Chapter 8

Incidence or Cohort Studies

Of the various types of observational epidemiologic studies, *incidence* or *cohort* studies are generally thought to provide the most definitive information about disease etiology. They do provide the most direct measurement of the *risk of disease development*. However, if carried out prospectively, they can be expensive and time-consuming, requiring a long-term commitment of funds and dedicated personnel. Furthermore, as will be discussed, they are not free of potential biases and other scientific problems.

How Incidence Studies Are Carried Out

Defining the Study Population Initially, a study population or cohort is identified. This population is to be followed up over a period of time for the development of the disease(s) under investigation. The cohort chosen may be a rather general population group,

such as the residents of a community, or a more specialized population that can readily be studied such as an occupational group or group of insured persons. Or, the cohort may be selected because of a known exposure to a suspected etiologic factor such as a source of ionizing radiation or a drug or pesticide. If exposure to the suspected factor characterizes all or virtually all cohort members, then a similar but unexposed cohort or some other standard of comparison is required to evaluate the experience of the exposed group.

The incidence study focuses on disease development. In order for a disease to develop, it must, of course, be absent initially. Thus the study population must be shown, in some way, to be free of the disease, that is, to be a population at risk for disease development. For a rare, rapidly fatal disease such as acute leukemia, a few cases initially present in the population will probably be self-evident. For a more common disease such as coronary heart disease in middle-aged men, an initial examination of the potential study population may be required to find and exclude existing cases of disease. As illustrated by the Evans County study (Chap. 6), this initial examination may be part of a prevalence study.

An initial examination may serve another important purpose. In it, some or all of the potential etiologic factors and other pertinent study variables may be measured. Nevertheless, some cohort studies with certain specific objectives do not require an initial examination since the data necessary to characterize the study subjects are available from other sources.

Follow-up Once the population is initially defined and the appropriate characteristics of its members have been assessed, the population must be followed up for the development of the disease. Follow-up procedures vary from study to study both in intensity and completeness, depending on the disease manifestations to be measured.

Simple, relatively complete follow-up is available for life-insurance-company investigations of factors affecting mortality. For their purposes, death is the only end-point of importance, and it must be reported to the company in order for the policy benefits to be paid.

On the other hand, follow-up to detect all new cases of coronary heart disease or stroke may require several different procedures, including periodic reexaminations, surveillance of deaths, hospitalizations, and physicians' office visits, and correspondence with subjects who have moved from the area. However, limitations on available resources may dictate that only a portion of all possible follow-up procedures be used, perhaps just hospitalizations and deaths, for example. Even though incomplete, such partial follow-up may be perfectly adequate for the purposes of the study.

The duration of follow-up required is determined primarily by the number of disease cases needed to provide reliable, statistically significant answers to the specific questions under study. This can usually be determined in advance, once the study population size and the disease incidence rate is known. For example, if the study population contains 1,000 persons and the incidence rate is 1 percent per year, about 10 new cases may be expected during each year of follow-up. If 100 cases are needed to provide answers with a certain degree of reliability, then the study may be expected to last about 10 years.

This example is somewhat oversimplified and does not take into account such factors as a possible reduction over the years in the number of new cases per year, due to losses of subjects to follow-up, or a possible increase in new cases per year as the population ages, if the incidence increases with age. Although it is often most practical to keep follow-up as short as possible, a study may be designed specifically with a long follow-up period in mind to assess factors which cause or predict disease in the distant future.

During the follow-up period it may be possible to repeat the initial measurements of population characteristics. In this way disease development may be studied in relation both to initial characteristics and to *changes* in these characteristics. For example, it is not only of interest to know whether serum cholesterol level is related to subsequent coronary heart disease, but also whether a *rising* level or a *falling* level adds additional predictive information.

There are other reasons for reassessing population characteristics in the follow-up period. During a long-term study there may be technological improvements in the measuring devices that were used initially. Also, new scientific information about the disease may

indicate the importance of measuring additional variables that were not included at first.

Data Analysis As in a prevalence study, the population is subdivided or classified according to the variables that are to be related to the disease. The disease incidence rate is determined for each subgroup, and the rates are compared to see whether the presence or absence (or differences in level, if quantitative) of the variable is related to subsequent disease development. If the study population is a special cohort exposed to a suspected etiologic factor, then its disease incidence is compared to that in a similar nonexposed cohort or to that in the general population.

If all or virtually all study population members are followed up for the same period of time, then a simple overall incidence rate can be used. For example, if the period is uniformly 3 years, then the 3-year incidence rate may be computed for each subgroup. If there are substantial differences among study subjects in length of follow-up, these will have to be taken into account in the data analysis. Follow-up durations may differ markedly when subjects are lost to follow-up before the study is complete—if, for example, they move out of the area or die. Also, some investigations require that new subjects be added to the study population over a relatively long period of time. As a result, if disease incidence is determined up to a specific point in time, subjects will have been followed up for different durations from their time of entry into the study.

The standard method of handling variable follow-up periods involves the use of "person-years" of observation in the denominator of the incidence rate (or person-months or person-days, etc., if more appropriate or convenient). With this approach, each subject contributes only as many years of observation to the population at risk as he is actually observed; if he leaves after 1 year, he contributes 1 person-year; if after 10, 10 person-years.

The assumption involved in adding all subjects' person-years into one denominator is that the disease risk remains relatively constant over time. That is, the third year of observation, for example, is not appreciably different as to disease risk from the first; or, stated in another way, following up three persons for 1 year is equivalent to following up one person for 3 years. The validity of this

assumption for any particular study should be considered in evaluating the person-years approach.

Another feature of the person-year method is that one person may contribute person years of observation to more than one subgroup. Suppose, for example, that in a 5-year study, disease incidence is determined for age-decade subgroups. A person entering the study population at age 48 will contribute two person-years of observation to the 40–49-year-old subgroup and three person-years of observation to the 50–59-year-old subgroup. This may also happen with other measurements if they change over time. A person may spend a few years in a particular quartile of serum cholesterol and then shift to a higher or lower quartile.

Interpretation and Evaluation of Incidence Studies

The emphasis in incidence studies is on the prediction of disease development. This type of investigation clearly demonstrates the time sequence between the presence or absence of a factor and the subsequent occurrence of the disease. However, even the prediction of disease does not necessarily imply a cause and effect relationship, as will be discussed in Chap. 11. Furthermore, as has been pointed out, factors associated with a disease can be shown to precede and thus predict the disease in prevalence and case-control studies as well.

A problem that has been emphasized with prevalence and case-control studies is the likelihood of overrepresentation of cases of long duration. This will not be a problem with incidence studies having complete and comprehensive follow-up; the full spectrum of the disease should be available for study.

Despite their good reputation, incidence studies can be subject to important biases. We have mentioned how, in a prevalence or case-control study, the presence or absence of disease may affect the factor under investigation or the measurement of that factor, using the example of cancer and its effects on one's emotional state. In a somewhat analogous fashion, the converse problem may be present in an incidence study. That is, the presence or absence of a study factor may affect the subsequent assessment of disease. This may be especially prone to occur if the decision as to the presence

or absence of disease is made by persons who are aware of the subject's status with regard to the study factor.

In a stroke study, for example, it is clearly possible for knowledge of a subject's prior blood pressure to influence, consciously or unconsciously, the decision as to whether or not a stroke has occurred. If this happens, the study will have a built-in correlation between blood pressure and stroke incidence. Similarly, if in a study of cancer, disease detection depends partly upon the initiative or cooperation of the subjects in seeking an examination, those with a family history of cancer or those who smoke might be especially motivated to have a checkup. This can result in bias or in a built-in correlation of the disease with a family history of cancer or with smoking. Thus, every effort should be made to ensure that disease development is detected or decided upon independently of the possible etiologic factors under investigation.

Incidence studies are also subject to possible biases due to loss of study subjects. Such losses may occur initially, if a portion of the target study population does not participate, or later on as members of the study population are lost to follow-up. Marked losses of either type do not necessarily invalidate the study. However, the investigators should consider whether the reasons for loss of subjects might reasonably have affected the study outcome. Sometimes it is possible to gather outside information concerning lost subjects, particularly whether they left due to illness or death or for any reason that might be related to the variables and the disease under investigation.

Example 1: The Framingham Study

Considering the barrage of information about "coronary risk factors" to which the public has been subjected, it may come as a surprise to health-care personnel now in training that only a few decades ago, atherosclerosis and its clinical consequences were generally viewed by the medical profession as degenerative changes that were an inevitable consequence of aging. However, by the late 1940's, descriptive epidemiologic findings and clinical observations were beginning to convince public health authorities that environmental factors might be playing an important role in the disease and

that, as a result, prevention was a real possibility. Because of the major importance of coronary heart disease as a cause of disability and death in this country, the U.S. Public Health Service decided to undertake a major long-term incidence study to better define the factors producing this disease.

When the Framingham Study began, around 1950, Framingham, Massachusetts was a town of about 28,000 inhabitants. There were several reasons for selecting this location for the study. At the time, it was a relatively self-contained community with both industrial and rural areas. In this and other ways it was not obviously atypical. There were sufficient numbers of residents in the desired age range to provide an adequate study group. There was evidence, both from a successful previous study of tuberculosis in the community, and from discussions with medical and lay residents, that the townspeople would be cooperative. The area of the town was sufficiently small that the residents could come to one central examining facility. Follow-up of hospitalizations would be relatively easy since most occurred at one central hospital in the town. Furthermore, Framingham was only 20 miles from major medical centers in Boston; thus, medical and scientific consultation would be readily available.

The study was planned to last for 20 years, in view of the slow development of atherosclerosis and its consequences. A long "incubation period" is believed to characterize many of the chronic noninfectious diseases and argues for a long-term study to identify predisposing factors early in life.

The lower and upper age limits of the study population were set at 30 and 60 years. It was felt that older persons should be excluded since many of them already had extensive coronary atherosclerosis and, as a result, to study them would reveal only immediate precipitating factors for clinical events. Persons under thirty were excluded primarily because their incidence of coronary heart disease would be very low and they were a more mobile, hard-to-follow group.

In selecting the study sample, the goal was a group of about 5,000, since this size sample in the 30–60-year age range would produce adequate numbers of cases over the 20-year follow-up period. Knowing that there would be some nonresponse, the investigators selected a larger systematic sample comprising two-thirds of

the 10,000 residents of the appropriate ages. The list of town residents was arranged according to precinct, and within each precinct by family according to family-size groups (one member, two members, three or more members, ages 30–60). Two out of every three families were selected. Selection of *families* rather than individuals was a wise decision since (1) one member of a family in the study's age range would not be denied an examination service offered to another member of the same family, (2) many reluctant men received examinations because of being "persuaded" by their more cooperative wives to go to the clinic at the same time, and (3) studies of spouse pairs and familial aggregation of characteristics would be fostered.

The 6,507 members of the sample were invited to participate in the study by town residents who recruited subjects living in their own neighborhoods. These recruiters were part of a group of volunteers who were given a cardiovascular examination at the clinic before the study officially began. Having experienced the examination that was to be given in the study, the volunteer recruiters would be able to describe it to the invited subjects on the basis of personal experience.

Despite this personal approach only 4,469, or about two-thirds of the sample, participated. A group of 740 volunteers were added, yielding a total of 5,209 subjects. The initial examination revealed that 82 subjects already had clinically evident coronary heart disease. These were excluded from the population at risk, leaving a total of 5,127.

This study population has been offered a relatively complete examination every 2 years since the study began. The examination has included a medical history, physical examination, and pertinent laboratory tests such as electrocardiogram, chest x-ray, and serum lipid levels. It has been directed primarily at detecting the development of coronary heart disease and other atherosclerotic conditions such as stroke and peripheral vascular disease. Variables to be related to disease development have also been measured every 2 years. As new types of measurements have acquired importance in this area of research, they have been added to the examination. Thus the investigators have not been limited to the first examination as their only source of information about possible etiologic variables.

Every effort has been made to maintain rapport with the community and with the medical profession in the town. Subjects are kept waiting as little as possible during the examination. A complete report of the examination findings has been sent to each subject's personal physician. No medical care or advice is given by the study's examining physicians except that persons with newly discovered serious abnormalities are advised to contact their own physicians.

Although the biennial examinations at the clinic have been the chief source of follow-up information, disease development has been detected by other means as well. These additional sources include records of hospitalizations and of local physicians' office visits, and information about deaths from death certificates, coroner's reports, and reports of relatives. The diagnosis of any disease studied has been made according to strict criteria so as to include only definite cases in the diseased group.

Maintaining a continuing program of biennial examinations for a few thousand persons has involved a major investment in the operation of the study clinic. A staff of physicians, nurses, laboratory technicians, receptionists, clerical personnel, and others have been necessary for the smooth operation of the clinic and to assure the collection of complete and accurate data. Epidemiologically oriented physicians and statisticians located both on-site and at the National Heart and Lung Institute headquarters in Bethesda, Maryland have carried out the research analyses of data and the preparation of scientific papers.

The study findings have emerged in a large series of reports over the years since 1951 and can only be summarized briefly here. Several representative papers are listed in the references under the first authors, Dawber, Kannel, Gordon, and Friedman.

The study has been able to confirm in great detail that the atherosclerotic diseases do not strike persons at random as they age, but that highly susceptible individuals can be identified in advance of any definite clinical manifestations. Indications of susceptibility, or "risk factors," that have been found in the Framingham Study and other epidemiologic investigations include male sex, advancing age, high serum lipid concentrations, high blood pressure, cigarette smoking, diabetes mellitus (or even milder degrees of carbohydrate intolerance), obesity, low vital capacity, and certain electrocardiographic abnormalities. Other risk factors that have been emphasized more by other studies include certain psychosocial factors, family history of coronary heart disease, and physical inactivity.

The detailed information and large population available at Framingham have permitted more intensive investigation of the unique role of each risk factor. For example, it was found that obesity is not related equally to all manifestations of coronary heart disease. Although it does appear to predispose to angina pectoris and to sudden unexpected death, it is not related to myocardial infarction per se. Also, sufficient numbers of cases emerged to permit the study of interrelationships of several risk factors. One important finding was that persons with combinations of risk factors (for example hypertensive male smokers with high serum lipid levels) are at especially high risk of developing coronary heart disease.

As the study population ages, more emphasis can be placed on the diseases of the elderly such as stroke. Furthermore, the wide scope of information collected in Framingham has permitted the epidemiologic study of other nonatherosclerotic diseases as well, for example, rheumatic heart disease, gout, and gallbladder disease. In addition, several studies of epidemiologic methods have been carried out there.

At present the major research efforts in the epidemiology of coronary heart disease are being switched more and more from observational studies, of which Framingham has been one of the most important, to experimental trials attempting actually to lower the risk of disease. The predictive value of serum lipids, blood pressure, and cigarette smoking have been repeatedly demonstrated. Many feel that it is now necessary to prove that actively changing these characteristics by diet, drugs, and other means will safely lower risk and prevent or postpone atherosclerotic disease before widespread measures are applied to the general public or to high-risk individuals. Thus, at the time of this writing the National Institutes of Health is initiating a large-scale Multiple Risk Factor

Intervention Trial which will be a controlled experiment (see Chap. 9) to evaluate active preventive measures, involving the collaboration of several medical centers in the United States.

While it is generally accepted, then, that enough has been learned about factors predisposing to coronary heart disease to justify serious attempts at prevention, this does not mean that observational epidemiologic studies and other efforts to identify causal factors are no longer needed. There are many individuals developing the disease who by present criteria are at low risk. Conversely, many persons in the apparent high risk groups remain free of clinical coronary heart disease. Thus, our power to predict coronary heart disease is limited, and further studies are needed to identify pertinent risk factors.

Example 2: Mortality in Radiologists—Does Radiation Shorten Their Lives?

As the use of man-made sources of ionizing radiation has increased, so has the concern that these may be producing a variety of adverse effects on life and health (MacMahon, 1967; Whittenberger, 1967). While intense acute exposures have clearly proved to be quite harmful or even fatal, the evidence is less obvious regarding the consequences of chronic exposure to relatively low levels of radiation. Experimental animals subjected to chronic exposure have died sooner than expected, but findings in animals are not always applicable to man.

The effects on man's life-span are clearly a matter requiring epidemiologic study. Laboratory investigations of radiation effects on animals, cells, and other biological or biochemical systems, however important and illuminating, do not answer the basic question, *Does exposure to mild and moderate levels of radiation actually shorten human lives?*

Since the intentional exposure of human beings to radiation for the sole purpose of answering this question is ethically unthinkable, one problem for the epidemiologist is to locate human groups who have been or are being exposed for other reasons, so that their mortality experience may be investigated. Groups already studied for a relationship between ionizing radiation and overall mortality or

cancers of various types include uranium miners, residents of Hiroshima and Nagasaki who survived the atom bomb, patients receiving radiation therapy for noncancerous conditions such as enlargement of the thymus gland or ankylosing spondylitis, and children exposed in utero to diagnostic x-rays of their mothers' abdomen and pelvis.

Radiologists have also been studied for possible life-shortening effects. Since the findings of some of the earlier studies of radiologists were inconclusive, either because of small numbers of subjects or because of questionable comparison groups and measures of outcome, Seltser and Sartwell (1965) undertook a study of all members of an organization of radiologists compared to members of other medical specialty societies.

The Radiological Society of North America was the radiologists' organization studied. Founded in 1915, it existed during some of the early years of radiology when many radiologists were much less concerned and self-protective about radiation exposure than they have been more recently. (Some of the old-time radiologists even placed their own hand next to the patient routinely, so that its image on the x-ray photograph would help in judging the exposure time.) It was hypothesized in advance that the radiologists were the high-exposure, *high-risk* medical specialty group. The American College of Physicians has been composed largely of internists and was studied as a probable *intermediate-risk* group, since some physicians in this group have fluoroscoped patients to aid in diagnosis. The hypothesized *low-risk* specialty society was the American Academy of Ophthalmology and Otolaryngology, whose membership would contain only a few persons exposed routinely to radiation.

This investigation is described here as an example of a *retrospective* cohort study, contrasting greatly with the Framingham Study in scope and expense. In this study, all the events to be studied had already taken place and the required data were already recorded.

Because the data were already recorded does not mean that preparing them for analysis was an easy task. Several years of work were required to extract the necessary information from the files of the specialty societies and the American Medical Association's Directory Department. All specialists studied were traced from the

time of joining their societies in or after 1915 until the end of 1958, and the time and place of death for all deceased members were noted. The cause of death was determined for over 99 percent of the deceased subjects by obtaining death certificates or reviewing other death records. The study was limited to men.

The end point of this study was, of course, mortality. The data were analyzed in terms of person-years of observation. Each physician was considered to have contributed one-half person-year of observation during the year he joined—a convenient approximation which represents the average—plus a full person-year for each subsequent calendar year survived through 1958. Subjects dying before the end of 1958 were credited with one-half year during the year they died, again a convenient approximation. All told, there were 16,339 physician specialists studied, of whom 3,521 were radiologists. Person-years of observation totaled 232,708, of which the radiologists contributed 48,895.

Mortality rates were summarized for three age groups, 35–49 years, 50–64 years, and 65–79 years as well as for the total group. Similarly, mortality experience was looked at in three separate time periods, 1935–1944, 1945–1954, and 1955–1958.

As hypothesized, the death rate was highest among radiologists, intermediate in internists, and lowest in ophthalmologists and otolaryngologists. The differences were larger in the earlier time periods than in later ones and more apparent in older than in younger men. In fact, after 1944, radiologists in the 35–49-year group showed no increase in mortality over the other specialists of the same age.

The authors interpreted these age and time relationships as being consistent with a cumulative harmful effect of x-ray exposure becoming manifest in later life, and a decreasing or disappearing effect in more recent years due to improvements in equipment, techniques, and safety measures.

It was of interest that the radiologists' death rates were similar to those of all U.S. white males. Since physicians are, on the average, of higher socioeconomic status and probably receive better medical care, they would be expected to show a lower mortality rate than all males. This illustrates the importance of selecting appropriate comparison groups when special cohorts, such as radiologists or other

occupational groups, are followed up. Comparison with all men would have revealed no mortality difference. The more appropriate comparison, with other medical specialists, *did* reveal a difference.

Putting the age-specific death rates into one cross-sectional analysis of life expectancy starting at age 40 (see Chap. 5, p. 57) was another way of looking at the data. This revealed a similar relationship to medical specialty. The median age at death for 40-year-olds starting in the three successive time periods, 1935–1944, 1945–1954, and 1955–1958, respectively, were radiologists—71.4, 72.0, and 73.5 years; internists—73.4, 74.8, and 76.0 years; and otolaryngologists and ophthalmologists—76.2, 76.0, and 76.4 years.

Recognizing the limitations of death-certificate diagnoses, the investigators noted that the causes of death for each medical specialist group would probably have been recorded with reasonably equal accuracy. They compared the rates for major causes such as cardiovascular disease and cancer. The mortality ratios for major causes in radiologists as compared to ophthalmologists and otolaryngologists were relatively close to the overall ratio of 1.4 for all deaths.

Leukemia showed a higher mortality ratio—2.5, based on 19 *observed* leukemia deaths in the radiologists as compared to the 7.7 *expected* if the eye and ear group's mortality rates had applied to the radiologists. This is consistent with the results of other studies showing that radiation increases the risk of developing leukemia. It was pointed out, though, that the approximate 11 excess deaths from leukemia (19 observed minus 7.7 expected) constituted only a small fraction of the 228 total excess deaths. Thus, the higher death rate in radiologists appeared to be largely a nonspecific across-the-board increase.

In evaluating the findings, the investigators considered other possible sources of the mortality differences among the specialties, such as place of residence and initial self-selection of a medical specialty on the basis of health. The additional information available suggested that these factors did not account for the relatively shorter life expectancy of radiologists and that occupational exposure to ionizing radiation was the most likely explanation.

The investigators stressed, rightfully, that their findings were enhanced by the fact that they had predicted the outcome in

advance. This deserves special emphasis because of the fact that epidemiologists and other scientists can be trapped by the so-called post hoc, or after-the-fact, explanation. Given a set of findings or measurements, the human mind is usually ingenious enough to produce a reasonable theory or explanation as to why they occurred. This is accomplished with special ease in fields like medicine or psychology which deal with systems of great complexity. Quite plausible explanations can be brought forth to explain diametrically opposite observations, and almost any result can be made to appear consistent with someone's pet theory. A much better test of a theory is whether it will predict specific outcomes of a study *in advance.*

This is not meant to detract from the importance of exploring data in order to develop new hypotheses or theories for further study. However, once such hypotheses are arrived at, they sooner or later will have to be tested to see whether they *predict* study outcomes.

Role of Incidence Studies

It should be clear from the description of the Framingham Study why prospective incidence studies of general populations are infrequently carried out. They are difficult and expensive, and require the initial willingness to make a long-term commitment and the continuing patience on the part of both the sponsoring agencies and the study personnel. Yet the investment may well prove its worth in the depth and variety of information that such a study can produce.

The need for either a long-term follow-up or a very large study population or both, rests fundamentally on the fact that most diseases studied in this manner have surprisingly low incidence rates. Coronary heart disease is the leading cause of death in the United States, and coronary atherosclerosis is well known to be common in middle-aged men at autopsy. Yet, the incidence of new *clinically identified* cases of coronary heart disease in middle-aged men is only about 1 percent per year. Similarly, although hypertension is a highly *prevalent* condition in U.S. adults, many hypertensives seem to have drifted gradually into their present state, making it difficult both to define and to find *new* cases in a population for an incidence study.

Retrospective incidence studies, of course, can be accomplished relatively quickly if suitable cohorts can be identified and if adequate data about them are available. Yet many diseases of interest are so rare that case-control studies currently represent the only practical epidemiologic approach to studying them.

It now appears that technological changes will increase the feasibility of cohort studies in the future. Storage of medical and demographic information in computer data banks is becoming an accepted approach to improving the efficiency and quality of medical care. A by-product will be the increased availability of information about a variety of cohorts that can be studied both retrospectively and prospectively. On-going efforts in the area of "record-linkage" (i.e., the combination of a variety of records about each person, such as birth, physical examination, illness, and death records) will increase the number of different relationships that can be studied—relationships between a variety of initial characteristics and a variety of disease outcomes.

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Chapter 9

Experimental Studies

Experimental studies resemble incidence studies in that they require follow-up of the subjects to determine outcome. However, the essential distinguishing feature of experiments is that they involve some *action* or *manipulation* or *intervention* on the part of the investigators; that is, something is done to at least some of the study subjects. This contrasts with incidence and other observational studies, where the investigators take no action, but only observe.

Experiments are believed to be the best test of a cause-and-effect relationship. Something is done to an *experimental group* and the observed outcome is presumed to be the effect of that action, provided that the same outcome did not occur in an equivalent *control group* that was not acted upon. A cause-and-effect relationship can also be demonstrated by *removing* or *reducing* the alleged causal factor in the experimental group and showing a disappearance or reduction in the effect, while no change is observed in the control group.