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Epidemiologic Approaches to Chemical Hazard Assessment

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I. INTRODUCTION

During this century, populations of industrialized nations have experienced dramatic changes in the pattern and relative importance of various life-threatening illnesses. At one time, diseases such as tuberculosis and

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smallpox claimed large numbers of lives, especially in younger age groups. Now, these and many other conditions of infectious origin are rarely encountered. The resulting increase in average life expectancy, however, has resulted in a new set of public health problems. One of these problems, chemical contamination of the human environment and the assessment of health risks that may result, is the focus of this article.

Perhaps one of the most difficult questions in contemporary epidemiology and public health stems from evidence suggesting that most malignant disease is of environmental, perhaps chemical, origin. This supposition is particularly significant in the context of public health since cancer is the second leading cause of death, accounting for approximately one in every five deaths. Furthermore, mortality from cancer has increased in recent years, leading to the hypothesis that the spread and diversity of chemical contamination of the environment may largely account for this trend.

To the extent that carcinogenic agents are exogenous in nature, there is potential for intervening in the environmental network and thus preventing the occurrence of disease. It is this concept that forms the cornerstone of epidemiologic research. The primary purpose of epidemiologic inquiry is to estimate quantitatively the effects of those factors that determine whether disease does or does not occur in human populations. Classic epidemiologic models, in combination with evidence from laboratory research, are powerful tools for both generating and testing hypotheses about the etiologic significance of environmental contaminants. Epidemiologic investigations often result in the institution of preventive or control strategies—i.e., interventions in the process of disease causation—even in the absence of knowledge regarding the underlying biologic mechanisms. Consequently, epidemiologic research assumes a central role in the protection of the public health.

In this article, the major features of the epidemiologic approach to chemical hazard assessment are discussed. At the outset the fundamental sources of epidemiologic data and the process of generating testable hypotheses are described. Next, the methods by which such hypotheses are tested are considered. In particular, the focus is on the ways in which measures of dose and measures of response are derived and evaluated in epidemiologic research. Finally, questions regarding the interpretation of dose and response measures are addressed.

The epidemiologic approach to disease may be described as proceeding in two major phases. The first phase, discussed in the following section, involves the conduct of "descriptive" epidemiologic studies. It is important to emphasize that the primary purpose of these studies is to *generate* hypotheses of cause and effect, a goal achieved primarily by examining

patterns of disease occurrence with respect to time and place. The second phase, discussed in Section III, involves conducting more rigorous "analytic" studies, studies whose purpose is to *test* hypotheses previously set forth.

II. DEVELOPING CLUES TO CHEMICALLY RELATED DISEASE: DESCRIPTIVE APPROACHES

A. Fundamental Epidemiologic Tools

1. Measures of Disease Frequency

In this subsection, measurements of disease occurrence that are fundamental to any epidemiologic investigation are discussed. Subsequently, the role of these measurements in typical epidemiologic models is considered.

There are several measurements that reflect various aspects of the frequency of disease in a population. In general, these can be divided into two major categories. The first relates to measures of morbidity, or illness; the second concerns mortality.

One of the most basic concepts with respect to the measurement of disease occurrence is that of a *rate*. Most simply, a rate may be defined as the frequency of a condition in a defined population over a specific period of time. Clearly, an absolute count of cases, without reference to a population of known size, precludes direct comparisons between groups. For example, if it is known only that n_1 cases of Disease X occurred in Community A, and n_2 cases in Community B, there is insufficient information to determine in which community the occurrence of the disease is greater. If, however, the size of the population in which the cases were detected is also known, the rate at which disease occurs can be computed, thereby yielding figures that are comparable.

With respect to morbidity, the rate that is usually of most interest is the incidence rate. This is a direct measure of the probability or risk of illness. Ideally, incidence rates would be based on prospective surveillance of a well-defined population in which only those individuals who are at risk of developing the disease under consideration are included in the denominator. Although denominators are rarely this precise, they should not include persons who already have the disease or are not susceptible.

Mortality rates, on the other hand, represent the probability or risk of death. The number of deaths in a defined group constitutes the numerator of a mortality rate, while the denominator represents the total number

of persons in the defined group, i.e., the number of persons at risk of dying.

Morbidity and mortality rates may be expressed as either crude, specific, or adjusted rates. Crude rates can be constructed from a minimal amount of information; they require knowledge only of the total number of events (e.g., births, deaths) and the size of the population in which the events occurred. However, to the extent that the risk of illness or death is not uniform (equally probable) across all members of a population, specific rates can provide more useful information. Typically, specific rates are defined with respect to age, race, sex, or some combination of these demographic characteristics. The basic formula for a specific rate includes in the numerator the number of events of interest in a homogeneous population subgroup, and in the denominator, the number of persons at risk in that same subgroup. Therefore, an age-specific death rate could be computed for persons 50–54 years of age; the rate could further be confined to white male members of the population in this age group.

The general advantage of specific rates, whether for morbidity or mortality, is that they do not obscure potentially significant differences among population subgroups. Since these rates provide a high degree of detail, they are very useful for both analytic and health planning activities. This is particularly true if the condition under consideration exhibits great variation in occurrence among different age groups. Most chronic diseases, such as cancer and cardiovascular disease, manifest such a pattern. When morbidity and mortality rates are, however, used to compare disease experience in two or more populations, specific rates can present problems. Age-specific rates are often computed for either 5- or 10-year intervals, thus yielding as many as 18 rates per population. For many types of comparisons the task becomes cumbersome and the results difficult to interpret. Therefore, it is often preferable to compute some type of summary figure, which usually implies an adjusted rate.

Adjustment is a procedure by which differences in the composition of groups are removed, so that the difference does not bias the comparisons of interest. The need for adjustment is illustrated by the difficulties that can be introduced when only crude rates are used. For example, if interest centers on a disease such as cancer, an illness occurring more frequently in older persons, the rationale for adjusting for age is clear. If Population A has a higher proportion of older individuals than does Population B, but the risk of dying for persons in any specific age group is the same, the crude rate will be greater for Population A. This would lead to a misinterpretation of the risk of dying in each population. What is required is a method of comparing the two groups as if the age distributions were identical. This can be accomplished by the "direct method"

of adjustment. By this method, age-specific rates are weighted not by the proportion of the population under study in the given age group, but rather by the proportion of an external standard population in the same age group. This procedure answers the question: "What would the rate in the study population be if its age distribution were equivalent to that of the standard population?" By adjusting several population rates to the same standard, direct, unbiased comparisons between groups can be made.

Although adjustment for age is probably the most common form of adjustment (or standardization), the same technique can be applied to remove differences with respect to other characteristics, such as sex or race. While the procedure is both well accepted and useful in a variety of analytic settings, it is not without disadvantages. First, it must be remembered that an adjusted rate is, in one sense, "fictional." That is, its magnitude depends not only on the "real" death rate in the study population, but also on the choice of the standard population. Second, because the adjusted rate is a summary figure, it may obscure different trends among subgroups. For example, if only temporal changes in age-adjusted rates are examined, differences across selected age groups with respect to the rate of change, or even the direction of change, may go unnoticed.

2. *Sources of Morbidity and Mortality Data*

This subsection considers some of the major sources of morbidity and mortality data commonly employed in epidemiologic studies of environmental phenomena. Some of the advantages and disadvantages of these sources are also discussed.

First, we consider mortality data, a source of information that appears to be quite straightforward, but in truth is rather complex. The fundamental resource for mortality data is the death certificate. A standard form for death certification has been developed by the National Center for Health Statistics, the agency responsible for the detailed tabulation of all vital records. The death certificate contains demographic information, such as the decedent's age, race, sex, place of birth, place of death, place of usual residence, marital status, and occupation. The medical portion of the certificate includes data on the immediate and underlying causes of death and on other significant conditions that may have contributed to the death. There is also an item indicating whether or not an autopsy was performed.

There has been a great effort to ensure uniformity in the death certification process and in the subsequent reporting of death records. In this regard, the *Physician's Handbook on Medical Certification* specifies rules for

recording the cause of death, rules that distinguish between the immediate cause and the underlying cause (*160*). The immediate cause of death is the disease or injury that directly preceded death; the underlying cause, which is the most important item for epidemiologic studies, is "the condition that started the sequence of events between normal health and the immediate cause of death."

Additionally, there are internationally accepted rules for coding the medical information contained in the death certificate. Numeric codes, as specified in the International Classification of Diseases (ICD) manuals, are assigned to each cause on the certificate. The most crucial part of the coding process is the choice of underlying cause of death, since this item becomes the officially reported cause. Rules for this section are outlined in a National Center for Health Statistics publication entitled "Instructions for Classifying the Underlying Cause of Death, 1979" (*161*). However, owing to differences in the way in which physicians complete the death certificate form, the process of choosing the underlying cause does involve judgment and is therefore subject to both random and systematic error.

In addition to outright errors in death certification and coding, there are some questions inherent in the way mortality data are reported that bear on their epidemiologic usefulness. One central question involves the forced choice of a single, underlying cause of death. Published statistics might lead one to believe that each death is the consequence of just one disease. However, the majority of death certificates, particularly for older persons, contain two or more diagnoses. This raises the medical question of how exact cause of death can be determined in an individual with multiple, potentially life-threatening infirmities (*93*). Furthermore, there is the data-management and statistical problem of tabulating multiple causes of death, which in practice is seldom done. Although computerization of death records is relatively recent, the coding of cause-of-death data into machine-readable form opens up the possibility of routine tabulations of multiple-cause data (*60, 91*).

The validity—i.e., the accuracy—of mortality data has been studied extensively. In this context, questions of validity relate to difficulties in ascertaining the exact cause of death. This issue is extremely important, since mortality data are perhaps the primary source of information on the consequences of illness experiences. For example, in several studies reported cause of death has been compared with autopsy findings (*64, 149*) and hospital diagnosis (*2*). Results of these studies indicate that complete concordance between clinical diagnosis and stated cause of death does not exist. Sources of discrepancies have been identified (*84*), and their effect on subsequently computed mortality statistics estimated

(*173*). While significant problems with the reliability and validity of death certificate data have been identified, the utility of this source of information remains high, assuming that the proper interpretive safeguards are heeded. Some of these cautions were pointed out in a study that directly compared the epidemiologic inferences that could be drawn using mortality versus morbidity data. In this study it was demonstrated that both sources of data lead to essentially the same conclusions (*182*).

For examining trends in the occurrence of disease over time or among selected populations, mortality data are the only resource that satisfies the criteria of continuity and coverage. As is discussed below, there is no single source of information on morbidity that is available for an entire country. In studies of cancer, for example, mortality data have been employed extensively because such data are assumed to be adequate surrogates for incidence data. This will be true for any condition for which the interval between onset of disease and death is reasonably short and for which the case fatality rate is high. Since mortality data are comprehensive, it is a reasonably straightforward task to compute death rates, assuming that appropriate population figures are available. These rates can then be applied in a variety of analytic models.

Although it is clear that mortality data are not error-free, morbidity data introduce additional complexities. With the exception of certain infectious and communicable diseases, incident cases of disease such as cancer are not reportable to any public health agency. Therefore, only through specialized programs are incidence data collected. With regard specifically to cancer cases, there are several data systems that compile information about individuals with malignant disease. The first such category of data systems is not population based, i.e., not all cases in a defined or definable population are included. Under these circumstances it is not possible to compute incidence rates. Despite this limitation, these systems have provided a substantial portion of our knowledge about the determinants of cancer. Most of these systems are hospital-based tumor registries, the purpose of which is to collect a standardized set of demographic and medical information for each cancer patient treated at the particular institution (*127*). However, since patients are not admitted or referred to hospitals on a random basis, the sample of patients in a tumor registry is rarely representative of all cancer cases in the community.

Although population-based analyses cannot be done with hospital registry data, these programs serve several useful research purposes. First, the health or vital status of patients is monitored over time, thus yielding data for the computation of survival rates. These are, of course, the most common endpoints for evaluating the effectiveness of cancer-directed therapy. Second, registry data allow for studies of specific variables

related to prognosis. Third, registries are extremely valuable for locating subjects for studies of factors related to the occurrence of disease.

An ambitious multiinstitutional tumor registry program has recently been undertaken in this country. The Centralized Cancer Patient Data System (CCPDS) is a network of tumor registries at institutions designated as Comprehensive Cancer Centers by the National Cancer Institute. Data for all patients treated at these major centers are entered into a common data base, and follow-up information is obtained annually. Between July 1, 1977 and December 31, 1980, data for 142,079 tumors were registered. Although these data are not population-based (therefore reflecting the selection factors intrinsic to referral centers), the value of the CCPDS lies in the high reliability and validity of the data that are abstracted. The system has rigid coding categories, a well-defined program of quality control, frequent training sessions for nonphysician abstractors, and computerized editing of each data item. The data base provides unique opportunities for the study of cancer etiology, particularly with regard to rare tumors, only a few cases of which may be treated at a single institution (*71*).

In addition to tumor registry data, there are some sources of population-based cancer incidence data in the United States. The largest of these is the Statistics, Epidemiology, and End Results (SEER) program (*234, 235*). The purposes of the SEER program include estimating cancer incidence in the U.S., monitoring trends in survival, and identifying etiologic factors. Each of these can be studied with respect to a variety of demographic and social characteristics of the population. There are 11 geographically defined areas that participate in the program, representing about 10% of the U.S. population. Although fairly representative of the entire U.S. population with respect to age, blacks and rural residents are somewhat underrepresented. This program is an outgrowth of the End Results program and the National Cancer Surveys (*49, 50*). Data are collected for all new malignancies occurring in the study communities. Cases are identified from hospital charts, pathology reports, radiation therapy records, death certificates, autopsy reports, tumor registries, and private laboratories. Complete information about the patient's demographic characteristics is collected, along with data describing the anatomic site and histology of the tumor, extent of disease, and first course of therapy. Active follow-up is maintained for all cases.

Although it has been established that cancer mortality rates are an acceptable surrogate for incidence rates, programs such as the Third National Cancer Survey (TNCS) and SEER provide certain information that cannot be obtained from death records. Most notable in this regard

are data on histologic type of the tumor and on stage or extent of disease at the time of diagnosis. The former is significant because cell type might be related to etiologic variables. The latter is important because of its relationship to survival.

B. Variations of Disease Occurrence in Time

The relation of disease occurrence to time is an important aspect of any epidemiologic evaluation of chemical hazards. While the occurrence of disease may be measured in terms of morbidity or mortality, time itself may be measured in terms of any appropriate dimension (hours, days, weeks, months, years, etc.). The relation between time and disease may therefore be viewed from a number of perspectives. In general, this involves examining fluctuations in disease occurrence that take place either over relatively short periods of time (e.g., over a number of hours, days, or weeks) or over relatively longer periods of time (e.g., over a number of years or decades). Although the temporal focus of the two approaches differs, the intent of each view is to gain insight into the reason or reasons why disease occurrence has fluctuated during the time period.

1. Short-Term Fluctuations

When a limited, well-defined, and homogeneous population is subjected to a single and intense chemical exposure, the effects of such exposure are likely to be manifested in a matter of minutes, hours, days, or weeks. Although the average amount of time that elapses before disease appears will depend on, at least, the mode and intensity of the exposure and on the toxicity of the agent involved, the pattern of disease occurrence in time over the short term may be expected to parallel (at least qualitatively) patterns demonstrated by common-vehicle, point-source epidemics of microbial origin. Following this type of exposure, such acute outbreaks may be described by the shape and location in time of their epidemic curves. Characteristically, onset of disease is explosive in nature; the epidemic curve is positively skewed (i.e., the distribution of onset times is log-normal); and the time interval between exposure to the agent and clincial manifestation of the illness is short. In this regard, Sartwell's method for estimating median incubation periods for infectious diseases is a traditional epidemiologic tool (*196*). Although originally developed to study temporal patterns of infectious diseases with relatively short incubation periods, this technique has been successfully applied to various neoplastic diseases resulting from certain chemical exposures, including

angiosarcoma of the liver following exposure to vinyl chloride (*208, 213*) and tumors of the urinary bladder following exposure to dyestuff intermediates (*4*).

Thus, conventional epidemiologic methods pertaining to the investigation of common-vehicle, point-source epidemics of infectious diseases may be appropriately applied to the study of acute outbreaks of chemically related illness. When the conditions of exposure previously set forth prevail (i.e., single and intense exposure of a limited, well-defined, and homogeneous population), the epidemiologic interpretation is usually straightforward, because cause and effect are close in time (*192*). However, when the introduction of the toxicant into the population is gradual or intermittent, and thus occurs over a long period of time, the incubation, or latent, period is likely to be measured in years or decades rather than in hours, days, or months. In this case, the epidemiologic interpretation, i.e., the linking of cause and effect, is much more difficult.

2. *Long-Term Variations*

The epidemiologic view of time and disease also involves the examination of changes in disease frequency over long periods of time. These "secular trends" are usually investigated in terms of mortality rates because adequate morbidity data are rarely available. For example, examination of the temporal trends in sex- and site-specific cancer mortality rates for the years 1930–1978 reveals several patterns worthy of further investigation. Particularly notable are the decline in gastric cancer mortality for both males and females and the disproportionate increase in lung cancer mortality among females as compared to males (*204*). By contrast, other neoplasms such as pancreas, bladder, and esophagus show little change over the time period. The observed increases in cancer mortality have raised questions about the role of chemicals in the human environment.

One such question focuses on toxic chemicals, the chemical industry, and their relation to recent temporal trends in cancer rates (*51, 179, 206, 217*). A related question focuses on quantifying the proportion of all cancers attributable to "environmental" factors (*29, 98, 99, 101, 232*). Although quite a debate has ensued and several articles addressing these issues have been published, there seems to be, at present, little chance of reaching definitive conclusions in the near future, given the overwhelming lack of relevant scientific knowledge.

Part of the debate alluded to above involves the interpretation of observed time trends in mortality rates. Although specific guidelines and techniques have been proposed (*123, 128*), the importance of systematically evaluating such trends is not always appreciated. It must be recognized that apparent changes in mortality over time may result from errors of

human origin (i.e., an increase or a decrease in a death rate over time may be artifactual), or that changes in mortality over time may indeed reflect a true change in the *incidence* of the disease. Real changes in death rates, of course, may result when the genetic composition of a population changes (possibly the result of population migration or the dilution of genetic isolates), or when the environmental milieu changes. Real changes in mortality may also result when the age distribution of a population shifts or when the case fatality rate for a given disease changes.

Before it can be concluded that changes in mortality rates are real, however, alternative explanations should be ruled out. In this context, at least two sources of error, both of which relate to the numerator of a death rate, must be considered. First, medical advances are likely to result in more accurate methods of diagnosis, which in turn might yield more precise determination of underlying cause of death. Consequently, a decline in the degree of misclassification of the underlying cause of death for a specific cause may result in an apparent, but spurious, decline in the cause-specific mortality rate. For example, improvement over time in the ability to identify correctly the primary site of malignant tumors in all likelihood explains the steady decline in mortality from primary cancer of the liver over the past 40 years.

Misleading trends in death rates may also result from revisions in the ICD, which occur approximately every 10 years. These revisions may involve either changes in the way various disease entities are defined or changes in the actual numerical code, or both. For example, Percy *et al.* (*172*) demonstrated that the 10% increase in the number of lung cancer deaths reported in 1968 over the number reported in 1967 was the result of a procedural change in the classification of malignant neoplasms that emphasized coding to a specific site rather than, as had been practiced before 1968, coding to unspecified or unknown categories. In general, changes in mortality that result from ICD revisions are likely to be quite striking and readily identified as such. With respect to changes in mortality rates that result from improved diagnostic methods, however, the evaluation is much more difficult. Specific techniques have been suggested in this regard (*128*).

The denominator of a death rate, i.e., the estimated population at risk, is also subject to error. This error is usually one of underestimation, the net effect of which is an artificial inflation of the rate. If the degree of error in population enumeration varies from census to census, a misleading trend in mortality may be observed. To complicate the picture further, inaccuracies in the census may not be of consistent magnitude across age, race, and sex groups (*203*).

Finally, we introduce a note of caution with regard to the interpretation of time trends in mortality rates. If it is observed that an increase in some disease is paralleled by a concomitant increase in some measure of a putative risk factor (and if it can be shown that the increase in disease is not artifactual), then can such an observation be used to support an argument of causality for the hypothesized factor? The answer is no, although one can legitimately say that such a result is *not inconsistent* with the stated hypothesis. If, on the other hand, there is no coincident rise (or fall) in the disease and the "risk factor," can it then be legitimately concluded that no causal link exists? The answer to this particular question is an emphatic no. Even if artifact is considered and judged negligible or somehow appropriately adjusted for, the general approach is sufficiently insensitive to support the hypothesis of no effect. Furthermore, it must be kept in mind that the results of time-trend analyses are only a small part of the overall process of making judgments about the causal role of some putative risk factor. In essence, time-trend analyses are most appropriate when the purpose is to *generate* hypotheses of cause and effect, not to *test* them.

3. *Other Perspectives of Disease and Time*

Although acute outbreaks of disease and secular trends in mortality dominate epidemiologic interest regarding disease versus time considerations, other perspectives may be taken. For example, many diseases (including infectious and noninfectious ones) show some sort of cyclic or repetitious pattern of occurrence in time. While the focus of study in this context has been primarily on infectious conditions and their seasonal periodicity in relation to insect vectors and certain human activities, studies of various noninfectious diseases of early life [e.g., congenital anomalies (*62*)] have revealed variations in risk by season of birth, suggesting the possible influence of environmental factors operating *in utero* or in the early postnatal period (*112, 128, 140*).

Another view of disease and time involves the investigation of temporal "clustering," i.e., the detection of epidemics (transient excesses in the incidence or prevalence of a disease or condition). In this regard, simple epidemic curves may be constructed, or more sophisticated methods like the scan statistic (*162, 222, 226*) may be applied. A related and somewhat broader view involves the examination of clusters of disease in time *and space*. So-called space–time clusters have been of interest with respect to several diseases, including leukemia (*113, 122, 216*) and Hodgkin's disease (*220*). Several statistical methods are available to test the significance of space–time clusters (*134, 167, 176*), although an in-depth discussion of these is beyond the scope of this article.

C. Variations in Disease Occurrence from Place to Place

The examination of geographic patterns of disease occurrence also plays an important role in the epidemiologic evaluation of chemical hazards. A number of strategies may be employed, each generally involving differing definitions of "place." In this regard, in order to determine if differences in disease occurrence exist among different geographic areas, basically two types of comparisons can be made: groups of countries may be compared with respect to available morbidity and/or mortality figures; or, comparisons of disease rates may be made on an intracountry basis.

1. *Intercountry Comparisons*

Differences between countries with respect to the occurrence of many diseases can be quite striking. For example, when cancer incidence rates (for both sexes and all sites combined) are compared worldwide, a threefold difference is obtained when the highest risk countries are contrasted with the lowest risk countries (*59, 159, 224*). When comparisons of high-risk and low-risk nations are of a sex- and site-specific nature, extremes in cancer incidence may vary by as much as a factor of more than 500 (*232*). Significant differences between countries with respect to cancer mortality have also been documented (*199, 232*). While racial or genetic differences among the populations compared, plus other endogenous factors, account for some of the observed variation between countries in cancer incidence and mortality, the magnitude of many of the differences suggests the influence of environmental factors (*57, 232*). Disease rates in the lowest risk countries may be considered "baseline" (i.e., spontaneous or genetically determined) levels of cancer. Thus, the amount of cancer (or other disease) above such "natural" levels may be the result of the action of environmental forces (*159, 232*). This particular inference, as some have argued (*29, 30, 69*), implicates exposures of human populations to chemical carcinogens. Others involved in the debate over the proportion of all cancers due to "environmental" factors have, however, used the word *environmental* in a much broader context—as a synonym for any extrinsic or exogenous exposure (*98–100, 232*). Thus, references to environmental factors, it must be emphasized, relate not only to chemical pollutants but also to physical carcinogenic agents such as ionizing radiation, biological carcinogenic agents such as tumor viruses, and life-style influences such as diet and behavior (*7*).

Although the results of international comparisons of disease rates have relatively limited epidemiologic utility, the exercise can serve the very useful purpose of generating hypotheses of cause and effect; it may even suggest preventive strategies (*159*). Moreover, once it can be established

that observed differences among countries are not spurious, studies of migrant populations may then be initiated to attempt a separation of the influence of genetic factors from that of environmental factors (*95, 111, 116*).

2. *Intracountry Comparisons*

Many diseases, for example, most forms of cancer (*25, 104, 138*), cardiovascular disease (*70*), and multiple sclerosis (*3*), to name a few, show a marked geographic variation in frequency when comparisons are made on an intracountry basis. Unlike intercountry comparisons, however, where the size of the geographic unit of analysis is fixed by national boundaries, intracountry comparisons may be performed at many levels; theoretically, any geographic unit, from the largest of subnational units (regions or states) to the smallest of subnational units (census tracts, block groups, or the like), may be used. In practical terms, though, it is usually necessary to select for study a geographic unit that best satisfies the need to compare populations that are as homogeneous as possible and, at the same time, large enough to yield stable disease rates. As Hoover *et al.* (*103*) and Blot and Fraumeni (*21*) indicate, the optimal geographic unit of study seems to be the county, at least when epidemiologic interest centers on environmental causes of cancer. The initial work of Mason and McKay (*137, 138*) illustrates the approach.

a. Mapping Cancer Death Rates. For the period 1950–1969, age-, race-, sex-, and site-specific cancer mortality rates were computed from National Center for Health Statistics death certificate data and U.S. Census figures for each of the 3056 contiguous U.S. counties (*137*). To allow valid comparisons among the counties, the death rates were age-standardized to the 1960 U.S. population, yielding average annual race-, sex-, site-, and county-specific rates for the 20-year period. From these summary data, an atlas of cancer mortality, color-coded to five levels, was created by comparing statistically each subgroup-specific county rate to the appropriate national rate and by, at the same time, classifying the rates into deciles (*138*). For the rarer malignancies, state economic areas (defined as groups of similar, contiguous counties) were used as the geographic unit of analysis. Virtually all of the resultant maps demonstrated that cancer death rates vary in magnitude across U.S. counties (or across state economic areas) in a nonrandom fashion. Furthermore, the number of identifiable "clusters" of high (or low) rate counties, the size of a given cluster, and the location of clustering depends on both the site of disease and on the sex–race subgroup examined. Striking geographic patterns emerged for several malignancies, including, notably, cancers of the bladder, esophagus, lung, stomach, and oral cavity.

This mapping approach is quite useful for a number of reasons. First, from a technical point of view, a large amount of data can be analyzed by computer relatively quickly and inexpensively. Second, because the data are presented visually, high-risk populations can be identified rapidly, which in turn, provides a firm basis to form causal hypotheses that can then be pursued by other means. Furthermore, mapping studies, sometimes referred to as the geographic pathology approach (*87*), serve as an important first step in a logical sequence of epidemiologic studies based on county-level cancer mortality data (*24*).

b. Correlation Studies. Although the benefits of mapping disease rates are clear, the identification of high-disease areas by this technique creates somewhat of an interpretational dilemma. Can the disease clustering be explained by the demographic and/or genetic characteristics of the people that inhabit the area, or are the chemical, physical, and biological (i.e., environmental) characteristics of the place responsible for the elevated disease rates in the resident population, or is the explanation some combination of these two factors? These questions give rise to a class of investigations often referred to loosely as "correlation" studies. The purpose of this type of study, simply stated, is to identify those demographic and environmental characteristics of the populations in question that covary with the disease rates, thereby providing etiologic clues. Such studies rely primarily on routinely collected data, such as U.S. Census figures and death certificate data. Quantitatively, although numerous statistical methods may be employed, correlation studies fall basically into one of two general categories: studies that employ standard univariate methods of analysis, i.e., studies that use the bivariate correlation coefficient to measure association between a *single* factor and a disease; and studies that employ multivariate methods of analysis. This typically involves the investigation of *multiple* risk factors for disease with standard multiple regression techniques.

Schroeder's paper on various chemical and physical properties of finished drinking water and cardiovascular disease mortality exemplifies the univariate approach (*198*). In this study, average annual age-adjusted mortality rates from cardiovascular disease for the period 1949–1951 for white males aged 45–64 years were plotted as a function of the average drinking water hardness in the 48 contiguous United States plus the District of Columbia. Bivariate correlation coefficients were computed for four categories of cardiovascular disease and for all causes of death combined;

four of the five correlation coefficients were negative in sign and were statistically significant at the $p < 0.01$ level. A similar analysis of coronary heart disease and 21 constituents of water in the 163 largest U.S. cities yielded highly significant (negative) correlation coefficients for magnesium, calcium, bicarbonate, sulfate, fluoride, dissolved solids, specific conductance, and pH, prompting Schroeder to write "the data offer a clue to an environmental influence associated with the nature of public water supplies which affects adversely the course of degenerative cardiovascular diseases in the United States."

This particular approach (i.e., the use of bivariate correlation coefficients to measure association between some factor and some disease) has some notable limitations. First, the magnitude of a correlation coefficient can be affected significantly by the size of the geographic unit used for analysis. Although the phenomenon is not always appreciated, the simple aggregation of geographic areas into larger units will usually result in an increase in the size of the correlation coefficient, an increase which can, in reality, be quite large. As Blalock (*18*) explains, a shift from smaller to larger geographic units will tend to reduce the effect of so-called nuisance variables, variables that are causally related to Y (the dependent variable of interest, i.e., disease) but that are unidentifiable and/or unmeasurable. Thus, as geographic areas are aggregrated they become more homogeneous with respect to the nuisance variables, which in turn allows the single independent variable of interest (X) to account for, or "explain," a greater proportion of the variation in Y. It is not surprising, therefore, that a fairly high (negative) correlation between hardness of drinking water and cardiovascular disease can be obtained when comparisons are made on a state-by-state basis, while the association, in general, disappears as the geographic unit of study gets smaller and smaller (*43*).

Another important consideration is that the correlation coefficient itself does not measure the *strength* of an association, but merely reflects the *degree of dispersion* of the data points about a straight line. Since it is the regression, not the correlation, coefficient that measures the effect of changes in X on Y, its use is preferred as a measure of association between factor and disease. Further, the magnitude of a regression coefficient (i.e., the *slope* of a line in a bivariate analysis) is theoretically not influenced by shifts in the size of the geographic unit of study.

The univariate approach discussed above, whether correlation or regression coefficients are used, cannot deal with the complex of factors related to the occurrence of human disease. Consequently, in order to help identify the cause (or causes) of environmentally related illness, a multivariate approach must be employed. In general, this involves the application of standard multiple regression techniques, a strategy based

on the assumption that disease rates (e.g., county-level cancer mortality rates) can be expressed as a linear or nonlinear function of a set of demographic, socioeconomic, and environmental characteristics of the population(s) in question.

To illustrate, once maps of county-level cancer mortality data reveal geographic clusters of elevated death rates for specific neoplasms, multiple regression studies may be performed to identify those demographic, socioeconomic, and environmental characteristics of the apparent high-risk populations that are statistically related to the cancer death rates (*21–23, 76*). The county-level cancer mortality data [their origin described earlier (*137*)] are treated as dependent variables in regression equations, and relevant county-level demographic, socioeconomic, and environmental data are entered as independent or predictor variables. Statistical significance of regression coefficients indicates which variables are significantly associated with the cancer rates, while the sign of each coefficient indicates the direction of the association. The county-level demographic, socioeconomic, and environmental data are obtained from such sources as U.S. Census publications and computer tapes. Quantities such as percentage of the population that is nonwhite, percentage that is urban, percentage residing on farms, population density, median family income, median number of school years completed by the adult population, percentage foreign stock, and various industrial indexes [derived from the U.S. Census of Manufactures (*219*)] are typically included in regression equations. For example, after controlling for the effects of demographic and socioeconomic differences, Blot and Fraumeni (*21*) found lung cancer mortality rates in white men to be significantly high in those U.S. counties where the paper, chemical, petroleum, and transportation industries tended to concentrate. Interestingly, death rates from lung cancer among white females were found not to be significantly associated with any of the industrial indices examined, a result consistent with the hypothesis that occupational exposures account for a measurable proportion of all lung cancer deaths.

A methodologically similar study by Blot and Fraumeni (*23*) reported a statistically significant (positive) association between cancer of the urinary bladder among white males and the geographic concentration of the chemical and printing industries. As with their lung cancer study, industrial indices were found not to be related to bladder cancer mortality in white females. Comparable studies, one of which describes their method in detail (*22*), have investigated demographic, socioeconomic, and industrial correlates of oral (*22*) and esophageal (*76*) cancers.

The initial focus of the multivariate approach described above is on a specific disease (or possibly on a group of diseases). In other words,

given a specific health outcome, a study is made to identify demographic, socioeconomic, and environmental factors of potential etiologic significance. It is possible, however, to reverse this logic by asking the following question: Given an a priori interest in a specific risk factor, what disease or group of diseases could be related to the factor in question? Thus, the initial focus of a correlation study might be on some environmental variable, perhaps a certain chemical exposure, rather than on a specific health effect. This approach, which generally utilizes the same multiple regression techniques discussed above, has been applied primarily to the investigation of various industries and/or occupations suspected of being cancer hazards (*87,211*), including the chemical (*102*), petroleum (*19*), metal electroplating (*17*), and furniture (*32*) industries. Studies of this kind have also addressed the possible cancer risk associated with the contamination of water by asbestos (*139*), fluoride (*105*), and organic chemicals (*228*); of air by arsenical compounds (*20*); and of soil by uranium mill tailings (*136*).

c. Nature of the Ecologic Study. The correlation studies referred to above, whether analyzed in univariate or multivariate fashion, share a very important characteristic: the data employed, and this relates to both the independent and the dependent variables, are in *aggregate* form, i.e., they (the data) are organized at a group level, thus providing information about human populations in a collective sense. Quantities derived from U.S. Census data, such as the *proportion* of a county population employed in a given industry, illustrate the point. Thus, investigations that rely on group- or aggregate-level data are commonly referred to as "ecologic studies," a descriptor having origins in the social sciences (*61, 89, 150, 184*).

Ecologic studies, by virtue of their use of aggregate-level data, possess various limitations. A major concern in this regard pertains to the interpretation of the results of an ecologic analysis. First and foremost, since study subjects cannot be classified on an *individual* basis with respect to the study variables, any results suggesting an association between some factor and some disease must be regarded as indirect and therefore not conclusive. It should be appreciated that the interpretation of ecologic data is subject to an "ecologic fallacy," in this case, the error of ascribing to individuals associations or characteristics based on an analysis of aggregate-level data. This particular fallacy, the "aggregative fallacy," pertains to improper inferences made from the aggregate to the disaggregate (*212*). Improper inferences may also be made in the other direction, i.e., from the disaggregate to the aggregate; this type of ecologic fallacy is referred to as the "atomistic fallacy" (*212*). Ecologic studies, therefore, cannot be used to test formally some hypothesis of cause and effect.

They can, however, be used quite successfully to generate *clues* to the etiology of disease, clues that are pursued by more rigorous methods of study.

Ecologic analyses are fraught with other methodologic problems. These include:

1. Inability to incorporate the concept of a latent period. It will usually not be possible with routine data to construct a proper temporal relationship between measures of the hypothesized cause and measures of the hypothesized effect, i.e., it may not be possible to take into account a latent period—the time between the biologic onset of disease and its clinical manifestation (*192*). For example, in studies (*120, 170*) of cancer and organic chemical contamination of public drinking water supplies, data on the hypothesized cause (drinking water) pertained to 1963 and data on the hypothesized effect (cancer mortality) pertained to the 20-year period, 1950–1969. In this case, for the measure of cause to precede in time in an appropriate fashion the measure of effect, the drinking water data should have pertained to a time period well before the 1950–1969 vicennium. The actual magnitude of a latent period to incorporate into such an analysis depends, of course, on the specific chemical agent and disease in question, as well as on the nature of the exposure. Moreover, if the study period overlaps with the latency period, regardless of when population exposures occurred, the full effect of the exposure cannot be determined because not all cases of disease attributable to the exposure will have had time to become manifest.

2. Artificial nature of the boundaries of geographic units of study. Geographic areas demarcated by natural boundaries such as mountain ranges or major rivers, as contrasted to areas defined by political or administrative boundaries, are more likely to be homogeneous with respect to demographic and environmental characteristics of etiologic significance, and thus would be more likely to define areas of high (or low) disease occurrence. The boundaries of most (though not all) states, counties, cities, etc. do not coincide with natural boundaries. Therefore, the artificial and arbitrary nature of politically established geographic areas creates problems in ecologic analyses because such boundaries may either subdivide homogeneous regions or combine heterogeneous ones (*140*). Further, it may not even be possible to obtain data on all variables of interest for a given type of areal unit. This creates a comparability problem, which may be compounded if the political/administrative boundaries shift over time. Such changes may then preclude any investigation of the temporal relationship between an exposure and a disease (*209*).

3. Difficulties in measuring human exposures to toxic chemicals in ecologic studies. With the kind of data typically available for use in ecologic studies it will usually only be possible to employ fairly crude

measures of human exposure to toxic chemicals. In general, such measures will be indirect (rather than direct) and qualitative (rather than quantitative). Since ecologic measures of exposure are in aggregate form, like the other variables in an ecologic study, they cannot be truly representative of the exposure experience of individuals comprising the study population. This aspect of conducting epidemiologic studies of chemical hazards is discussed in more detail in Section IV.

4. Effects of population migration. Migration of people between geographic areas will affect adversely the sensitivity of an ecologic study. As Polissar (*178*) points out, a geographic area assumed to be inhabited entirely by a so-called exposed population is actually inhabited by some who are and by some who are not exposed to the agent or factor in question because of in-migration of unexposed people. Polissar demonstrates how one measure of disease risk, the Standardized Mortality (or Morbidity) Ratio (SMR), can be affected by differing degrees of migration. He shows, with some simplifying assumptions, that the SMR is a function of (i) the proportion of the exposed population that is truly exposed because they have not migrated, (ii) the size of the exposed population, (iii) the rate of death or disease in the control (unexposed) population, and (iv) the ratio of death or disease in the exposed population to that in the control (unexposed) population. Polissar also shows that the magnitude of excess risk observed in ecologic studies in the presence of migration varies with the age of the population, the particular disease in question, the duration of the latency period, and the type of geographic unit used for study.

5. Some technical issues. Most of the technical (statistical) problems in ecologic analyses relate to assumptions associated with any multiple regression problem. In many cases, underlying assumptions of the general linear (or nonlinear) model cannot be met strictly by the data. These include assumptions of normality with respect to predictor and dependent variables, homoscedasticity of variances, and independence of observations. Fortunately, the regression model is quite robust with respect to the first two assumptions, i.e., they can be violated substantially before the validity of results is threatened. The third assumption, however, can pose serious problems. In many instances, the distributions of two or more predictor variables are not independent, which means that they are correlated. This situation adversely affects the estimates of the regression coefficients and their subsequent interpretation. In many cases, however, this problem, called multicollinearity, can be solved by the use of two-stage or even three-stage least squares, rather than ordinary least squares, regression.

Perhaps the most serious problem in ecologic analyses relates to the question of specification of the model to be evaluated. If a predictor

variable that is significantly related to the dependent variable is omitted (owing to lack of data or lack of knowledge that the variable is important), specification errors will result. If the omitted variable is correlated with a variable that is specified in the equation, the included variable will appear to be more strongly related to the dependent measure than is actually the case. If this occurs, a variable might erroneously be associated with the disease under consideration. Errors of this type in hypothesis-generating studies can be dangerous, since they will mislead the investigator and probably result in an untenable etiologic hypothesis. Unfortunately, there is rarely enough knowledge available at the time of a preliminary study to determine whether a specification error has indeed occurred. However, the possibility emphasizes the caution noted earlier that causal inferences cannot be drawn from correlational results, but that such findings must be regarded as tentative.

Once descriptive epidemiologic tools have generated hypotheses regarding the potential adverse effects of chemical exposures on human health, studies will then be conducted to test formally such hypotheses. Studies of this type, "analytic" studies, require individual-level data on the traits and characteristics of study subjects. With such disaggregate data it will be possible, as it is not in ecologic studies, to classify each study subject with respect to the study variables.

III. TESTING ETIOLOGIC HYPOTHESES: AN OVERVIEW OF ANALYTIC APPROACHES

In this section the major analytic approaches typically employed to estimate potential associations between an exposure and a defined health outcome are discussed. The two primary methods can be distinguished on the basis of how the study samples are selected. In the case-control approach, individuals with a specific disease are compared with persons believed to be free of the condition under study. The cohort approach evaluates the occurrence of disease within a group defined in terms of characteristics prior to the diagnosis of disease. Both cohort and case-control methods can be defined further on the basis of whether the study is conducted retrospectively or prospectively. Many case-control studies are conducted retrospectively, i.e., the data collected are historical in nature. However, it is also possible to conduct prospective case-control analyses, in which the sample is accumulated over time as new cases of the disease occur. Cohort studies can also be conducted forward or backward in time. In either case, the distinguishing characteristic of such analyses is the long-term observation of a group of people, which is accomplished by prospective monitoring of the study subjects or by

historically tracing the experience of the sample over a defined time interval. Prospective cohort studies are sometimes referred to as concurrent studies, while historical cohort analyses may be called nonconcurrent (*123*). The major features of each analytic model and some of their relative advantages and disadvantages are now described.

A. Case-Control Studies

Case-control studies are an excellent method for evaluating the relationship of an exposure or hypothesized etiologic factor to the occurrence of disease. In its most fundamental form, the purpose of a case-control study is to determine whether individuals with a disease are more (or less) likely to possess some characteristic (or exposure) than persons without the disease. These studies are designed to assess whether exposure to some factor of interest places individuals at higher risk of disease than those individuals not exposed. Statistical techniques applied to data from case-control studies can evaluate risk associated with two or more levels of exposure.

Perhaps most fundamental to the conduct of a case-control study are those issues that bear on the selection of the study subjects. In selecting cases it is essential to confirm that the potential subject is indeed a case, i.e., that he or she strictly meets the diagnostic criteria of the condition under study. With respect to studies of cancer, for example, such confirmation could be in the form of microscopic pathologic analysis of a tissue sample, rather than merely a clinical or radiologic diagnosis. Even under conditions of laboratory confirmation, misclassification can occur, so it is important to minimize this bias, where feasible (*63*). Furthermore, it has been suggested that cases have a reasonable probability that their disease might have been caused by the hypothesized agent, and not by another identifiable factor (*109*).

Cases can be identified through several sources. These include all persons (or more usually a probability sample of persons) diagnosed during a specified period of time in a given community or in a single hospital or group of hospitals. Often it is more practical to identify cases through the records of one or just a few medical care facilities. However, this can introduce a bias into the sample, since there are systematic selection factors that guide certain individuals to a particular facility. If such a bias is present, study cases will not be representative of the entire population of persons with the disease, possibly leading to erroneous inferences about the etiologic factor of concern. In principle, sampling cases from a general population has great theoretical appeal, but can be laborious and expensive. To the extent possible, the assumption of representativeness should be met or the possible extent of bias estimated. Even with a condition such as cancer, certain nonrandom cases do escape medical attention.

The question of selecting appropriate controls poses even more difficult questions. Simply defined, a control is an individual with no clinical evidence of the disease under study. Ideally, the control group will be a representative sample of disease-free persons. Furthermore, it is desirable that the controls be members of the same general population from which the cases derive. Control groups can be selected from several sources. These include hospital patients, residents of the same geographic area as the cases, and relatives or other associates of the cases. Selecting cases from the same geographic area is appropriate if the cases are representative of that population. Hospital controls are often used since they are a relatively easy source to obtain. The major disadvantage of this source is simply that hospitalized persons are ill and may therefore be unrepresentative of the general population with respect to a complex of illness-related factors. This may introduce a particular type of selection bias, especially if many of the controls are of a similar diagnostic group. This effect may be minimized by choosing controls from several diagnostic categories (*41, 135*). The extent of selection bias has long been known (*94*) and has been comprehensively discussed (*10*). Although selection biases do not necessarily invalidate study findings, one must carefully interpret whether an observed association is likely to be real or spurious (*34, 58*).

Another significant issue with regard to the selection of cases and controls involves the question of matching. Since the purpose of a case-control study is to measure the effect of a defined exposure, it is desirable to eliminate by design those factors that might potentially confound the results. Matching is a process of selecting controls known to be similar to the cases with regard to specific characteristics such as age, race, sex, or socioeconomic status. Effects of variables known to be associated with both the disease and the study factors can be controlled by matching (*152*). The primary disadvantage of matching is that the etiologic role of the matching variable cannot be evaluated, since, by definition, cases and controls are alike with regard to that characteristic. Also, matching can increase the complexity of a study, with respect to both design and analysis (*13, 14, 143*). Finally, there is a risk of overmatching or unnecessary matching. In general, inappropriate matching can reduce the statistical efficiency of the case-control comparison (*151, 200*).

Collecting accurate and valid information on exposure for both cases and controls is a crucial aspect of case-control studies, since resulting estimates of risk are directly related to these measures. The precise

meaning of exposure (to be expanded on in Section IV) must be defined, with regard to both intensity and duration. Most importantly, the exposure information must be comparable, with respect to reliability and validity, for cases and controls. If the data are incomplete, spurious associations will result.

Medical or vital statistics records and interviews with study subjects provide the major sources of exposure data; both sources entail potential biases. For example, as discussed earlier, there are possible sources of error with public records, such as death certificates. Clinical records may exhibit some of the same problems, or they may simply be incomplete with regard to data concerning the exposure of interest. Since the purpose of the record is to chart the clinical course of disease, information required to study other phenomena may not be available (*72*). Additionally, questions of validity of data recorded in the medical record have been raised (*115*). Finally, reliable (reproducible) abstracting of clinical data from existing records cannot always be achieved (*28*). Despite these potential limitations, the medical record remains a key source of data regarding exposure; its intrinsic value in the study of disease etiology is unchallenged (*119*).

Data collected by interviewing cases and controls also presents some possible biases, but this method also assumes great importance in epidemiologic analyses. Information obtained through personal interviews (or self-administered questionnaires) is subject to the pitfalls of faulty respondent memory, unintentional errors in reporting, or outright prevarication. Bias might occur, for example, if the occurrence of disease has prompted the respondent to recall certain related information that might otherwise have been forgotten. If corresponding information does not emerge for the control, a bias is introduced (*194*). Further, the passage of time since the relevant event might affect the validity of the reported information (*210*). In other instances respondents might have been unaware of exposure and consequently are unable to report it. A number of studies have been conducted to evaluate the reliability and validity of self-reported data, many of which offer encouraging results (*67, 114, 187*).

Errors in the collection of exposure data or noncomparabilities of data between cases and controls can result in serious misclassification problems, i.e., erroneously determining an individual's exposure status. The result of misclassification is an inaccurate estimate of risk. It has long been appreciated that even random and independent errors can reduce the measured association between exposure and outcome (*33, 164*). This topic has been reviewed extensively, and methods to adjust for misclassification under specified conditions have been proposed (*45, 85, 110*). Careful attention to study design can preclude or diminish many errors

of misclassification. Standardized provisions for data collection may at least ensure a high degree of reliability, a major prerequisite for validity.

The analysis of data from a case-control study is primarily a comparison between cases and controls regarding the presence of hypothesized etiologic factors in each group. Results of these analyses indicate whether there is an association between the factor and disease. In principle, one desires to estimate the relative risk associated with exposure (i.e., the incidence rate among those with the factor divided by the incidence rate for persons without the factor). However, the method by which cases and controls are assembled does not include all exposed and all unexposed individuals. Consequently, the incidence rates of interest cannot be calculated. If, however, assumptions about the representativeness of cases and controls can be met, a measure known as the odds ratio can be computed as an estimate of relative risk (*46, 47*). In the simplest case, data from a case-control study can be presented in the form of a 2×2 table, with columns representing the classification of cases and controls, and rows representing the presence or absence of the exposure factor (Fig. 1).

The odds ratio, given by the expression $(ad)/(bc)$, summarizes the probabilities of having or not having disease. The statistical properties of the odds ratio have been analyzed extensively. Numerous methods have been proposed for tests of significance (*83, 230*) and for approximating confidence intervals (*46, 96, 214*). Furthermore, there are techniques to adjust the odds ratio for the effects of confounding variables through stratification (*15, 90, 135*). Appropriate statistical management of the odds ratio also depends on the degree of matching in the study design (*148*). In addition to stratification, control can be introduced by logistic

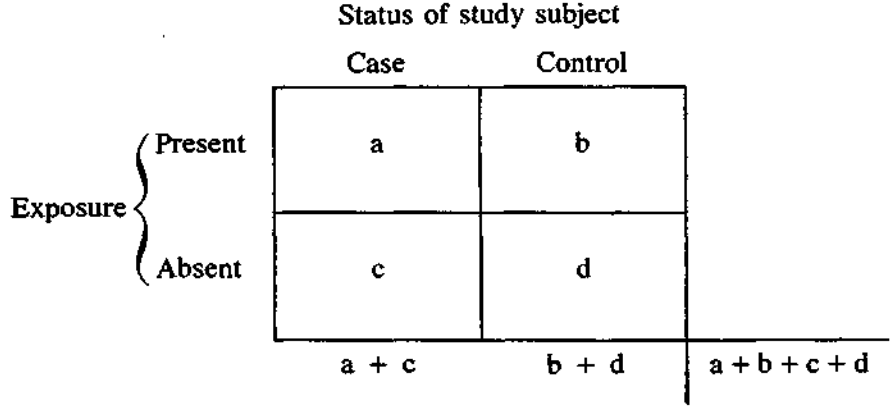

Fig. 1. Cross-classification of subjects in a case-control study.

models, which permit adjustment for variables that were not matched in the study design (*31*, *180*).

The epidemiologic literature is replete with examples of investigations employing the full range of study designs and analytic techniques described above. For example, death certificates were used as a primary source of data in an analysis of sinonasal cancer among males (*193*), for which several chemical agents are hypothesized etiologic factors. Exposure to a variety of agents was inferred from occupational data on the death certificate; complete occupational histories and quantitative exposure data were not available. However, probability of exposure to nickel, cutting oils, and wood dust was estimated from occupational titles and industry of work. The odds ratio computed for nickel exposure was not statistically significant, but was with respect to cutting oils and wood dusts.

An example of the evaluation of a multiplicity of factors can be found in an ambitious study of bladder cancer (*106*). The effects of several exposures, including tobacco, coffee, various nutrients and nitrates in food, and occupation were estimated. A logistic model was used to deal with the multivariate design, thereby affording an opportunity to measure the independent effects of exposures, their interaction, and the effects of confounding variables. The applicability of case-control studies to provide preliminary information that might account for an unusual cluster of cases is demonstrated by an analysis of mortality from pancreatic carcinoma (*175*). Although the findings are somewhat constrained by the limited residential and occupational information available on the death certificate, a significant odds ratio was obtained for persons who worked in oil refining or paper manufacturing. A small effect was detected among persons living near refineries. A study of this type is useful for defining requirements for a more extensive interview study and is particularly interesting because of the implication of occupational and ambient environmental risk. Finally, the conduct of an interview study is shown in an analysis of exposure to artificial sweeteners (*157*), and the use of more than one control series is demonstrated in another investigation of pancreatic cancer (*129*).

B. Cohort Studies

The second major approach in analytic epidemiology is the cohort study, of which the primary design features are discussed here. Although cohort studies differ from case-control studies with respect to the way in which study subjects are selected, the majority of issues that pertain to the validity and analysis of data obtained in cohort studies are equivalent

to the issues considered with respect to the case-control method. Specifically, similar and equal attention should be given to the representativeness of the sample, the effects of both disease status and exposure misclassification, other selection biases, sources of exposure data, and problems of confounding variables. Indeed, many of the statistical approaches to the resulting data are the same, or entail the same assumptions, and therefore are not considered in detail here.

The basic concept of a cohort study is relatively straightforward. A sample of a population is selected, and it is determined which members of the cohort possess the study characteristic or are exposed to the hypothesized etiologic agent. The cohort is then followed over time, and the incidence rate of the disease under consideration is calculated for the exposed group and for the unexposed group. If the rate of disease is higher among those exposed, an association between the risk factor and disease is inferred. In the retrospective, or nonconcurrent, cohort approach, the period of observation is historical, a method often used to study specially exposed groups such as industrial populations. Several examples of this method will be discussed in the context of measuring response by computing standardized and proportionate mortality ratios (Section IV). One difficulty in retrospectively assembling a cohort is in assuring that all members can be identified. Sometimes, comprehensive data are not available (*37*, *221*), thus limiting the generalizability of the findings.

In addition to special exposure groups, cohorts can be defined because they can be followed over time and because methods for identifying outcomes of interest are available. Examples of groups that have been studied include persons enrolled in prepaid medical care plans, groups of insured persons, obstetric populations, and volunteer groups. Additionally, a cohort may be defined on the basis of geography, such as all members of a specifc community.

One of the most crucial aspects of a cohort study relates to follow-up, i.e., the task of determining outcome, usually the appearance of morbidity or mortality. It is important that determination of outcome be equally complete for exposed and unexposed cohort members, or for cohort members in each level of exposure in the nondichotomous case. Otherwise, measures of association between exposure and disease will be biased. Therefore, it is important to establish a follow-up (or tracing) mechanism that applies equally to all study subjects, whether the surveillance entails review of routine records or special data collection efforts.

The length of follow-up is also a significant determinant in the results of a cohort study. If follow-up is not sufficiently long, cases of the study

disease will not have yet become clinically apparent (especially if the latent period is long), and the rates of disease will therefore be underestimated. Comparisons of findings under two different follow-up periods have been reported. One such example involves two analyses of a cohort of workers exposed to beta-naphthylamine and benzidine (*130, 131*). The time-of-measurement effect has also been discussed in a theoretical framework (*231*).

The consequences of losing some proportion of persons during follow-up can be considerable, particularly if the losses are not random. If losses are biased with respect to outcome, the absolute rates of the study condition will be influenced, but their relative relationship to each exposure category will remain the same. Substantial losses, however, can distort the measurement of risk. A more serious situation will result if follow-up losses are biased with respect to exposure category, since this will affect the relative rates of disease between exposure groups. In some circumstances it is possible to estimate the effect of follow-up losses, particularly if the date on which an individual leaves the cohort is known.

There are many examples of cohort studies designed to evaluate the effects of environmental exposures. Despite limitations in data availability, results of these investigations can be very revealing. For example, analysis of a cohort of persons engaged in the manufacture of mustard gas was limited in that only 84% of the cohort could be traced (*133*). To compensate, additional calculations were made under the extreme conservative assumption that all persons untraced were alive at the termination of the follow-up interval. Even under these conditions, a positive association was detected.

The relative advantages and disadvantages of case-control versus cohort studies can be summarized briefly. Case-control studies are reasonably efficient and inexpensive to conduct. Comparatively few subjects are required, since the study begins with the identification of cases. This efficiency is particularly apparent in etiologic investigations of rare diseases, although the same advantage can accrue to retrospective cohort studies. By contrast, it is impractical, if not impossible, to assemble a large enough cohort to study in prospective fashion the occurrence of a rare condition, since the probability of any cohort member exhibiting the disease is extremely small. Case-control studies also offer an advantage with respect to time, since it is not necessary to wait for the development of new disease. Analytically, the major disadvantage of a case-control study is that relative risk cannot be measured directly, and there is controversy regarding the most appropriate estimation and testing of the odds ratio. Further difficulties, such as selection of the most appropriate control group, have been alluded to above and are discussed extensively in the literature (*41, 108, 109*).

By comparison, cohort studies have the advantage of classifying persons with respect to exposure prior to the development of disease. This can minimize (although not necessarily eliminate) problems of bias and misclassification. Most significantly, cohort analyses can yield actual incidence rates, thereby providing a direct measure of risk. The primary disadvantages of the cohort method relate to obstacles encountered in the follow-up of a large number of study subjects. Prospective cohort studies are expensive to execute and generally represent very large-scale undertakings. Consequently, they are not efficient for exploring new hypotheses; their strength lies in the provision of additional evidence after a specific hypothesis has been posited.

IV. CRUCIAL ASPECTS OF ENVIRONMENTAL STUDY DESIGN

To estimate accurately health risks resulting from chemical exposures, the relation between the amount or concentration of the agent in the critical organ or tissue (i.e., the dose) and the proportion of the population at risk manifesting a specified biological effect (i.e., the response) must be determined. In the following two subsections, epidemiologic approaches (and attendant problems) with respect to making measurements of dose and response in human populations are examined.

A. Measurement of Dose

Perhaps the most problematic aspect of designing epidemiologic studies of chemical hazards in human populations involves the measurement of dose. Although attention in this regard centers (properly) on considerations of the intensity, duration, and mode of external exposure to environmental chemicals, the problem of dose estimation is actually much more complex. The difficulty is easily appreciated by considering the many factors, conditions, and forces that affect the actual degree of external exposure, and thus, ultimately, the amount of toxicant reaching the critical organ or tissue. Therefore, if at first just those factors that determine the transport and fate of chemicals in the ambient environment are considered, many relevant questions may be posed. For example, what is (are) the source (sources) of the chemical agent in question? Is it a point or a nonpoint source? In what amounts and at what frequency is the substance discharged into the environment? Is the substance primarily of natural or anthropogenic origin, or a combination of the two? What are the patterns of use and of disposal of the material? Once the substance enters the human environment, how does it behave in air, in water, in soil, in

biota? To what extent is the substance transported between the various environmental compartments? To what extent will the chemical undergo a transformation in either air, water, soil, or biota? If a transformation does occur, will the product be more hazardous or less hazardous than the parent material? Is it possible to identify populations that are most likely to be exposed and/or most likely to be exposed to the highest levels of the substance? Are there subgroups of the population that are particularly sensitive to the agent in question? And once human exposure does occur, what information is available on the absorption of the agent into the body, on the distribution of the agent in plasma and tissue, and on the pathways and rates of excretion?

Before proceeding further, the difference between exposure and dose must be clarified. Unfortunately, the distinction is not always made. *Exposure* to a given chemical substance refers simply to the extent of contact between the toxicant and those surfaces of the human body where absorption may occur. Thus, measures of exposure, i.e., measures of external exposure, are expressed in terms of the concentration of the agent in environmental media (air, water, food) that interface with relevant body membranes (*11*). *Dose*, on the other hand, refers to the amount or concentration of the toxicant in a critical organ or tissue [the critical organ or tissue being that which exhibits the first or the most serious effect (*11, 165*)]. It is the dose that must be obtained in order to quantify health risks resulting from chemical exposures. In general, however, the amount or concentration of a toxicant in a critical organ or tissue cannot be measured directly. Thus, dose must be measured in some indirect fashion and in such a way that the index used will result in an observed dose–response curve that accurately depicts, in both qualitative and quantitative terms, the true or actual dose–response relation for the substance in question. Surrogate measures of dose, then, will generally be derived from data either generated by some form of biological monitoring [the "systematic collection of human or other biological specimens for which analysis of pollutant concentrations, metabolites, and biotransformation products is of immediate application" (*11*)] or by some form of environmental monitoring [the "systematic collection, analysis, and evaluation of environmental samples, such as air, water, or food for pollutants" (*11*)].

1. Biological Monitoring

Given the usual inability to measure directly dose of the toxicant at the effector site, it would seem appropriate to assume that levels of the toxicant (or of its metabolites) in blood or other accessible tissue(s) would correlate with levels in the critical organ or tissue and thus could serve as a reliable and valid index of dose. If so, data derived from measurements made on human tissues or excreta could be used to clarify dose–response relationships. For example, levels of lead and other heavy metals (such as cadmium and mercury) in blood (*185, 233*), urine (*233*), hair (*97*), or nails (*107*) have been used in the past as dose indices. Other tissues or excreta, including breast milk (*186*), adipose tissue (*218*), expired air (*44*), and others (*11*), are at present amenable to biological monitoring. Unfortunately, there are relatively few applications in epidemiologic studies of chemical hazards (*42, 88*). However, there is a growing opportunity and need for a greater integration of toxicologic and epidemiologic data for purposes of health hazard assessment, as evidenced by recent papers (*88, 215, 229*). For a more detailed discussion of biological monitoring per se, see references *11* and *236*.

2. Environmental Monitoring

Most surrogate measures of dose used in epidemiologic studies are actually measures of external exposure to some agent, since they are usually derived from some sort of environmental data. Further, indices of dose based on such data may be divided into two categories: those that can be characterized as simple classifications and those that are based on Haber's law.

a. Simple Classification Schemes. Measures of external exposure to toxic chemicals should, ideally, reflect the intensity, duration, and mode of the particular exposure. Further, such measures should be quantitative in nature, should accurately summarize the exposure experience over time of any individual study subject, and should reflect the amount or concentration of the toxicant in the critical organ or tissue.

In order to develop such measures, detailed, extensive, and individualized environmental data are required. Such data, however, are not, for a number of reasons, usually available. For one thing, the substance or group of substances in question may have only recently come to be thought of as hazardous, in which case ambient and/or occupational environments will probably not have been routinely monitored in past time periods. Further, there may exist no analytical techniques capable of measuring the substance or substances in air, water, soil, and/or biota; or, if analytical methods are available, they may be grossly inadequate. Also, there may be no mechanism, practical or otherwise, to link levels of exposure to the environmental contaminant(s) in question with specific individuals. Consequently, when numerical estimates of external exposure cannot be calculated for individual study subjects, for whatever reason,

what may be described as simple classification schemes are developed instead. Although these simple schemes may be devised from either qualitative or quantitative environmental data, they generally take the form of ordinal-level measurements, measurements that do provide a rank ordering of exposure categories but do not provide an indication of the "distance" between categories. Further, exposure classification schemes of this sort are usually (but not always) employed in aggregate population studies, i.e., in studies comparing morbidity and/or mortality rates among large geographic units such as states, counties, communities, etc.

When the classification scheme is based on qualitative information only, the exposure variable itself will likely be constructed as a simple high/medium/low, or a simpler high/low dichotomy. For example, in the prevalence study of chronic obstructive respiratory disease by Detels *et al.* (*55*), several lung function parameters were compared between the populations comprising two California communities. The "high" exposure community was described as "chronically exposed to relatively high levels of photochemical/oxidant-type pollutants," and the other, the "low" exposure community, was "subjected to low levels of chemical ambient air pollutants."

In addition to high/low schemes and variations thereof such as exposed/unexposed, aggregate populations have also often been categorized in terms of their degree of urbanization. Since U.S. Census data make this a relatively straightforward procedure, many studies report comparisons of morbidity and/or mortality rates among "urban" and "rural" populations, as well as among populations classified in similar ways (such as, for example, SMSA[1] county with central city/SMSA county without central city/non-SMSA county). A number of studies employing this general approach, including notably several studies of air pollution, have focused on the differences in sex- and site-specific cancer death rates between urban and rural populations. In this regard, attention has centered on the cancer death rates among populations characterized by differing levels of urbanization. After a review of several such studies the general conclusion, as Carnow and Meier (*35*) point out, is that mortality from respiratory cancer is roughly twice as high in urban areas as in comparable rural areas, results consistent with the hypothesis that the higher levels of airborne carcinogens generally found in urban areas are etiologically involved in pulmonary neoplasms.

Similarly, recent studies of organic chemical contamination of drinking water supplies report the classification of numerous aggregate populations with respect to various raw water source and treatment characteristics,

[1]Standard Metropolitan Statistical Area.

from which several types of comparisons have been made (*228*). For example, sex- and site-specific cancer mortality (and in some cases cancer incidence) rates in populations served surface water have been compared to cancer rates in populations served groundwater. Populations served chlorinated water have been compared to populations served unchlorinated water, and so forth. Although the interpretations of these studies differ, the results of all of them to date seem to suggest a slightly elevated risk of certain gastrointestinal and urinary tract cancers in populations consuming drinking water containing the highest levels of trace organic chemical contaminants.

Because the schemes previously discussed are generally based on qualitative information only, they may be improved somewhat by using quantitative environmental measurements to assist in the construction of exposure classes. Studies of air and water pollution, again, illustrate the approach. Morris *et al.* (*156*) compared mortality between two small Pennsylvania communities, one of which was in close proximity to a coal-fired electric power plant (and therefore presumably had higher levels of air pollution than the other). Unlike the study by Detels *et al.* (*55*), which assigned exposure categories (high/low) without, apparently, using quantitative environmental measurements, Morris and co-workers used specific air quality indices (dust fall, sulfation rate, suspended particulates, and sulfur dioxide levels) to verify that a significant difference in air quality existed between the two study populations. Similar air quality measurements have been used to assign communities some air pollution exposure ranking in a number of other studies (*38, 77*). Studies of the organic chemical content of public drinking water supplies by the U.S. Environmental Protection Agency (USEPA) have provided quantitative measurements on the levels of various waterborne organic chemical contaminants, data that have been used in several epidemiologic studies (*228*).

To summarize, the simple classification schemes previously discussed (1) are based on either qualitative or quantitative environmental data, (2) take the form of ordinal-level measurements, (3) are usually used in aggregate population studies, and (4) are perhaps the crudest of techniques available for measuring human exposures to chemical hazards. It is, however, possible under certain circumstances to refine these simple schemes. For example, in epidemiologic studies of occupational hazards, in which "exposure" data of some kind are usually available for individual study subjects, qualitative information such as the occupation and/or industry of each worker can form the basis of the classification scheme. This "occupational title" (OT) approach, as described by Gamble and Spirtas (*82*), assigns workers to categories of jobs that are functionally similar (i.e., jobs that involve the same equipment or process) and/or

that are materially similar (i.e., jobs that involve similar products). Appropriate morbidity and/or mortality measures can then be compared among the various groups of workers, since the groups can be thought of as fairly homogeneous with respect to occupational exposures. For example, in a study of mortality among workers in a rubber tire manufacturing plant, McMichael *et al.* (*146*) needed to identify 60 separate OTs in order to characterize the work histories of approximately 1500 men. In their analyses, the 60 OTs were grouped into 16 major work areas and the frequency of employment in each OT group (i.e., the "rate of exposure" to each work area or OT group) was compared among the case and a control series for 7 cancer and 2 noncancer causes of death. The strongest associations were observed between several neoplasms and those work areas most likely to have involved the greatest exposures to organic and inorganic chemicals. Notably, exposure to solvents at several stages of tire building was associated with lymphatic leukemia. Other studies by McMichael and co-workers (*144, 147*) of the rubber industry, including one that focuses on leukemia and exposure to solvents (*147*), illustrate the OT approach. The OT approach has also been employed in a study of steelworkers (*124*), and in studies of occupational exposures to asbestos (*132*) and chloromethyl methyl ether (*54*).

The OT approach has several advantages. First, even in the absence of quantitative environmental sampling data it is possible to characterize systematically chemically complex environments, such as those encountered in rubber tire manufacturing plants. Second, what is usually a very large number of specific jobs can be reduced to a manageable number (at least from a statistical point of view) of fairly uniformly exposed OT groups. Also, the results of such an analysis can be quite useful in either generating or refining hypotheses of cause-and-effect relationships, because it is not necessary to state a priori an interest in some specific health effect, nor is it necessary to have a clear understanding of the induction and latency periods involved. Furthermore, if the results of a study employing the OT approach identify a particularly hazardous work area, intervention strategies may be implemented without knowledge of the specific chemical substances responsible. Additional studies could focus in detail on the process and/or product related to the apparent high-risk work area in attempts to identify the specific causal agent or agents.

Before attention is turned to other ways of measuring external exposure to chemicals in epidemiologic studies it is important to realize that the classification of aggregate populations into ordinal-level exposure categories involves, at least implicitly, the following assumptions:

- The degree of exposure among the individuals comprising each class is uniform, or nearly so.

- The designated categories make a clear distinction between the groups with respect to exposure levels.

In order to gain some insight into the implications of these assumptions, imagine that two well-defined communities (A and B) are selected for study. Imagine further that Community A is in very close proximity to a point source of pollution, say a lead smelter, and that the mere existence of this smelter serves as the basis for labeling Community A the "high-exposure" population. Community B, without smelter, is therefore considered the "low-exposure" population. If it is then assumed that the only difference between the two populations is the existence of the smelter, the situation may be conceptualized with the help of a simple sketch (see Fig. 2). Inspection of the figure suggests that exposure to lead in both communities is not precisely uniform, but rather the definitions, high/low, reflect an *average* amount of population exposure. Certainly, exposure levels in each community vary about a mean, and these means are significantly different from each other. (For simplicity, the distributions have been given a "normal" shape, although the actual distributional form is more likely to be log-normal.) Since, in this case, the exposure classification scheme reflects a sizable difference between the mean population exposure levels—i.e., the exposure definition employed discriminates between the two populations—a comparison of lead-related health measures will be valid. Consider, however, two reasons why this hypothetical situation is not realistic. First, even if the actual (true) underlying distributions of exposure to lead for the study populations are significantly different, the "looseness" or imprecision of simple classification schemes such as with smelter/without smelter, high/low, etc. can, in the general case, create categories that are not homogeneous (with respect to exposure) like those portrayed in Fig. 2. In other words, a certain amount of misclassification will occur, weakening the "purity" of comparing health effect measures between the two groups. Second, it is quite unlikely that

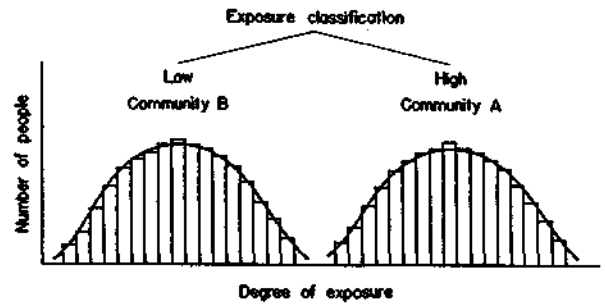

Fig. 2. Hypothetical example of lead exposure in two populations.

we will be able, realistically, to find two or more well-defined populations so vastly different with respect to the degree of exposure to the agent in question, thus compounding the effects of misclassification. This is certainly true for chemical contaminants like lead and organic pesticides that are widely distributed in nature. Further, while the hypothetical communities A and B are rank-ordered in terms of exposure to lead, the "distance" between categories, i.e., the actual degree of difference between A and B with respect to lead exposure, cannot, with such a scheme, be estimated without more information. And, in the particular case of community-wide exposure to lead, exposed/unexposed categories would be unjustified since there are numerous pathways of exposure including food, water, and air.

What, then, are the epidemiologic implications of employing simple exposure classification schemes? For one, there are statistical implications. Artifact (resulting from the way in which exposure classification schemes are constructed) and/or the "natural" or environmental characteristics of the agent in question will tend to result in the mixing of individuals with different exposure experiences, thus creating heterogeneous rather than homogeneous exposure categories. The greater the degree of "mixing," i.e., the more "impure" the comparison, the more alike the comparison groups will be in terms of exposure, which in turn means they will be more alike with respect to any health effect truly related to the particular exposure. Consequently, the difference between the comparison groups (with respect to the measure of effect) will diminish, compromising the sensitivity of the study. Health effects, particularly modest ones, may therefore go undetected, possibly giving the illusion of "safety."

b. Variations on Haber's Law (Unweighted Models of Cumulative Exposure). A common way to model human exposures to environmental chemical involves the application of Haber's law, an elementary concept in toxicology. This approach can be taken when quantitative environmental data are available and when it is possible to relate such data to individual study subjects, as is often the case in epidemiologic studies of workplace chemical hazards. Mathematically, Haber's law states that the magnitude of toxic effect E is a function of the product of the intensity of exposure (in concentration units C) and the duration of exposure (in time units t), so that $E = C \times t$ (*73*).

With this concept it is possible to compute, for each person in a study population, an index of total cumulative exposure (TCE) by simply summing the product $C \times t$ for each period of exposure to the substance in question (if exposure levels change over time) over the entire study period. The (artificial) data in Table I illustrate the calculations for two

TABLE I

Calculation of Individual Total Cumulative Exposures

Worker i	Job j	Intensity of exposure, C (arbitrary units)	Duration of exposure, t (arbitrary units)	$C \times t$
1	1	1	1	1
	2	2	3	6
	3	3	9	27
		Total cumulative exposure for worker 1: Σ =		34
2	1	2	2	4
	2	5	1	5
	3	15	6	90
		Total cumulative exposure for worker 2: Σ =		99
n	1			
	2			
	3			
	.			
	.			
	.			

(of n) hypothetical workers, each having worked for varying amounts of time in three different jobs entailing differing degrees of exposure to a single chemical substance. Since C and t are given equal weight in the computations, this particular method is often referred to as a simple or unweighted model of cumulative exposure.

Once the total cumulative exposures are computed for each study subject, categories of TCE are then created, and appropriate morbidity and/or mortality measures compared across the classes. For example, in a study of coke oven workers (*142*) an index of total cumulative exposure to coal tar pitch volatiles (CTPV) was computed for each worker as follows:

$$\text{TCE}_{\text{worker } i} = \sum_{\text{all jobs}} (\text{mean level of exposure, job } j) \times (\text{duration of exposure, job } j)$$

Mortality rates for all causes of death combined, for all cancers combined, and for lung cancer were then compared across four (increasing) categories of total cumulative exposure, for white and for nonwhite workers. Notably, mortality from all cancers combined and from lung cancer increased sharply with increasing total cumulative exposure to CTPV among the nonwhite coke oven workers, results suggesting a dose–response relation.

The applicability and validity of the simple, unweighted model of cumulative exposure rest on several assumptions. First, it is assumed that quantitative environmental data are available for all relevant time periods and that such data are accurate. Unfortunately, the quantitative characterization of local environments (ambient or occupational) over long periods of time is often not possible. In order to investigate properly the cause or causes of chemically related illness, measures of which (like death rates) are usually contemporary, information must be obtained on exposures occurring prior to the development of the disease. For diseases with substantial induction and/or latent periods, exposure levels dating back years and perhaps decades are required. Even when data on historical conditions are available, the accuracy and representativeness of such data can be questionable, reducing individual exposure histories to crude "guesstimates."

Second, when satisfactory environmental monitoring data are available, it is assumed that it will be possible to select the most appropriate way to summarize exposure levels. Since, by nature, the concentration of most toxics in air, water, soil, etc. will fluctuate over time, so will human exposures. Depending on the substance in question, levels of the agent in environmental media may vary by the hour, by the day, by the week, by the month, and by the year, which raises several questions. Will simple arithmetic means appropriately summarize exposure levels? Would time-weighted averages be better? Should sharp peaks over the short term be given more, less, or equal weight, compared to steady, consistent, long-term trends? Although the answers are not usually clear, they are important questions, questions that relate to yet another assumption of the model: since simple cumulative models of exposure give equal weight to C and t, the *rate* of exposure can be ignored. The essence of this assumption is that the risk of disease would be the same for a given TCE achieved as a result of high exposure over the short term or as a result of low exposure over the long term. Exposure-time units, which are analogous to the familiar and widely used concept of person-time units (*201*), may be accumulated in virtually an infinite variety of ways: 100 exposure-time units = 1 exposure unit × 100 time units = 100 exposure units × 1 time unit. The problem here arises because, at least for certain types of chemical exposures, the risk of disease for a given TCE is not independent of the mode of exposure. For example, in a study of asbestos workers (*66, 68*) the risk of respiratory cancer was, on average, about twice as high for men who had had intermittent (and relatively high) asbestos exposures compared to men who had had steady (and relatively low) asbestos exposures. Since the mean total cumulative exposures in both groups were about the same (230.7 versus 236.0 exposure-time units), this finding suggests that the rate at which exposures are accumulated must be taken into account.

Another aspect of this "transient dose states" problem is something that has been referred to as the wasted dose phenomenon (*197*). Because disease in this particular model is viewed as dependent on the maximum TCE, i.e., dependent on the highest level or category of cumulative exposure achieved, the possibility of a "lower effective dose" is not considered, as Schneiderman *et al.* (*197*) point out. Exposures occurring after the biologic onset of disease (disease presumably resulting from the TCE *up to that point*) continue to be added to a person's cumulative exposure. Since the TCE responsible for disease would be overestimated by including exposures occurring during the latent period, the risk of disease would be underestimated at any TCE above the causative or "effective" TCE. Clearly, the longer the latency, the greater the discrepancy between the effective TCE and the TCE employed in the analysis, and thus the greater the underestimation of risk (as long as exposure-time units are accumulated beyond the time of biologic onset of the disease).

Underestimation of risk may also occur when the exposure period and the follow-up period overlap. As Enterline (*66*) views it, a "dose–response fallacy" can occur because entry into the highest TCE categories can only occur for study subjects who survive long enough, i.e., to the end of the follow-up period. As he suggests, "a high dose and death tend to be incompatible states." Although one possible remedy here, at least for occupational studies, is to limit the investigation to retired persons only, this type of study entails other kinds of problems.

On the other hand, risks may be overestimated when the disease of interest has a latent period and when the amount of time elapsed from the onset of exposure is not taken into account. In this case, persons falling into the lowest cumulative exposure classes will tend to be those with the least amount of exposure time, thereby artificially reducing the risk in the lower TCE classes and, accordingly, artificially inflating the risk in the higher TCE classes. As Pasternack and Shore suggest (*171*), a solution would be to simultaneously assign persons to their rightful category of TCE and to the appropriate category of time since exposure began, thus controlling for differences across TCE classes with respect to length of time exposed.

Finally, the simple, unweighted model of cumulative exposure cannot be used to study chemically complex environments, i.e., when exposures to more than one chemical agent occur simultaneously. This is not surprising since, in general, the investigation of health risks resulting from multiple chemical exposures is quite difficult. One reason for this is that the

necessary environmental data are rarely available (*225*). Another reason, as Saracci points out (*195*), is that it may be impossible to study enough subjects to isolate the effects of exposure to one agent in the presence of one or more other agents, particularly when the statistical analysis involves the cross-classification of the sample into contingency tables. And third, even if a large enough sample could be obtained, choice of the most appropriate statistical approach would be a matter of judgment. In point of fact, studies of interaction may be based on either additive models of disease risk (*189, 190*) or on multiplicative models (*100*). See also references *117, 191, 223* for a more thorough discussion of synergy and antagonism. Recent attempts have been made to refine the epidemiologic study of the health effects resulting from multiple chemical exposures (*205*), an area of research in which the knowledge base is rudimentary at present.

c. Other Variations on Haber's Law (Weighted Models of Cumulative Exposure). A major deficiency of the unweighted model is that it does not take into account the concept of a latent period, i.e., the notion of an "effective" cumulative exposure is not addressed. In seeking to measure an effective cumulative exposure it has been argued that some portion of exposure occurring during the exposure period may legitimately be discounted, i.e., differentially weighted, because the portion of exposure in question presumably plays little or no causal role. A strong case can probably be made that contemporary risks are independent of very recent exposures, particularly for diseases with substantial latent periods. The central issue, of course, is the lack of knowledge about when the biologic onset of disease occurs, which severely limits the estimation of latency. One approach to this problem involves, first, making certain assumptions about the temporal pattern of disease occurrence following a single exposure, i.e., assumptions are made about the latent period. After making assumptions about the shape, the standard deviation, and the central tendency of the distribution of latent periods, the distribution itself is used to derive a series of weights, which in turn are applied to the cumulative exposures in appropriate time periods. For example, in the Lundin *et al.* (*126*) study of lung cancer mortality in underground uranium miners, weights were derived by, first, assuming that the time between the first exposure to underground uranium mining and death from lung cancer was log-normally distributed with a standard deviation of 0.1761 and a median latency of 10 years. Data on the miners were used to estimate median latency, while estimates of the shape and the spread of the distribution were based on those observed for leukemia following a single high exposure to atomic radiation (*16, 121*). The log-normal density function was then integrated over the relevant time intervals and these

areas used as the weights. This method is also discussed by Land and McGregor (*121*).

Other attempts have been made to take latency into account by either partially weighting late exposures or by ignoring them altogether (i.e., giving them zero weight). This is the so-called lagged-exposure model, which assumes that exposures occurring a certain number of years prior to disease or death may be discounted. Mazumdar and Redmond (*141*) discuss this technique as applied to their study of lung cancer in men exposed to coal tar pitch volatiles. Pasternack and Shore (*171*) discuss the application of the lagged-exposures approach to actually estimating the average latent period in a set of data.

B. Measurement of Response

As described earlier, the morbidity or mortality rate is a useful measure of the risk of disease or death in a population. In practice, however, there are often situations in which a rate, in its usual form, cannot be computed as a measure of response in a population to a given exposure. In other situations the computed rate is not reliable and therefore should not be employed. For example, the problem of unreliable rates is common in the study of cancer. Although cancer is a leading cause of death, the actual probability of an individual dying of cancer in a given year is quite small. If the population under study is not sufficiently large the resulting rate, particularly the age-specific rate, will be quite unstable, and the confidence interval encompassing that rate will be very large. A measure called the standardized mortality ratio (SMR) is commonly used in such situations.

The major advantage of the SMR is the introduction of information from a large, stable population. Using this method it is possible to compare the mortality experience of a defined subgroup with the total population. The SMR is computed as a ratio of the observed number of deaths in the study population to the number of deaths that are expected to occur in that group. It is with respect to the denominator of this ratio that the concept of a standard population is required. To compute the SMR it is not necessary to know the number of deaths that occur in each age group of the study population; one only needs to know the number of persons at risk in each age group. An expected number of deaths is generated by multiplying this figure by the age-specific mortality rate of the standard population. Both observed and expected numbers of deaths are then summed over all ages, and the ratio computed.

The SMR is interpreted with respect to its deviation from unity. To the extent that it exceeds unity, the risk of death is said to be greater in the study population. Statistical properties of the SMR are known and

therefore significance testing is possible. In this regard, tables containing critical values of SMRs are published[2] (*6*).

The choice of a standard population is not a trivial matter, nor is the most appropriate selection always obvious. For example, a comparison of death rates for different socioeconomic groups in a population might use as a standard the highest socioeconomic group (*207*). Resulting SMRs for lower groups would then reflect the assumption that excess deaths occur because living conditions, medical care, etc., are inadequate. Interpretively, this raises different issues than might surface if the entire population had served as the standard. In selecting a standard population, attention should be given to the purpose of the comparison and to its potential limitations.

SMRs are frequently utilized in the study of defined occupational groups. One such investigation evaluated the mortality experience of iron foundry workers (*53*). Death rates in this cohort were compared to rates for the general U.S. male population. Potentially confounding variables, such as length of employment in the industry and race, were considered. Although silicosis has historically been a health problem in the foundry industry, unusually high mortality from chronic respiratory disease was not observed in this analysis. However, it cannot be discerned from the data whether this was a result of exposure to low levels of silica-containing dusts, or of insufficient numbers of workers with long exposure histories, or of too short a follow-up interval to allow for the clinical expression of disease and subsequent death of cohort members. Overall, this investigation revealed lower total mortality in the worker population. This finding is not unusual in occupational studies, a phenomenon discussed later (*8, 155*).

A similarly designed study of workers in a chemical company was intended to determine whether socioeconomic status or job classification was related to overall or cause-specific mortality (*169*). This type of study is important because it recognizes the variability of individual characteristics within a broadly defined worker cohort. SMRs were computed using the U.S. white male population as the standard. Overall mortality was lower than expected, but certain malignancies (such as urinary organ neoplasms) yielded high SMRs. Stratification of the data by socioeconomic level showed statistical differences: low SMRs in the high socioeconomic group. Differences with respect to job category were also detected. For example, plant mechanics and machinists had more malignancies than expected, while inorganic chemical production workers

[2]Although this discussion pertains to mortality, morbidity data can be treated in the same way.

showed a decreased rate of cancer. Additionally, the analysis addressed the question of age at entry to the study and age at death.

This approach is significant because it presents the investigator with a new set of paths to follow to explain notable trends in the health of industrial populations. Careful stratification of the cohort is particularly important, since, as the study of the chemical workers demonstrates, there is measurable heterogeneity within the cohort. For example, the low rate of cancer mortality in the high socioeconomic group might reflect a lower prevalence of smoking. Once the specific mortality pattern of a well-defined group is understood, there is opportunity for careful testing of such hypotheses. Other investigations have also used the approach of employing data on job classifications and have reported increased rates of malignant disease for specific categories (*124, 125, 168*). This has been noted for mechanics and machinists in more than one industry.

In addition to SMRs, a measure called the proportional mortality ratio (PMR) has been used in a large number of analyses, particularly in studies of occupational groups. The PMR differs from the SMR in that the demographic composition of the population at risk is not known. Rather, the PMR represents the proportion of total deaths attributable to a specific cause in a study population. Consequently, the PMR is not a rate. It is simply a measure of the relative importance of a given cause of death, not a measure of the risk of death (*154*). Despite this inherent limitation, PMRs do have a role in epidemiologic analyses. First, the data necessary to compute a PMR are relatively easy to obtain—they are essentially only the data that would normally constitute the numerator of a mortality rate. Hence, PMR studies are sometimes referred to as "numerator studies." Second, although the absolute risk of death cannot be determined, knowledge of the relative importance of a cause of death can lead to testable hypotheses about potential etiologic factors. That is, if a cause of death is proportionately greater in one group than in another, exposures unique to the former might explain the observed differential.

The validity of a PMR study depends on the extent to which certain assumptions are met by the data. The difficulty is that the assumptions cannot be tested empirically, since they require data that are not available, namely population data. The basic assumption is that the relationship between the PMRs of two groups being compared is equivalent to the relationship between the actual mortality rates in the populations. If this latter information were known, however, there would be no need to compute PMRs; rather the rates or SMRs could be compared directly. There is a danger of erroneous interpretation of PMRs if this assumption is not tenable or if the PMR is inappropriately interpreted as a measure of risk. For example, consider a hypothetical case of two study populations,

in each of which 1000 total deaths are observed. Also assume that 200 deaths in each group are due to cancer. The PMR for each group would thus be 0.20. Clearly, cancer assumes the same relative importance in each group—20% of all deaths. But if the population of the second group is larger, the actual death rate from cancer would be smaller than in the first group. That is, the risk or probability of dying of cancer can vary even if its proportionate contribution to total mortality is the same. Consequently, in interpreting PMRs one must not be tempted by the false impression that the comparative risk of death is being analyzed.

There are many examples of PMR studies in the literature. One such analysis investigated mortality patterns among employees exposed to polyvinyl chloride (PVC) (*40*). Since the population at risk could not be determined, the proportional mortality in various subgroups of the worker population was compared to similarly defined PMRs for the U.S. population. A comparison of these figures is an indication of whether or not relative excess mortality has occurred in the study population. In this particular investigation, there appeared to be an excess number of cancer deaths among both white males and white females. For the reasons already given, however, this finding must be interpreted with caution. The suggestion, however, of excess cancer mortality does provide a lead for more definitive investigation, thereby demonstrating the value of PMR analyses.

The importance of such analyses is similarly demonstrated in a study of mortality among workers in a newspaper printing factory (*92*). This example is noteworthy because it demonstrates that PMR analysis can be an efficient method for very preliminary investigation of a new hypothesis. This study was undertaken following anecdotal reports of a high incidence of bladder cancer among the printing workers. In the particular group studied there was no evidence that bladder cancer assumed unusual importance as a cause of death, although the PMR for all neoplasms combined was very high. However, this appeared to be the result of a large number of deaths from lung cancer, implicating smoking rather than an industrial hazard.

The comparability (and differences) of the PMR and SMR methods is demonstrated in an analysis of workers exposed to low levels of methylene chloride for up to 30 years (*78*). Specifically, the investigators wanted to determine whether this cohort exhibited high rates of mortality from ischemic heart disease, since exposure to chlorohydrocarbons may result in increased cardiac sensitivity (*183*). Since population data were not available for this group prior to 1964, a PMR approach was adopted. The post-1964 cohort was analyzed by an SMR approach. Proportional mortality ratios did not reveal any unusual mortality trends for any of

the 17 major diagnostic categories that were analyzed. Further breakdown of the data for specific malignancies also failed to show any statistically significant differences. In the second part of the analysis, two different standard populations were selected. The first was the group of all other males working in the same plant; the second was a general population standard. The results obtained exemplify the point noted earlier regarding the effect of a particular control population on study findings. With respect to the industrial standard, the methylene chloride-exposed group did not have significantly different SMRs for any major cause of death studied. However, when compared to the general population, significantly fewer deaths than expected were observed for malignant neoplasms and circulatory diseases. Specifically, ischemic heart disease mortality was reduced.

While it has been emphasized that PMRs are not direct risk-assessment measures, their usefulness for preliminary screening of data is generally accepted. The methylene chloride study, however, demonstrates a case in which potentially erroneous conclusions might have been drawn if only the PMR analysis were available. In this study the PMRs and SMRs are not directly comparable, since the data for each were derived from different time periods. However, one might argue that the differences are small and that the conflicting results reflect the method of analysis. The findings of this investigation do not negate the relative value of PMR analysis, nor do they wholly validate the SMR approach. Rather, they point out the need for cautious interpretation.

There are in the literature several rigorous comparisons of the two approaches described here (*52, 118, 181*). Although these issues will not be discussed in detail, it is important to recognize, at least in concept, some of the primary constraints. Some, such as the choice of the standard population and the failure of PMRs to measure risk, have been previously alluded to. Other problems of the SMR have also been identified (*80, 81, 145*). For example, the SMR does not reflect the effect of a hypothesized hazard on life expectancy; it counts only the number of deaths, not the ages at which they occur (*81*). It has been demonstrated that populations with different life expectancies can yield the same SMR. Additionally, the SMR is dependent on the age distribution of the study population. If younger workers have a lower mortality rate than the standard population, the SMR will not correctly estimate the probability of death, since this probability is not precisely (mathematically) equivalent to the mortality rate (*74*). These two figures are related, however, and consequently one can compute the degree of age dependence in the SMR (*39*). Finally, the SMR is not independent of the length of follow-up of the study cohort. That is, if calculated periodically during follow-up, the SMR is not expected

to remain constant. If the risk of death in the study group is high, SMRs might exceed 1.00 early in the study, but decline as follow-up continues.

A final point about the measurements of outcome that have been discussed in this subsection relates to a question of sample selection bias known as the "healthy worker effect." A variety of data indicate that the fact that persons are healthy enough to be employed intrinsically predicts that their mortality experience will be more favorable than that of the general population. This effect was first identified nearly 100 years ago and has been widely recognized in contemporary epidemiology (*86*, *166*). Furthermore, it has been demonstrated that the magnitude of the bias is related to the age distribution of the industrially employed cohort and to the specific causes of death being considered (*65*). In addition to the fitness of workers at the time of employment, the issue is further complicated by the fact that the composition of the cohort is influenced by the dynamics of individuals leaving the industry for health-related reasons. The empirical effects of these questions on SMRs has been reported. One of the more comprehensive analyses involved a study of all PVC workers in Great Britain (*75*). The findings supported an association between exposure to the vinyl chloride monomer and angiosarcoma of the liver; furthermore, it was demonstrated that the observed rates of mortality were indeed related to the selection of workers into the industry, their continued employment, and the length of time the cohort was followed. The cause-specific nature of these biases has been shown in a study of workers in five chemical plants, using an approach designed to minimize selection effects on the resultant SMRs (*202*).

V. RELATING MEASURES OF DOSE TO MEASURES OF RESPONSE

There are several important aspects of the process by which the functional relationship between measures of dose and measures of response is determined. For example, in the case of cancer this process is influenced by the investigator's assumptions regarding the underlying biologic mechanisms of carcinogenesis. Although cancer has been recognized as a distinct disease for thousands of years, only recently has there developed some understanding of the mechanisms responsible for the transformation of a normal cell into a malignant one. Clearly, an elucidation of the biologic mechanisms of carcinogenesis will substantially increase the potential for prevention and control of neoplastic disease. The lack of this type of evidence, however, does not thoroughly preclude the ability to intervene; associations discovered in epidemiologic investigations can

sometimes provide sufficient information for designing intervention strategies, thus interrupting the causal chain of events even if they are not fully known. Even with this inherent strength, epidemiologic assessment of health risks resulting from chemical exposures can be enhanced by incorporating knowledge derived from theoretical studies of the pathogenesis of cancer. In this section we do not provide a comprehensive discussion of the molecular theories of carcinogenesis; rather, we highlight a few general principles that bear on the design of epidemiologic investigations and the interpretation of their results.

Of particular importance in this context are the concepts of initiation and promotion. These terms were coined in the 1940s to define operationally the extended period between the initial exposure to a carcinogen and the expression of a malignancy (*158*, *188*). Early empirical demonstrations of this process involved the direct application of a confirmed chemical carcinogen (usually a polycyclic hydrocarbon) to the skin of a mouse—the initiation phase. Tumor promotion was accomplished by the application of another chemical agent, which was by itself incapable of inducing neoplasia (*9*). Although this general procedure has been refined in recent years, it still provides one of the fundamental models for studying chemically induced cancer. Subsequent experiments have confirmed that certain compounds, such as benzo[*a*]pyrene and methylcholanthrene, possess both initiation and promotion activity, and therefore are complete carcinogens (*26*, *27*).

The various stages of carcinogenesis have been demonstrated in organs other than the skin. For example, a breast cancer model in rats and mice has indicated that application of a carcinogen without the appropriate hormones does not result in a malignant tumor (*79*). Additionally, both initiating and promoting agents have been identified for tumors of the dog and rat bladder, the mouse lung and forestomach, and the rat colon, bone marrow, liver, and thyroid (*177*). In each case the initiator is an agent whose metabolites can react with DNA. The corresponding promoters range from natural products to normal circulating hormones.

There are several general characteristics of the multistage carcinogenic process that have implications for the ultimate control of malignant disease in human populations. One important finding in this regard is that the process of initiation is not reversible, while the process of promotion is. This bears directly on the potential for prevention of neoplastic disease. That is, if the exposure is discontinued before cells in the target tissue develop the ability to multiply in the absence of the promoter, then formation of a tumor may be avoided. Reduction of risk of lung cancer following cessation of cigarette smoking may be an example of this type of intervention (*174*). The declining risk suggests that promoters are the cancer-causing elements in cigarette smoke.

The concepts of initiation and promotion are inextricably bound to the phenomenon of latency. The importance of accounting for the latent period is well understood in epidemiologic research. Investigators attempt to introduce appropriate temporal relationships between measures of dose and measures of response. The latent period is a general feature of the natural history of neoplasia, whether the relevant exposure is chemical, radiologic, or viral.

In the practice of epidemiologic research, however, the concept of a latent period and the temporal relationships between initiation and promotion phases pose various difficulties. In general, the duration of the latency period is unknown. Furthermore, the relationship between dose level and duration of latency is uncertain. Experiments with laboratory animals have indicated that an increased dose does shorten latency, and attempts have been made to quantify this relationship (*1*). However, the same mathematical model does not appear to hold for human populations (*121*). For example, in a study of bladder cancer among persons occupationally exposed to dyestuff intermediates, no relation between dose and latency could be detected (*36*). These findings have led to speculation that the duration of the latent period is affected by variables other than the dose of the initiator. Some of these factors are probably endogenous characteristics of the host, such as levels of pituitary hormones and the genetic makeup of the host (*12*). Other modifiers are thought to be exogenous and may include dietary constituents (*153, 163*). To the extent that these factors are unknown, the assessment of risk in human populations becomes more complicated, since the variation in dose rate over time, the reversibility of initiation, and the distinction between initiation and promotion must be accounted for if causal inferences are to result. Although a number of diverse quantitative approaches to modeling carcinogenesis in human populations have been proposed, none is entirely consistent with available empirical evidence (*48, 227*). Many of these models have incorporated information regarding the age distribution of cancer cases and have measured the effective duration of exposure before onset of disease over a wide range of ages (*5, 56*). By this method the comparative risk of exposure to the same agent at different ages could be analyzed in relation to dose, duration of latency, and the effect of altering various promoters.

VI. CONCLUSION

The purpose of this article has been to discuss some of the concepts fundamental to the epidemiologic evaluation of potential health risks stemming from chemical contamination of the human environment. These methods assume a central role in any comprehensive attempt to understand the effects of chemical exposures on human health. Combined with evidence derived from the fields of chemistry and toxicology, the quantification of human risk should ultimately result in substantially improved methods for intervening in the process of disease causation.

The epidemiologic approach is characterized by its systematic examination of patterns of exposure and response in human populations. Since the occurrence of disease is not a random phenomenon, epidemiologic investigation is uniquely suited to the generation and testing of etiologic hypotheses. The development of clues to explain chemically related illness generally begins with descriptive methods, whose major purpose is to detect variations in disease occurrence with respect to time and/or place. Observed secular trends may reflect alterations in exposure to environmental hazards. Notable geographic differences in disease occurrence may result from the presence of a risk factor in some populations and its absence in others. Once observed temporal or geographic patterns are established as real (as opposed to artifactual), epidemiologic investigation may proceed to a variety of aggregate population studies, usually entailing correlation or regression techniques. In this phase of the process, attention focuses on the identification of demographic, socioeconomic, and environmental factors that may have etiologic implications. Although the methodologic problems associated with ecologic analyses are well recognized, the method has substantial utility for generating hypotheses that may subsequently be tested by more rigorous methods.

If descriptive epidemiologic studies suggest a potentially adverse effect from a chemical exposure, investigations can then be designed to test formally the possible association between the agent and the disease. The analytic methods employed in this phase of epidemiologic inquiry incorporate data for individual study subjects, as opposed to aggregate or summary data for a population. Although the two primary methodologic approaches, case-control and cohort studies, differ with regard to the assemblage of subjects, they share a number of characteristics. In both cases, the desired endpoint is some quantitative (statistical) measure of risk associated with the exposure in question. Concern for proper classification of study subjects with respect to exposure and disease, selection of appropriate comparison groups, the requirement of reliable and valid exposure data, and the need to control confounding factors are common elements in both approaches. Although there are a variety of advantages and disadvantages intrinsic to both methods, the choice for a particular study depends on the hypothesis to be tested, the availability of necessary data, the rarity of the disease under consideration, and the prevalence and intensity of the exposure factor.

To a great extent, the applicability of results from case-control or cohort studies is dependent on the method by which exposure (and by implication, dose) is measured. The exposure variable may range from a simple qualitative classification to a more complex quantitative estimate of total cumulative exposure. What is important to recognize is that the measurement of exposure must be consistent with an underlying biologic theory of disease causation. For example, studies of malignant neoplasms must account for periods of latency and possible differential effects between initiating and promoting agents. Finally, methodologic attention must focus on appropriate measures of response to a chemical contaminant. Quantitative measures, such as standardized and proportional mortality ratios, need to be carefully constructed and statistically analyzed.

Each aspect of the epidemiologic approach we have described is itself an area that continues to be subjected to intense critical scrutiny. For example, there is a rich literature regarding the statistical properties of the odds ratio, the choice of controls for case-control studies, the appropriate length of follow-up for cohort analyses, etc. That controversy exists in each area does not invalidate the overall approach; rather, it enhances the investigator's ability to reach critical decisions about all phases of study design, execution, data analysis, and interpretation. Perhaps more than for anything else, the epidemiologic method can be recommended for its vigilance regarding the possibility of alternative explanations to account for any observed finding. In the ideal case, the interpretation of epidemiologic data guards against the chance that a hazardous exposure is judged to be 'safe.'

Epidemiologic analyses thus contribute to the control of disease by quantifying the probability that a chemical exposure may pose risk to human health, and by specifying the co-occurring conditions under which such risk might exist. If a hazard is confirmed, appropriate intervention strategies may be devised to interrupt the causal chain, thereby reducing morbidity and mortality. In this context the epidemiologic approach is fundamental to the assessment of chemical exposures, their effects on human health, and the benefits to society that might result from reduced environmental contamination.

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