic agent?
2. Step 2 involves preparation for the actual field investigation. In this phase, consideration should be given to legal and ethical responsibilities for notifying governmental health agencies such as the U.S. Occupational Safety and Health Administration (OSHA) and state health and labor departments of the circumstances leading to initiation of an investigation. In this stage, an investigative team is identified and formed, capable of delineating exposure as well as investigating disease. To eliminate confusion in the field, a lead investigator, as well as a spokesman for the news media, should be identified.
3. Step 3, a "line listing" of purported cases, should be generated on paper or computer. Abstracted information about each possible case should be added to the line listing as soon as it is reported. Initially, even approximate information should include personal identifiers, source of information about the case, diagnosis (tentative or actual), and date of onset. If each case represents a row, then columns should be left available for adding other variables to the line list later. The investigator should guard his or her prerogative to use the line listing as a practical method for keeping track of a sizable amount of data. An entry on a line list should not be confused with confirmation of a case for epidemiologic, medical, or administrative reasons such as qualifying for compensation.
4. This step may lead to confirmation of the existence of an epidemic. At this stage, determination of whether the accumulation of cases on the line listing constitutes an epidemic is based upon qualitative rather than quantitative information. A few cases of a severe or rare entity should qualify as an epidemic, as should a longer list of more common diagnoses. The optimal outcome is that the line list would demonstrate multiple individual reports of the same few cases which may dispel concern that an epidemic exists.
5. This is the confirmation of cases and verification of diagnoses. Cases are verified by reviewing medical records, discussions with physicians, interviews of the cases, and the like. The goal of verification is both to better identify the epidemic disease and to further confirm the existence of an epidemic.
6. In step 6, there should be a search for other cases meeting the case definition. At each step, cases—whether confirmed or refuted—should be added to the line listing in an effort not to have the epidemiologist repetitively investigate the same case or become bogged down in separate and overlapping lists.
7. In this step, the investigator/epidemiologist begins to use the data to discern patterns that help to identify the etiologic agent and the means of transmission. Most (if not all) risk factors for disease can be subsumed into three descriptors: time, place, and person. Each of the categories of time, place, and person connotes a large number of other potentially important variables.
   - Time can be the time of onset of symptoms, the time of exposure, or the time interval between exposure and onset
   - Place may be the place of residence if an epidemic in the community is suspected, or the location within the work site, or distance from a common source of contamination
   - Person refers to attributes of the individual such as age and sex, as well as job, shift, exposures, and the like

There are two basic approaches to analysis of data from an epidemic: the calculation of rates and the display of cases of epidemic curves. An epidemic curve plots the distribution of cases by time of onset (Fig. 3-1).

The height of the column represents the number of cases occurring during a day, week, or month. This simple method allows display of the epidemic curve over time. Three different patterns may sometimes be discerned from this display that provide clues to the mode of transmission of the epidemic.

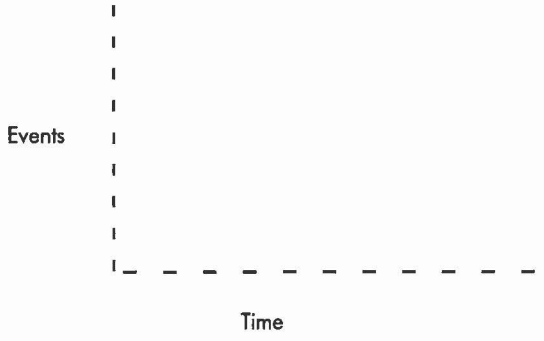

Fig. 3-1. Epidemic curve.

In an epidemic with person-to-person spread, there is often an index case followed by more cases separated by an incubation period, followed by another interval and even more cases, and so on until the epidemic becomes synchronous and loses its periodicity. This would be the pattern of an epidemic of hepatitis A propagated by person-to-person transmission.

In a common source epidemic, such as contaminated food served on a special occasion or the acute contamination of an air supply with a toxic gas, the distribution of cases is much like a bell-shaped curve with the tails representing cases at the extreme of the incubation period.

An epidemic with a continuing common source can have a random pattern until the interval between the exposure and onset is plotted, in which case it will have the normal bell shaped distribution of a common source epidemic.

The second basic approach to the analysis of data in epidemics is to calculate rates of disease by the same three variables of time, place and person.

SOME BASIC MEASURES AND TERMS

"Rate" is a basic unit in assessment of risk which may be associated with a particular exposure and requires an event (a response, such as symptoms, signs, frank disease, or death) in the population perceived at risk:

$$\text{Rate} = \frac{\text{Number of events}}{\text{Population at risk}} \times 100$$

Rates can be calculated by time, place, or person. For analysis by place, maps are also useful. Analysis of rate of disease by these factors, such as age, job, exposure to particular chemical, and the like, can be revealing in identifying high-risk attributes of the cases.

MORBIDITY RATES

"Incidence" is new cases developing in a population over some period of time:

$$\text{Incidence Rate} = \frac{\text{Number of new cases in a population during a prescribed time period}}{\text{Number of persons at risk of developing a disease during the same period of time}} \times 1000$$

Incidence rates are used in attempts to determine etiologic importance of different factors.

"Prevalence" is the total number of "cases" present during a specified time:

$$\text{Prevalence rate} = \frac{\text{Total number of cases present in a population at a specified time}}{\text{Number of persons in the population at the time period}} \times 1000$$

"Point prevalence" may refer to only a day and "period prevalence" may refer to a month or a year. Prevalence measures the total amount of "disease" in a population group and depends on incidence and duration:

$$\text{Prevalence} = \text{incidence} \times \text{duration}$$

MORTALITY RATES

a. Mortality rate is a measure of risk of dying. A death certificate is commonly used to describe the medical cause of death, but "occupation" recorded on the death certificate is often missing and generally unreliable.
b. "Specific rates" include cause-specific death rates, cause-specific incidence and prevalence rates, sex-specific rates, and age-specific rates. An example for age:

$$\frac{\text{Number of new cases among persons 50 to 60 during a specified period}}{\text{Number of persons age 50 to 60 during same period}} \times 1000$$

c. "Proportionate mortality" rate (PMR) relates to: "What proportion of all deaths (cases) are due to a particular disease?" (i.e., if 120 cancer deaths occur out of a total of 800 deaths, then the PMR is 110/1100 = 10%). The population at risk is not necessary. The PMR is hypothesis-generating only and should be interpreted with caution.
d. The "case fatality rate" may be used for acute diseases to indicate the proportion dying from a particular disease. It is the ratio of two numbers:

$$\frac{\text{Number of deaths from a particular cause in a given population during a specified time}}{\text{Number of persons with the disease in the same population during the same time period}} \times 100$$

e. The "standardized mortality ratio" (SMR) is the ratio of the number of deaths in a study population to the number of deaths expected if the study population had the same rate structure, such as "age-specific death rate": the "standard population." An SMR markedly greater than 100 indicates "an excess risk" and acts only as an "indicator" or concern.

$$\text{SMR} = \frac{\text{Observed number of deaths}}{\text{Expected number of deaths}} \times 100$$

Some other common words and terms found in epidemiologic reports are as follows:

"Bias"—This word refers to a systematic error in the design, conduct, or analysis of a study, inadvertent or deliberate. Some examples:

Surveillance or "diagnostic bias" can occur if "exposed workers" are "screened" and examined more intensively than nonexposed workers.

Knowledge and concerns about exposure (legal influences?) could influence validity of a diagnosis when symptoms/signs are uncertain or when a pathology specimen or a chest x-ray reveals an equivocal reading. The "test reader" should be "blind" to each worker's exposure status.

Interviewer bias may occur whether the interviewer is aware of worker "exposure." Helpful in minimizing this bias is a sound and tested questionnaire with strict adherence to answers as reported by the workers.

"Bias" is subjective; difficult to assess; and heavily based on judgment, experience, and skills of both investigator and reviewer.

"Confounding"—(means just that). This is a frequently used word which must be explained in detail when used. Simply stated, this may occur when a variable is associated with the factor under study and the disease (e.g., age). Control of "confounding" prevents a "confounding factor" as being the association between "exposure" and disorder or disease. Well-known examples are studies of lung diseases (cancer, etc.) and various work exposures if the smoking status is absent or not adequately dealt with in the study. Methods to deal with "confounding" may be found in the references.[3]

Another expression used with increasing frequency is the "healthy worker effect" (HWE). McMichael has redefined HWE:

> The HWE refers to the consistent tendency for the actively employed people to have a more favorable mortality experience than the population at large. Despite the clarity seemingly implicit in its name, the HWE is *not* an intentional measurement of the relatively good health of a working population; *nor* does it quantify the beneficial effects of the occupational environment upon those working within it. Rather it is an unintended bias, of uncertain magnitude, in an unavoidably imperfect comparative measure of the health status of a working population.[21,22]

Hernberg[15] emphasizes the HWE results in the SMR for the total mortality of an exposed cohort as being well below 100, provided there are no work-related or social factors increasing the mortality. In plain words, the HWE *is a negative bias.* An example is shown in Table 3-1. This is succinctly explained by Hernberg in that these and other employed populations have a better-than-expected outcome because of the incomparability of the large "third category" of the general population, which contains unemployed, disabled, and asocial people, all of whom have a higher-than-"normal" mortality. In addition, the general population and a cohort of blue-collar workers differ as to social structure. Thus, according to Hernberg and another world authority on epidemiology, Miettinen,[24] the use and emphasis on "HWE" ought not be used.

Table 3-1. Some SMRs Showing the Healthy Worker Effect (General Population = 100)

OCCUPATIONAL GROUP	SMR
Finnish foundry workers[17]	90
"Typical" foundry occupations[17]	95
American steel workers[20]	82
American rubber workers[23]	87
Finnish granite workers[1]	83
Finnish dock workers[2]	81
American chemical workers[29]	81

From references 14 and 15.

COMPARABILITY

An occupational epidemiologic study compares certain repeated findings (tendonitis), disease or death in a working population to a normal population. If the two populations are identical except for a specific hazard in the work setting, an elevated risk for death or disease in that working population is likely related to the particular hazard. Without careful comparability, an occupational study is meaningless, as it will remain unclear if any difference found is due to a work exposure or a basic demographic characteristic such as age or smoking. Comparability is achieved either during selection of cases and controls or during analysis by standardization with either the direct or indirect methods of standardization:

8. At this stage in the epidemiologic investigation, there may be compelling descriptive epidemiologic evidence to justify instituting preliminary control measures, which is step 8.
9. In step 9 the epidemiologist formulates reasonable hypotheses, if any, for the observed epidemic and tests those hypotheses using information already in hand. For example, there may be differential rates of illness between those who were exposed or not exposed to a particular chemical or food.
10. Tests of hypotheses may also involve other disciplines such as microbiology in search of infectious agents, toxicology, ventilation engineers, and so on.
11. Further control measures may be warranted based upon findings from these further studies.
12. In this step, the epidemiologist considers conducting other studies that further test the association between exposure and disease that was suggested in steps 9 and 10. Consistency between studies is a strong point in concluding that an association between exposure and disease is causal rather than a chance finding.

In the aftermath of the epidemic investigation (step 12) the epidemiologist should establish a surveillance system to insure that the control measures are preventing recurrence of disease. The Centers for Disease Control defines public health surveillance as "the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know."[6] Implementing surveillance after presumed cessation of an outbreak is basic and effective means of evaluating the public health measures instituted to control the epidemic. The final step is communication of the results, both locally to the immediate community involved in the epidemic and broadly through the literature, so that further epidemics are prevented.

Epidemiologic Research

While the principles and methods of analytic epidemiology are used in the study of epidemics, descriptive epidemiologic methods are often sufficient to delineate the relationship between exposure and disease. The development over the past few decades of modern methods of analytic epidemiology is more closely associated with the investigation of chronic diseases. Chronic diseases differ from most epidemic diseases in that their incidence is usually substantially lower than the incidence in epidemics. The interval between exposure and onset of illness, known as latency, is usually years or decades rather than days or weeks.[8] Finally, there are often multiple causes for chronic diseases, and multiple effects from the exposures that cause

chronic disease, as compared with the less complicated one-to-one relationship between agent and disease in many acute epidemic diseases. There are many exceptions to these generalizations.

The overriding difference between investigations of epidemics (usually of acute disease) and epidemiologic research (usually of chronic diseases or endemic diseases) is the motivation for the investigation. In the epidemic situation, the immediate goal is usually the control of the epidemic. The means to that goal are elucidating the etiology of the disease and the means of transmission or exposure. In epidemiologic research the immediate goal is to conduct research in service of the long-term goal, which is the prevention of disease.

The methods used in epidemiologic research are the same as in epidemic investigations, although the luxury of planning an epidemiologic study, with extensive forethought about detailed information to be collected and collection of sufficient cases and one or more comparison groups, allows for the collection of more complicated data, and, in sufficient numbers of cases, allows for application of more complex epidemiologic methods. However, there are essentially two salient approaches to studying the relationship between exposure and disease: prospective or concurrent cohort studies.

These studies include two groups of workers ("exposed" and "nonexposed") followed forward in time to determine how many in each group develop a disease. Data from the general population are often used to represent the nonexposed group. Two incidence rates are computed and compared: "Ie" and "Ine," incidence in the exposed and nonexposed, respectively. The basic study design is:

Exposed	⟶	Diseased
		Not Diseased
Not Exposed	⟶	Diseased
		Not Diseased
(Present)	⟶	(Future)

Exposed and nonexposed are considered free of disease at the beginning of the study and are thought to be comparable. Such studies are expensive and time-consuming, especially with diseases that have long latency periods, such as cancers. The exposure and occurrence of disease may have occurred in the past or the population may be followed into the future.

The alternate approach is to assess the comparative frequency of prior exposure among cases as compared to noncases or controls. This is known as a *case-control* or *case-referent* study. Case-control/referent studies are called *retrospective studies* by some because the search is for prior exposure among cases.

Retrospective Cohort Studies

This is the most commonly employed epidemiologic method in occupational settings. It is essentially similar to a cohort study except *exposure and nonexposure are designated for the past instead of the present.* Exposed and nonexposed workers are identified from past medical and personnel records and followed forward in time to the present to determine the development of disease among the members of respective groups. Data for the general population are usually used to represent the nonexposed group. The basic study design is:

Exposed	⟶	Diseased
		Not Diseased
Not Exposed	⟶	Diseased
		Not Diseased
(Past)	⟶	(Present)

The study population may consist of (1) all hourly employees of an industry (e.g., iron foundry), (2) all hourly employees of a company, (3) all hourly employees of a particular plant within a company (e.g., welding), or (4) all hourly employees associated within a company (e.g., styrene/butadiene production of synthetic rubber). Selection depends on study objectives and available information.

Reviewing records requires taking personnel data and abstracting pertinent aspects. Data are needed to identify the cohort at risk, conduct a follow-up for vital status, assess comparability with the comparison group (e.g., age), evaluate the effect of specific jobs (exposures), and attempt to determine if a "dose–response" effect exists. Follow-up requires locating and interviewing all members of a cohort in a morbidity study or ascertaining vital status in a mortality study by utilizing Social Security Administration (SSA) records or other data registers and obtaining a copy of the death certificate.

When choosing a comparison group, investigators often select the general population and the data available from national data sources. Analysis of the data occurs after the data have been collected, coded, and computerized. Computing the standardized mortality ratio is a frequently used method.

While in a case-control study, one identifies cases and noncase controls and determines the comparative probability of prior exposure. Epidemiology tests describe in detail the derivation of a variety of ratios used to describe the comparative rates in cohort studies or comparative exposure in case-control studies.

"Risk" and "Relative Risk"

Another basic measure of association in epidemiologic studies is the "relative risk." The relative risk is the ratio of the incidence of disease in the exposed to the incidence of disease in the nonexposed. Relative risk can be derived directly from a cohort (prospective or concurrent) study.

The occupational physician's role in epidemiologic research will usually be limited to interpreting studies in the literature,[5] collaborating with an epidemiologist, or serving as gatekeeper to insure that epidemiologic research conducted in his or her workplace is of high quality. In evaluating the worth of an epidemiologic study either reported or proposed, there are several issues that should be addressed.

The plan for epidemiologic research should be stated in a research protocol. The value of the protocol should be weighed in its clarity in presenting a meaningful and feasible hypothesis to be tested, presentation of appropriate methods for the study, and review of relevant literature. Since there is always the possibility of chance as an explanation for a positive or negative finding in a study, it is very important that the hypothesis be specified in sufficient detail in the protocol so that the reviewer can judge whether to accept or reject, based on the completed study that a causal association between exposure and effect before the research is conducted and again in light of the results of the research. A parallel concern has to do with manipulation of results

by a short-sighted investigator or in a subsequent re-analysis. It is usually possible, but of course inappropriate, after perusing the data, to manipulate case definitions or categories of exposure to insure a positive or negative finding. To insure against this and to defend against this allegation, it is best to present in the protocol one or more methods for categorizing data or actually specify the cutpoints that will be used to define a case, level of effect, or exposure.

The protocol for any epidemiologic study should be reviewed and commented upon by a panel of peers, since epidemiologic studies are important and are often the subject of substantial contention. This fact, combined with multiple appropriate options for designing and conducting a study, can lead to endless rounds of debate which divert from a study having an appropriate contribution. Conceptual and calculation errors also occur in the design of a study. Peer review of a study and periodic review of its progress and the study results are extremely useful in helping to insure that the study makes a valuable contribution to prevention.

There are three major elements in the design of occupational studies that can lead to falsely negative conclusions: the size of the population studied, its level of exposure, and the length of time since it was exposed.

It has become standard to calculate the *power* of a study. Power is the ability of a study to avoid a false negative conclusion. Intuitively larger studies are more powerful but also less feasible, as they are more expensive to conduct, and it is more difficult to identify sufficient numbers of exposed participants for a cohort study or cases for a case-control/referent study. In considering the calculation of power in the protocol, the occupational physician should determine whether the estimate of power assumes that all members of the cohort are sufficiently "exposed" to expect the postulated effect. Often, power is calculated using all members of the cohort, while in reality only a fraction of the cohort is in a high risk category. The power estimate for the high risk subcohort may be substantially lower than for the entire cohort.

Estimation of exposure has not uniformly received adequate attention in study design. Substantial effort must be expended to delineate the level of exposure of a spectrum of cohort members. It should not be assumed that all cohort members are equally exposed or substantially exposed. It may be that only a small subcohort of a very large population had sufficient exposure to expect an adverse effect. Attention should be directed at all levels of exposure in order to conduct dose–response analysis.

In summary:

1. Biologic measurements (e.g., blood, urine, spirometric tests, audiometry, chest x-rays, etc.)
2. Air samples collected from the breathing zone with the aid of portable samplers
3. Area sampling by stationary samples
4. Classification of the exposed subjects by work area, type, and time on job, and occupation title (e.g., supervisors, even crane operators and inspectors are often overlooked)
5. Classification into "exposed" and "nonexposed"

Exposure should not only be classified according to intensity but also to duration, fluctuations (peak exposures may be highly relevant), and calendar time (which is important, for example, when studying occupational cancers or diseases with a long latency). Concurrent other exposures should also be accounted for. Reports all too often delineate "exposures" arbitrarily: "light" ("minimal"), "medium" ("moderate"), and "high" ("heavy"); lacking quantifying hygienic data may make such terms meaningless. Investigators surely ought to visit the work site(s) being studied. (Refer to Appendix for details of workplace inspections.)

Mentioned earlier, *latency* is often overlooked in calculations of power. Latency is the time interval between the beginning of exposure and the onset of disease. The length of latency is variable and depends upon the type of disease. For viral diseases, latency, also known as the incubation period, can be weeks. For occupational cancers, intervals between exposure and disease can be decades. Clearly, a calculation of power would be inadequate, even if the cohort were very large, if the cohort members did not have sufficient time to develop the disease of interest.

Power is only one factor that should be considered in attempting to design a study likely to produce an accurate, rather than falsely positive or negative study. Biases are a major cause of erroneous studies. There are a multitude of biases that have been defined. For example, ascertainment bias, in which cases with the exposure of interest are either less or more likely to be included in the study than any other participant who does not demonstrate the effect or exposure of interest. A major role of the protocol is to determine if the researcher has made an appropriate attempt to identify and avoid relevant biases.

Another commonly seen and used term to check "validity" is the "*P*-value," a statistic known to many, but understood by few, as reiterated by Hernberg.[14,15] The *P*-value depends not only on the magnitude of the difference between two groups but also on the amount of information in the data. If the information is scant (very small groups), the point estimate of the rate ratio (RR) is subject to great random variation and the *P*-value is rather uninformative. By contrast, if the information is very ample, even a small difference will produce a very low *P*-value. Such a small difference is usually without any biologic significance and can often be due to undetected confounding or other bias. Therefore, the *P*-value is uninformative also in this situation. One can say that it is too *sensitive* to be of any use.

For example, a rate ratio of 1.5 is significant ($P = 0.01$) in a study of 1000 exposed and 1000 referents if the mortality is 10%. However, the same level of significance in a study of 50 exposed and 50 referents requires a rate ratio of 11. Assume that the issue is occupational lung cancer caused by exposure to chromates. Smoking could confound the "significance" of the larger study, whereas such confounding would be impossible in a smaller study, assuming the same level of significance in both ($P = 0.01$). Of course, a rate ratio of 1.5 would have been far from significant in the smaller study, and a rate ratio of 11 in the large study would be even more convincing than in the small study. The conventionally used levels of significance (i.e., $P = 0.05$ or 0.01) are arbitrary and without any theoretical grounds.

The difficulty of interpreting the *P*-value whenever the information is very ample should of course not lead to one overlooking such data. Instead, a quantitative assessment of the group difference becomes meaningful. In other words, one should regard the rate ratio rather than the *P*-value. Hence, in large studies, the magnitude of the rate ratio is more informative than the statistical significance. But the smaller the amount of information, the more the rate ratio is influenced by chance, and the more uncertain its absolute value (point estimate) is.

No significance test can separate a bias from a true effect. If biases are present, statistical testing loses its meaningfulness, and it may be highly misleading in the hands of uncritical so-called scientists. A *P*-value is, therefore, never a summarized package truth but only one of the several tools we have to evaluate the data.[15]

To reiterate and reinforce, the study plan should include the following elements, according to Hernberg:[15]

0. Summary
1. Background
2. Objectives
3. Study design
4. Methods and procedures
5. Control of confounding
6. Preparation of data and computerization
7. Statistical methods
8. Ethical considerations
9. Publication and information
10. Time schedule
11. Project organization
12. Budget
13. Approval (by appropriate authority) *[editor's note: C.Z.]*

Role of Epidemiology in Prevention

Review of a model developed for prevention[19] will help to orient the physician to the roles of epidemiology in prevention. The first step in prevention of a public health or occupational problem is the recognition that there is a problem. There are various routes to the identification of a problem. The sudden occurrence of an extraordinary number of cases of occupational or communicable disease, an epidemic, is a blunt announcement of the arrival of a new problem. In occupational health, the situation can have more subtleties. For example, recognition that workers do or may have exposure, coupled with an experimental study that the agent is or may be a carcinogen, reproductive toxin, or the like, also constitutes a problem needing the attention of the occupational physician. Epidemiology, particularly surveillance, plays a major role in the recognition of new health problems.

A health surveillance system provides an organization work force the capability of assessing the health status of its employees, of identifying any excess disease, and, especially along with industrial hygiene data, of ascertaining specific health hazards in that workplace. The extent and frequency of the surveillance program is determined by the type of work environment, as well as the perceived hazards or risks. "Biologic monitoring" may be part of measurement of exposure (see Chapter 10).

Another step in the process is definition of the size of the problem. Intuitively, one or a few cases of some diseases, such as polio or plague, may equal or overshadow the occurrence of many cases of other less consequential diseases. When there is debate whether there is a causal association between exposure and disease, identification of a biologic mechanism that is a plausible explanation for the suspected disease adds substantially to the recognition of a cause/effect relationship. Epidemiologic research often contributes to delineating the etiology of public health problems.

Falsely negative conclusions can also be reached when:[15]

- The measures of morbidity are crude
- There are random errors
- Nondifferential misclassification occurs
- Wrong or irrelevant morbidity indicators are used
- The study material is too small
- The study design is inefficient
- Wrong exposure categories are studied
- The exposure is too low and/or short
- The follow-up is too short or incomplete
- Allowance is not made for a latency period

Whether a disease can be prevented depends upon the design or discovery of effective preventive measures. Much depends on societal, economic, and other issues beyond the technical ability to intervene in the disease process.

After reading this chapter and reflecting on one's capabilities and available resources, is an "epidemiology study" of a perceived problem feasible? Some cautions and advice follow:

- Does the company (enterprise, e.g., hospital, foundry, herbicide plant, etc.) understand what is involved? Is the owner/managing director/president willing to stand behind the intended study (not just verbally, but with a budget for support)? Is there hesitation or subtle (often overt) influence from the lawyers? If so, caution should prevail.
- If experienced and if the above factors are positive (and agreed in writing), proceed with recommendations found in this chapter.
- If not, is professional aid available (e.g., private or academic consultant or within the organization)? If funds to pay these experts are unavailable, local public health departments, state, or other jurisdictions are often willing to provide assistance. National institutes should be queried, but funding is a problem everywhere.
- Will results, positive or negative, be made public to employees, public, and possibly for publication?

If boldness prevails and with solid support, proceed! Begin with a study of Greaves,[12] Hernberg,[14,15] Monson,[25] Morton,[26] Axelson,[4,5] Last,[18] Mullan and Murthy,[27] and the other listed references.

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