1

The Study of Occurrence Problems in Medicine: Introduction

1.1. THEORETICAL EPIDEMIOLOGY AS THE DISCIPLINE OF OCCURRENCE RESEARCH IN MEDICINE

Epidemiology originally dealt with *epidemics of communicable diseases* only. In this context there developed certain principles of how to study the occurrence—prevalence and incidence—of communicable diseases. Naturally, the occurrence rates were related to various characteristics of persons—age and other determinants of occurrence rates, including suspected causal ones.

A small extension of this original concern was to subsume under epidemiology the study of *endemic* occurrence of communicable diseases, and the occurrence, epidemic or endemic, of noncommunicable (noncontagious) *infectious* diseases.

Major expansion resulted from the observation that the principles of studying the occurrence of infectious diseases could be applied to the study of the occurrence of noninfectious diseases as well. This gave rise to so-called *chronic-disease* epidemiology. The term, a misnomer, refers to non-

infectious diseases, chronic and acute, and defects as well as diseases. In other words, infectious-disease epidemiology was extended to the epidemiology of any *illness*, whether infectious or noninfectious, acute or chronic, and whether it be a process of ill-health (disease or *morbus*) or a state of ill-health (defect or *vitium*).

Naturally, students of the occurrence of illness, infectious or not, have taken an interest in the occurrence of various states of *health*, insofar as they may be considered to have potential bearing on the occurrence of illness. Thus, an infectious-disease epidemiologist is concerned, for example, with the occurrence of states of immunity; and the "chronic-disease" epidemiologist is interested in issues such as the occurrence of various levels of blood pressure.

The traditional practice of stratifying epidemiologic problems according to the type of illness has led to prevention-oriented specialties such as cardiovascular epidemiology (preventive cardiology) and cancer epidemiology (preventive oncology). This *illness-centered* outlook is not ideal as a basis for preventive intervention. Thus, preventive cardiology has led to recommendations and programs for lowering cholesterol, but there is reason to suspect that these may result in an increase in the risk of cancer.

A more appropriate basis for prevention is *determinant-centered* epidemiology. Thus, when the focus of research is on nutrition, one studies *all* the health effects of a cholesterol-lowering diet; and even if the merits of such a diet be conflicting among different categories of illness, such research provides for evaluating the overall effect. In addition to the field of nutrition, this outlook is common in toxicology, occupational health, and various other fields.

With each of these two outlooks, epidemiology has traditionally been associated with disease *prevention*, and it has been viewed as a *public-health* science and discipline. Indeed, it has been described as "the basic science of public health." In this spirit, there have been attempts to distinguish between epidemiology and clinical medicine, arguing that the former deals with populations and the latter with individuals. This distinction applies, however, more to health care itself in these two areas than to research in them.

Prevention-oriented epidemiology has given rise to the concept and discipline of *clinical epidemiology*. It deals with the occurrence of states and events of medical concern in the clinical context, that is, among patients under medical care. Analogously with more traditional epidemiology, the focus of such research may be on the occurrence of a particular type of health state or event in relation to its various determinants or, alternatively, on the effects of a particular determinant on the occurrence of various outcomes. Thus, a clinical epidemiologist studies the occurrence of infections among hospitalized patients (nosocomial infections) as opposed to the occurrence of infections among people in the community. Similarly, the clinical

epidemiologist studies the occurrence of sudden cardiac death among patients with known coronary heart disease rather than among people with no known heart disease in the community. With the research focus on a determinant of illnesses or related phenomena, the clinical epidemiologist interested in nutrition studies the occurrence of various complications of adult-onset diabetes in relation to diet among such diabetics, instead of the effects of diet on the risk of diabetes and other states and events of health among people at large. Similarly, the clinical epidemiologist may be concerned with the various health effects of a particular type of clinical intervention, medical or surgical.

The discipline of epidemiologic research that has developed in the context of these problems of scientific research in preventive and curative medicine is being increasingly applied to medical problems that are of *administrative* rather than scientific interest. Thus, those concerned with planning and/or evaluating health *education* acquire information on the occurrence of health-related knowledge, attitudes, and behavior in the population at issue, with the rates of occurrence related to their major determinants, known or surmised. Similarly, planners of health-oriented *regulation* require knowledge of the occurrence of the target problem of regulation—an industrial or health-care practice, for example—and of matters that have bearing on the feasibility and reasonableness of its solution by regulatory means. The associated evaluation work is a matter of quantifying the occurrence of compliance with the regulation in relation to potential impediments to the willingness or ability to comply. In the context of administrative research on health *service*, whether an innovation (demonstration project) or a routine (established program or practice), the concerns include the occurrence of various types of need or demand for the service, various response actions by the service, impediments to proper response, and so on. The concern is with frequencies of various occurrences, just as in scientific problems of the epidemiologic type. However, the states or events at issue commonly characterize health care more than health or illness per se, and the units of observation may not be persons but, for example, instances of care action. Most significantly, though, the concern is not with abstract issues of science but with here-and-now administrative problems of health-care action within a particular facility or agency for care (see Section 1.6).

As has been seen, epidemiologic research addresses both scientific and administrative problems of practically all areas of medicine. Thus the subject matter of epidemiologic research is catholic and incoherent and therefore does not constitute a field of knowledge per se. Instead, a multitude of medical sciences and areas of practice embody epidemiologic problems. Hence, cancer epidemiology is a specialty within oncology, malformation epidemiology within teratology, health-care epidemiology within health-care administration, and so on. In this regard epidemiology is akin to morphology, for example—an *aspect of various sciences and other fields* as opposed to

a science or other subject-matter field in itself. (This feature of modern epidemiology has remained regrettably ill understood, and so there are journals, societies, and other forums of epidemiology—and academic departments besides—with completely catholic subject-matter coverage, in principle at least.)

The evolution of epidemiologic research has, however, maintained coherence in terms of the generic type of problem. Throughout, epidemiologic research has been concerned with the *frequency of occurrence* of illness and related phonomena (states and events) of health and health care. The *discipline* of such research, that is, the aggregate of *principles* of studying the occurrence of illness and related states and events, including those of health care, in man has also maintained coherence.

These principles are the subject of this text, under the board headings of study design and data analysis. In contrast to epidemiologic subject-matter, these principles constitute *general*, or *theoretical, epidemiology*.

1.2. GENERALITY OF THE EPIDEMIOLOGIC DISCIPLINE

It is apparent that the form of epidemiologic problems is not unique to medicine. There is research into the occurrence of phenomena other than medical ones, and into occurrence problems regarding nonhuman objects in addition to humans. Nor are the principles unique to medicine: the principles of occurrence research in medicine should be directly applicable to the study of occurrence in general, regardless of the nature of the state or event and of the unit of observation. Thus, the one who knows how to study the occurrence of sudden death in humans should know how to quantify the risk of airplane crash in relation to its determinants.

For a clear understanding of this generality it may be helpful to take note of some examples of problems that are *not* of the epidemiologic form.

Example 1.1. Although the occurrence of malnutrition is an epidemiologic problem, the occurrence of famine is not. The reason is that malnutrition affects individuals in a population, whereas famine is an affliction of a population in the aggregate, rather than of its individuals. (One might think of a population of populations and thereby reach the epidemiologic formulation.)

Example 1.2. The occurrence of individual violence is a problem of the epidemiologic form, but the occurrence of war is not.

Example 1.3. In contrast to bankruptcy and frostbite, the occurrence of economic depression (national or global) and of exceptionally cold weather are not problems of the epidemiologic form.

Example 1.4. The occurrence of *epidemics*, the focal concern of classical epidemiology—a coherent subject-matter field—is not a problem of the form

characteristic of modern epidemiologic research. The scientific issues regarding epidemics are analogous to those of the genesis and spread of cancer in the individual, which are matters more of pathologic mechanisms and processes than of cancer epidemiology. The issues are also analogous to those in recurrent attacks of disease in the individual, epileptic seizures for example, where the focal concern is mechanisms of precipitation. The paradigm for modern epidemiology is not the study of epidemic but of *endemic* occurrence of illness.

Given the applicability of the formal aspects of the epidemiologic discipline of research not only to nonmedical states and events in man but to nonhuman objects as well, and given that epidemiology is not coherent as a science but only as a discipline, it would be good to replace the term "epidemiology"—which refers to people—with something less specific, but an appealing suggestion has not yet been made. On the other hand it is worth noting that in some ways the principles, and to a large extent the factual content, of the discipline are quite peculiar to *medical* occurrence research, as they are dependent on professional value systems, biomedical and public health facts, ingrained patterns of thought and behavior, and so on. These matters, however, are generally outside the scope of this text.

1.3. OCCURRENCE RELATIONS AS THE ACTUAL OBJECTS: OCCURRENCE PARAMETERS, THEIR DETERMINANTS, AND MODIFIERS OF RELATIONS

It has been noted in the philosophy of science that any science is concerned with *functional relations* of its objects (Friend and Feibleman, 1937). This proposition is quite evidently tenable for epidemiologic objects of research. *Parameters of occurrence*, such as the incidence rate for a particular illness, are not constants of nature. Rather, their magnitudes generally depend on—are functions of—a variety of characteristics of individuals—constitutional, behavioral, and/or environmental. Such relations, even if only remotely credible, are generally the objects of medical occurrence research. For example, one is quite usually interested in learning whether the rate of occurrence of some particular illness depends on (is related to or is a function of) gender—regardless of whether there is any express reason to surmise that it might be.

Example 1.5. The prevalence of any given blood type based on the ABO antigen system, while constant over gender and essentially constant over age, is not a constant of nature. It varies by ethnic groupings, for example. Thus the prevalence must be quantified in relation to—as a function of—ethnic group.

Example 1.6. For the occurrence of various values of blood pressure among people, one descriptive parameter is the median of the pressure. (This

is a value such that the prevalence of its exceedance is 50%.) This parameter, again, is not a constant of nature but depends on age and other characteristics of individuals. For the quantitative nature of the age relation of systolic blood pressure, a rule of thumb used to be that it is, in mm Hg, "100 plus age in years." This rule expresses a regression model—a regression function—of the form $P = A + B \times \text{Age}$. In this example, P, the occurrence parameter, is the median of systolic blood pressure, $A = 100$ mm Hg, and $B = 1$ mm Hg/yr.

The characteristics on which the magnitude of an occurrence parameter depends (causally or otherwise) are *determinants* of the parameter. Thus, in the examples given above, ethnic grouping is a determinant of the prevalence of any given blood type, and age is a determinant of the median of systolic blood pressure. "Determinant" has no implication as to causality in science—any more than in everyday locution: the current age of a person is "determined" by his/her year of birth (noncausally), just as the expected outcome of a disease is "determined" by the treatment that is used (causally).

The relation of an occurrence measure to a determinant, or a set of determinants, is naturally termed an *occurrence relation* or an *occurrence function*. These relations are in general the objects of epidemiologic research.

Even though the general inconstancy of occurrence parameters leads to the consideration of occurrence relations, this latter outlook affords only a partial accommodation of the inconstancy, because occurrence relations also vary according to the type of individual. In particular, measures of the degree of relation (Appendix 2) have determinants of their own.

Example 1.7. Recall Example 1.6 and the occurrence function for systolic blood pressure therein. That function may apply reasonably well to populations with high consumption of sodium in the diet. However, in primitive populations with no "artificial" use of sodium, there is essentially no age trend in the level of blood pressure among adults. For this reason and others, it seems that sodium consumption is a determinant of the degree of the age relation of blood pressure (reflected by the *slope* of the regression relation). (See Figure 1.1.)

The subject characteristics on which a measure of occurrence relation (Appendix 2) depends—its determinants—are termed *modifiers* of the relation. Thus, the slope of the age relation of blood pressure is modified by sodium consumption (Example 1.7); measures of the age relation of the prevalence of immunity to measles are generally modified by crowding; measures of the age relation of the incidence of breast cancer are modified by gender; measures of the absolute efficacy of screening-and-treatment for tuberculosis are modified by socioeconomic status (because the prevalence of the disease depends on socioeconomic status); measures of the relation of mortality in coronary heart disease to bypass surgery are modified by what vessels are stenosed; and so on.

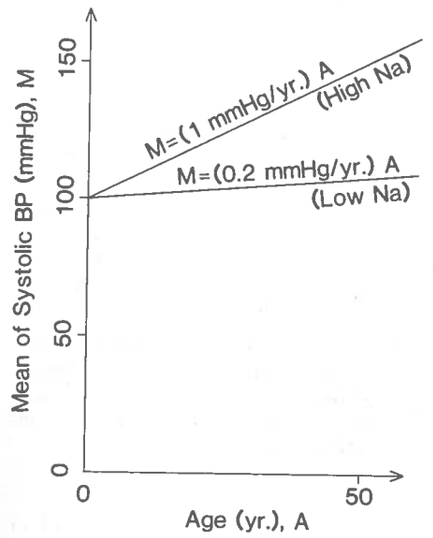

Figure 1.1. Mean systolic blood pressure in relation to age. The parameter of relation—the regression slope—is modified by the level of sodium consumption.

The existence and even the nature of modification can sometimes be surmised on general theoretical grounds. Consider, for example, the relation of the incidence of invasive cervical cancer to screening-and-intervention, as modified by the "background" rate. One would expect, in parsimonious terms, that such a program reduces the prevalence by a fraction that is invariant over the "background" rate, that is, that the preventive fraction is constant over the "background" rate (see Appendices 2 and 3). This means, in turn, that the difference in incidence according to intervention is modified by the "background" rate. This is illustrated in Figure 1.2.

In the context of a causal exposure, it is parsimonious to think of the proportion of people who are causally susceptible as proportional to the proportion of those on whom the illness would not develop in the absence of the cause at issue (see Appendix 3). Again the implication is that the rate difference (or regression slope) as a measure of relation of the parameter of occurrence (cohort incidence, see Appendix 1) to the determinant is modified by the "background" level of the parameter. This is illustrated in Figure 1.3.

A source of modification (of measures of occurrence relation) totally distinct from determinants of the "background" level of occurrence is arbitrariness in the choice of the occurrence parameter. Consider instances in which the "effect" of the determinant is additive with the "background" level of the parameter, as determined by some particular covariate (e.g., age). In these situations the covariate is a determinant of the intercept (the "background" level) but not of the slope (the measure of relation) of the basic occurrence function:

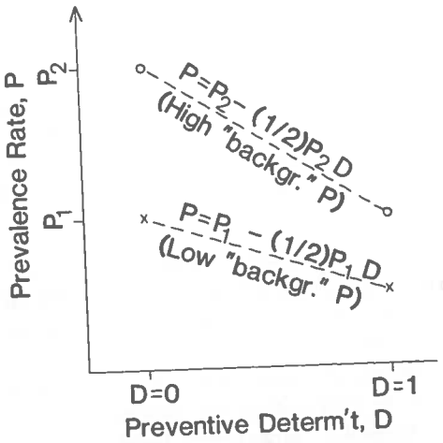

Figure 1.2. Prevalence in relation to preventive intervention, with the rate difference (regression coefficient) modified by "background" prevalence, in the context of invariant preventive fraction ($\frac{1}{2}$).

$$P = A + B_1(C) + B_2(D), \tag{1.1}$$

where P represents the occurence parameter, C the covariate, and D the determinant at issue; for example, P = incidence density of coronary heart disease, C = age, and D = indicator of cigarette smoking ($D = 1$ for smokers, $D = 0$ for nonsmokers). Here the intercept of the relation of P to D is

$$A' = A + B_1(C), \tag{1.2}$$

a quantity that depends on the covariate, whereas the slope (B_2) of the relation—the actual measure of relation—is invariant over it. If one considers the ratio of the occurrence parameter P to the value of its "background" level A', the relation shown in Equation 1.1 takes on the form

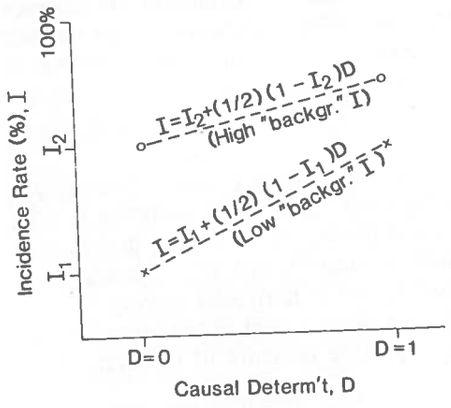

Figure 1.3. Incidence in relation to causal exposure, with the rate difference (regression coefficient) modified by "background" incidence, in the context of absolute effect proportional to the complement of the "background" incidence.

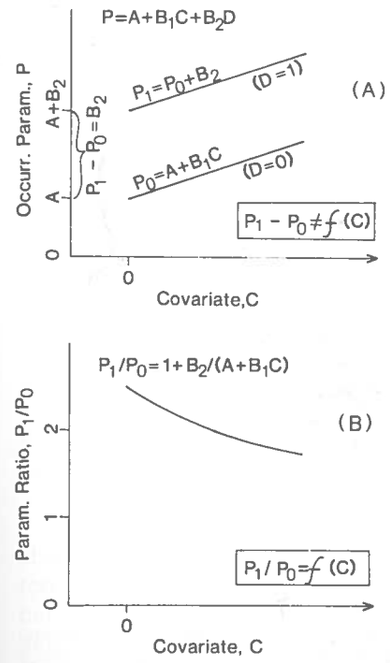

Figure 1.4. Relation of occurrence parameter P to a binary determinant D, with the intercept $A + B_1C$ but not the slope B_2 dependent on the covariate C. For the contrast ($D = 1$ vs. $D = 0$), the parameter difference ($P_1 - P_0$) is invariant over the covariate, but the parameter ratio (P_1/P_0) is modified by it.

$$PR = 1 + \frac{B_2}{A'}D, \tag{1.3}$$

where PR is the parameter ratio P/A'. In this reformulation of the occurrence relation in Equation 1.1, the covariate bears not on the intercept (as in Equation 1.1) but on the slope (through A'). Conversely, additivity with respect to the relative measure of occurrence, PR, means nonadditivity in terms of the corresponding absolute measure, P. This dependence of modification on the choice between absolute and relative measures of occurrence is illustrated in Figure 1.4.

Apart from modification by determinants of the "background" level of the occurrence parameter, and modification that results from the use of an arbitrary measure of occurrence, there is modification that reflects actual interdependence of effects between the determinant at issue and a particular other factor (see Appendix 3).

Modifiers of the relation of an occurrence parameter to a particular determinant are themselves also determinants of that parameter. The concept of modifier in the context of determinants at large results from a hierarchy

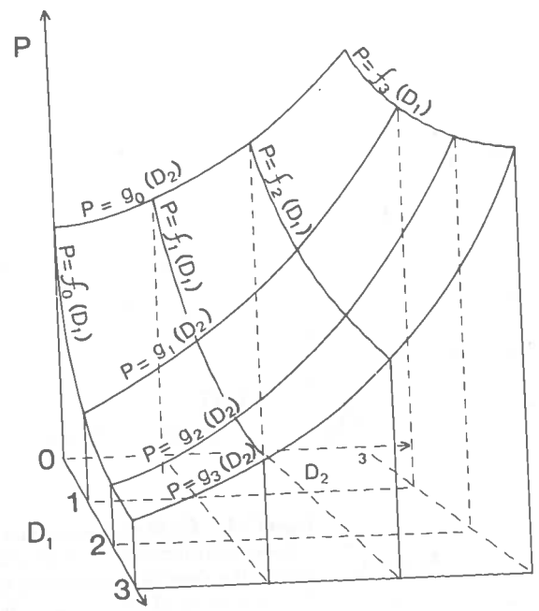

Figure 1.5. Relation of occurrence parameter P to determinants of D_1 and D_2. The relation of P to D_1 depends on D_2, and conversely, its relation to D_2 depends on D_1. The dependence involves the slopes (measures of relation) in addition to the intercepts ("background") levels. The slope variations imply mutual modification: the relation of P to D_1 is modified by D_2, and conversely.

of interests or concerns in any given instance. Thus, when the concern is with the age relation of the incidence of breast cancer, gender assumes a secondary role—that of a modifier of the relation of primary interest. Conversely, if the primary concern is with the gender relation of breast cancer incidence, age is viewed as a modifier of that relation. This interchangeability of roles is illustrated in Figure 1.5.

Determinants of incidence are commonly referred to as *risk factors*. This term is a misnomer. Since the relation of an occurrence parameter to a determinant need not be the result of a causal connection, and since the term "factor" (from the Latin word for doer) suggests causality, "risk factor" is not a proper substitute for "determinant of risk." A proper synonym is *risk indicator*—analogously with "economic indicator," "health indicator," and so on.

The terms "determinant," "risk indicator," and "modifier" refer to subject characteristics (including environmental) without specificity to category or level. Thus, "hypertension" is not a determinant of the risk of stroke; it is a high-risk category—an *indication* of high risk—based on blood pressure as the determinant or indicator of risk.

1.4. DESCRIPTIVE VS. CAUSAL RELATIONS

In medical occurrence research—and presumably in any research of this form—occurrence relations are viewed as either descriptive or causal. In a *descriptive* problem, a parameter of occurrence is related to a determinant without any view to causal interpretation of the relation. Descriptive occurrence relations are of interest for risk assessment or prognosis, diagnosis, allocation of case finding and other services, service evaluation, and other purposes. Etiologic insight and rational intervention, by contrast, rest on information about occurrence relations that may be interpreted in *causal* terms.

Example 1.8. The relation of the incidence (risk) of coronary heart disease (CHD) to age, gender, serum lipid levels, relative body weight, personality, blood type, and other personal characteristics, jointly, is of interest for *risk assessment* as to CHD. This use of the occurrence relation does not require any regard for causality.

Example 1.9. The descriptive relation in Example 1.8 is of consequence also for the *diagnosis* of CHD. But for the latter purpose one is more interested in the *prevalence* of CHD in relation not only to indicators of risk but also to potential *manifestations* of this disease—chest pain, electrocardiographic patterns, and the like. Again, the concern is merely with descriptive relations, not causal ones.

Example 1.10. Prevalence functions are of interest for the allocation of case-finding efforts, again with no regard for causality. In this sense one is interested in the relation of the prevalence of tuberculosis to age, area of residence, and socioeconomic status; the prevalence of venereal disease in relation to occupation; and so on.

Example 1.11. In normative evaluation of health care, actual practices are compared with norms for proper practice. This involves the acquisition of descriptive data. They might deal with the frequencies of various levels of quality (from malpractice to proper) in the treatment of breast cancer, related to type of disease manifestation, type of hospital, and so on. In the context of care for cases of myocardial infarction such data might deal with the duration of hospitalization, related complications, type of hospital, and so on.

Example 1.12. Consider the incidence of complications of the basic disease in adult diabetics in relation to treatment in the sense of insulin vs. no insulin. This relation is of interest in descriptive terms, since it characterizes prognosis in relation to the type of the disease—juvenile (Type I) vs. adult-onset (Type II). In causal terms it is devoid of interest, since the patients receiving the two types of treatment are very different (juvenile and adult-onset, respectively).

Example 1.13. The occurrence of complications in diabetes in relation to type of oral medication is of little or no descriptive interest, but in causal terms this relation is of major interest because it bears on the choice of therapy. Similarly, the risk of stroke or heart attack in hypertensives in relation to drug treatment is of major interest in causal terms but not descriptively. By contrast, the relation of mortality to heroin addiction is of interest in descriptive as well as causal terms.

As noted, descriptive relations bear on such passive matters as prognosis setting and risk assessment, whereas knowledge of causal relations is the basis for interventions, that is, for willful alterations of the outcome through perturbations in the determinant. For this reason, only strong relations are of descriptive interest, while knowledge of even minor causal relations is of value whenever the determinant is subject to ready interventive change. Such a change is particularly easy to accomplish when the determinant of concern is itself an intervention, with the choice between the options based on presumptions about relative benefit-risk characteristics.

1.5. CONDITIONAL RELATIONS: CONFOUNDERS

Causal interpretation of a crude (unconditional) empirical occurrence relation involves the premise that in the absence of the effect at issue there would have been no relation between the outcome parameter and the determinant. For example, the difference in mean blood pressure between treated and untreated hypertensives can be interpreted as a manifestation of the effect of the treatment only insofar as it can be presumed that, in the absence of the treatment effect, the treated would have shown the same mean of blood pressure as the nontreated. Hence, for causal interpretation of an unconditional occurrence relation, all *extraneous determinants* of the occurrence parameter must have suitably balanced distributions between/among the compared categories of the determinant. Thus, in the context of antihypertensive treatment discussed above, distributions by, for example, blood pressure before potential treatment should be similar between the treated and the untreated in order that the unconditional difference in the outcome parameter (mean blood pressure) have causal interpretation.

When an extraneous determinant of the occurrence parameter has imbalanced distributions between the compared categories of the determinant in a causality-oriented study, it is said to *confound* the crude relation, or to be a "confounding factor" for the relation under study.

Example 1.14. Consider a pair of individuals: one is observing an "antihypertensive" diet (low sodium, high potassium, and high linoleic acid) and the other is not. Their difference in blood pressure cannot be viewed as the effect of the diet, unless there is assurance that in the absence of the treatment the two individuals would have had identical blood pressures.

Such assurance is unlikely. In particular, random allocation of the two persons to their respective dietary regimens provides no basis for presuming absence of confounding by the level of "natural" blood pressure.

Example 1.15. Consider two communities: one is subjected to an intervention program directed to blood pressure and the other is not. This is analogous to comparing two persons or two rats; the relative levels of blood pressure on follow-up cannot be interpreted in causal terms. That there are many individuals in each community is not much more relevant than the multicellular character of two compared persons or rats.

Example 1.16. When the treated and untreated series (of individuals or communities—of units of observation) are very large and the allocation of the units to treatment is based on randomization, there is a strong presumption that the occurrence measures for the two series would be essentially identical in the absence of any difference in treatment. Therefore, the empirical relation between treatment and outcome is essentially unconfounded and thus reflects the effect of the treatment.

Example 1.17. Suppose that no randomization is used, but the untreated are matched with those to be treated according to the "baseline" blood pressure. Again, there is no confounding—unless the "natural" course of blood pressure is apt to be different between the two series. In particular, even if these two series have different distributions by some determinant of blood pressure (such as age), this does not mean confounding by those extraneous determinants of the "baseline" level, except insofar as they also are determinants of the course of blood pressure conditional on the initial level.

Example 1.18. Consider focusing not on those *to be* treated but rather on those who *have been* treated for at least 5 years, for example, relative to those with no treatment. Suppose again that the untreated have been matched to the treated according to the "baseline" level of blood pressure. Now there is a good likelihood that the "natural" course of blood pressure would *not* have been similar between the treated and untreated. The reason is that the "natural" course of blood pressure has important bearing on the initially untreated remaining untreated and, differently, on the initially treated remaining under treatment. As a consequence, despite the matching on initial values, the treated, in the absence of the treatment, would likely have had higher "natural" blood pressures than the untreated. Thus, confounding by the indication for treatment—its inception and continuation—could persist.

Where the crude (unconditional) occurrence relation is confounded by a particular covariate, the relation that is *conditional* on that factor is still free of such confounding.

Example 1.19. Suppose blood pressure (BP) is measured for "baseline" values (BP_0) on untreated people, and that treatment is initiated in some of

these people. The effect of treatment among the treated at the time of the first follow-up visit cannot be assessed by comparing the treated group as a whole with a representative sample of the untreated, as the respective distributions by the level of "baseline" pressure are different. However, within narrow categories of the latter there is no such confounding.

Example 1.20. Another way of approaching the conditional relation is to fit the regression model $P = A + B_1(BP_0) + B_2D$, where P is the mean value of BP on follow-up and D is the determinant at issue—an indicator of treatment ($D = 1$ for treated, $D = 0$ for untreated). The effect of treatment is B_2.

Whereas conditioning by a particular confounder removes confounding by that factor, actual causal interpretation presupposes that such conditioning be applied with respect to *all* confounders. Thus, insofar as an empirical occurrence relation is to be interpreted in causal terms, it must have the structure

$$P = f(D \mid C), \tag{1.4}$$

where P is the occurrence parameter, C is the total set of confounders (C_1, C_2, . . .), f denotes functional relation, and "|" denotes "conditional on." The meaning of this expression is that the causal relation of P to D is manifest when D is permitted to vary while C remains fixed. The *effect* (see Appendices 2 and 3) of any given category (index category) of D relative to any chosen reference category of it is the *difference* between the respective values of P (value for the index category minus that for the reference category). As the conditioning itself is but a technicality, the fundamental challenge in nonexperimental research on causal relations is one of insight and judgment, one that has to do with the sufficiency of the set of extraneous factors that are being controlled by the conditioning.

In the context of *descriptive* problems there is no general imperative to consider *all* determinants of the outcome as potential confounders. Yet some conditionalities tend to be inherent in descriptive problems as well.

Example 1.21. To say that level of blood sugar is indicative of the risk of degenerative cardiovascular disease is vacuous insofar as it is only a rephrasing of the familiar relation between diabetes and accelerated atherosclerosis. For a relation of the risk of cardiovascular disease to glycemia level to be of prognostic interest, it must be conditional on diabetes status.

Example 1.22. Whereas the relation (if any) of the risk of degenerative cardiovascular disease to height is of prognostic interest unconditionally (in adults), its relation to weight is of interest only conditionally on height.

These considerations indicate that, with descriptive as well as causality-oriented problems, *certain occurrence relations are of interest only conditionally on some other determinants of the occurrence of the outcome at issue*. Such other, extraneous determinants of the outcome are referred to as *potential confounders* of the conditional relation of interest. When such covariates have, in the study experience (study base), different distributions between/among the compared categories of the determinant under study, they constitute actual confounders—factors by which the analysis of the empirical occurrence relation must be conditioned in order that it address the causal (conditional) relation of interest.

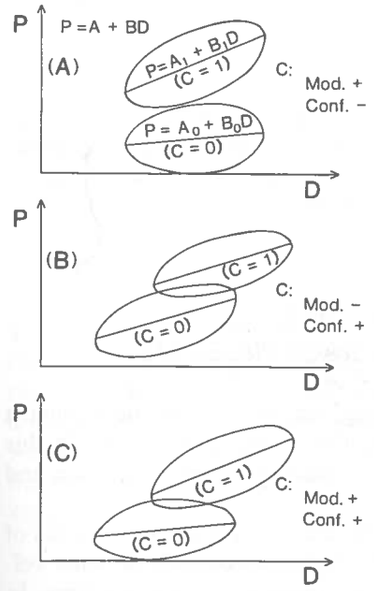

Figure 1.6. Relation of occurrence parameter P to determinant D, with a view to the role of covariate C. (A) C modifies the measure of relation B but does not confound it. If C is ignored, the average (in a sense) of the conditional slopes is obtained. (B) No modification, but confounding. (C) Modification and confounding.

The distinction between modification and confounding of occurrence relations (Miettinen, 1974a) tends to pose some difficulty for students of epidemiology. The key to understanding is to appreciate that modification has to do with details of the relation of interest, as illustrated by the regression lines in Figures 1.4 and 1.5, regardless of how the study subjects are distributed by the covariate (modifier), whereas confounding represents an impediment for learning about the conditional relation of interest, arising from an association between the determinant and the covariate and the latter's role as a determinant (extraneous) of the outcome. Modification is an aspect of the study object, and one may elect to study it for closer understanding of the relation at issue. By contrast, confounding is not an aspect of the object of study (the occurrence relation); it is to be removed or "controlled."

A graphical illustration of the distinction between modification and confounding is given in Figure 1.6.

There is no necessary relation between the modifying and confounding roles of a covariate. Thus, whether age does or does not confound a relation has no express implication as to whether age is a modifier of the relation to the determinant at issue, and conversely. This basic outlook applies with considerable force to the basic measure of relation, which is a rate difference (Section A.2.2) or, more generally, a difference of means (possibly expressed as a regression coefficient). Rate ratios and other relative measures of relation (Section A.2.2.2) tend to be modified by determinants of the outcome, including confounders.

1.6. REFERENT OF THE RELATION: PARTICULARISTIC VS. ABSTRACT PROBLEMS

For an occurrence relation to have meaning, one must understand what it refers to, that is, in what realm or domain it is supposed to obtain. In this regard, research problems fall in two broad categories, particularistic and abstract.

In *particularistic* occurrence research the interest is in the occurrence of the phenomenon (state or event) of interest with express and singular reference to a particular population experience, specific in place and time. In medical occurrence research such particularism (spatiotemporal specificity) of the research problem is characteristic of administrative projects directed to description of the health profile of the community being served ("community diagnosis"), description of care utilization, evaluation of programs or practices, and the like. It is not difficult to imagine analogous needs for particularistic research among those responsible for the maintenance of fleets of aircraft, or for administrators of other programs directed to particular populations of subjects or objects.

Naturally, when the object of research is particularistic, the study is conducted in the framework of the very experience of express concern.

In *scientific* research, by contrast, the concern is not with any particularistic experience per se. Such experiences are only exploited to learn about the relation at issue in the abstract (in general), that is, without any spatiotemporal referent. For example, various particularistic research experiences, which are uninteresting per se, have led to the proposition that smoking causes lung cancer—an idea that does not refer to any particular place or time, a relation that for this reason is abstract (general). (Cf. Chapter 3.)

Scientific occurrence problems and results are not general in the sense of having to do with, or applying to, all sorts of persons (as to constitution, behavior, and environment). Thus, the antonym of "generality" in science is not "specificity" but, as pointed out above, "particularism." The aim is always to make the scientific generalizations as specific as possible: the more specific abstract propositions are, the more useful they are for theoretical development and for application. Thus, one is not really satisfied to know

that smoking makes lung cancer incidence 10-fold; one is concerned to know the effect specifically for particular types of smoking on particular types of person (as to constitution, behavior, and environment).

Clearly, when the problem is abstract (scientific), the problem itself does not dictate a particular experience for consideration in empirical research; the specification of the experience in place and time is a matter of choice, a question of study design (cf. Chapter 3).

1.7. LEVELS OF STUDY

The point that occurrence research has to do with occurrence relations (Section 1.3) should not be interpreted too ambitiously. It does not mean that the relations are necessarily studied quantitatively, let alone in terms of the *absolute* magnitudes of, for example, the coefficients of such functions as were sketched in Section 1.3. It does not even mean that a relation is studied: the number of determinants in a descriptive occurrence study may well be zero.

1.7.1. Qualitative Exploration and Hypothesis Testing

The most elementary level of viewing an occurrence relation is the *qualitative* one. On this level, the question is *whether* there is a relation between the parameter of occurrence and the *potential* determinant at issue.

In the realm of qualitative questions, the most elementary one concerns the existence of an *unconditional* (crude) relation, a question that ignores all other potential determinants of the phenomenon at issue. On the next level one is concerned with the existence of an association *conditionally* on (within categories of) some other determinants, but still in the framework of purely *descriptive* relations. For example, the question may be whether relative body weight serves as a predictor of the occurrence of heart attack conditionally on blood pressure (which is associated with relative body weight and is also an indicator of the risk of heart attack). Finally, the concern may be with the existence of a *causal* relation. In this context, as has already been suggested (Section 1.5), the challenge is to identify and make allowance for—to condition the relation on—*all* confounders in the situation at issue.

Qualitative questions present a hierarchy also in terms of their origins. Questions may be elementary in the sense of having no express rationale, coming up simply in an exploratory context during a search for relations. Alternatively, a question may be rooted in a *hypothesis*—an idea originating from insight and creativity or simply "suggested" by previous data.

Qualitative questions about occurrence relations need not raise issues of modification. Thus, when Ziel and Finkle (1975) tested the hypothesis that the use of exogenous estrogen is conducive to endometrial cancer, they did

not consider modification of the relation, by age even. Their concern was with the very existence of a causal relation, and since that remained in doubt even in the face of their data, it would have been premature to consider modification. They did present *data* on the *magnitude* of the empirical relation in their study base, but the purpose was to address the qualitative question of the existence, in the abstract, of a causal relation. It had bearing on the credibility of confounding as an explanation of the empirical relation. It also bore on the credibility of the data in terms of their ostensible implication—that 50% of endometrial cancer was attributable to the hormone use, even though the relation had not been noticed up to the time of their study.

In qualitative research it is common malpractice to regard *lack* of evidence of modification as evidence in favor of the hypothesis. In point of fact, it does not add to the evidence that the relation was apparent "consistently" in all categories of age, for example. By the same token, the persuasiveness of the overall evidence is not diminished by evidence of modification of the relation according to a covariate.

Another common malpractice is entertaining modification in the absence of not only persuasive evidence for the relation in the aggregate but also any theoretical basis for the relation's confinement to the particular subdomain in which the evidence is (happens to be) strongest (see Section 9.3.3).

1.7.2. Quantification, Relative and Absolute

A level of research more ambitious than the qualitative one is quantification of the relation at issue. It may be viewed in either relative or absolute terms.

In relative quantification the concern is with the *ratio* of the magnitude of the occurrence parameter in any given (index) category of a determinant to that in a chosen reference category. For example, one may wish to quantify the incidence ratio of lung cancer contrasting smokers of two packs of cigarettes per day relative to those who never smoked, without seeking to learn the absolute magnitudes of the incidence rates in the compared categories of smoking (cf. Figure 1.4 and Appendix 2).

The outlook of relative quantification is very popular for three major reasons. First, in certain study situations, only relative magnitudes can be addressed (see Section 4.1). Second, relative magnitudes have the appeal of simplicity: there is only one quantity to consider instead of two, and it is dimensionless even when the absolute magnitudes are not. Finally, relative magnitude is commonly the essential aspect of quantitative interest; even when the absolute magnitudes are on hand, the main interest scientifically tends to be in their relative magnitudes (cf. Appendix 2).

Despite the appeal of relative quantification, there is a need for absolute occurrence relations, particularly in nonscientific contexts such as individualized prognosis-setting (descriptive relation) or individualized prediction of the effect of intervention (causal relation).

In the context of scientific (abstract-general) occurrence relations (see Section 1.6), the quantitative outlook involves a deep problem: the empirical relation generally includes only a small subset of the totality of modifiers of the relation (cf. Section 1.3). Thus, the quantitative pattern in the studied experience is not at all guaranteed to obtain *in general*. Indeed, there is substantial subtlety and difficulty in defining even the *meaning* of the target values of the parameters in the occurrence relation, except in the context of particularistic problems (cf. Section 9.1 and Appendix 5). Therefore, even in the scientific context, technical quantification is closely connected with the (particularistic) study experience itself (cf. Sections 4.1 and 9.1, and Appendix 5); anything beyond that—and such generalization is the real thrust of scientific research—remains judgmental.