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Feinstein AR. Clinical Epidemiology.

PART ONE

AN OVERVIEW OF RESEARCH ARCHITECTURE

The next five chapters contain a broad overview of the contents, methods, and results of clinical epidemiologic studies. They provide a classification for the research activities that challenge investigators who do the work and that confront readers who try to make sense of the results.

The research activities are divided into three main types: cause-effect evaluations, process evaluations, and descriptive studies. These early chapters in the text offer an outline of basic principles and standards for each type of research. The outline can be particularly helpful to a reader trying to decipher what appears in medical literature, but further details, to be presented in later chapters, are needed for a more profound or sophisticated understanding.

Chapter 2

A Classification of Medical Research

To arrive at an orderly scheme for discussing the epidemiologic methods of medical research, we need a taxonomy with which to classify the diverse activities that can take place. The candidates available as basic taxonomic choices are listed in the next section.

2.1. POSSIBLE TAXONOMIES FOR MEDICAL RESEARCH

Medical research can be classified in at least four different taxonomic arrangements, which might be labeled *eclectic, goal-oriented, group-oriented,* or *architectural.*

2.1.1. *Eclectic Arrangement*

In the eclectic approach, no specific scheme is used to classify the research. Each activity is simply cited according to the particular question that it answers. Thus, we might contemplate research projects intended to answer the following questions:

Is screening and/or the periodic health examination a worthwhile procedure?

Should we use the Salk or Sabin polio vaccine?

Are the potential medical benefits of nuclear magnetic resonance imaging worth its costs?

When a new physical finding is reported in a patient, is it really new?

Do oral contraceptive pills cause thromboembolism?

How is probability applied in genetic counseling?

Should major changes in diet be instituted to prevent atherosclerosis and, if so, at what age should these efforts begin?

Is surgery better than medical therapy for patients with coronary artery disease?

What is the best system of nomenclature for use in the diagnosis of psychiatric disorders?

Can nurse practitioners deliver a suitably high quality of primary health care?

Each of these questions can be discussed according to the type of evidence and reasoning needed to provide an answer. The discussions can then lead to more basic scientific and statistical issues in the research. The main advantage of the eclectic approach is that it provides immediate practical answers to immediate practical questions. The main disadvantage is that it does not lead to an organized, formal set of standards and procedures for either the creation or the analysis of individual projects.

2.1.2. *Goal-oriented Arrangement*

In the *goal-oriented* approach, the research is arranged according to certain goals that recur as issues to be resolved in the diverse aspects of the health sciences. Among such goals are the following:

Physiologic mechanisms
Pathophysiologic mechanisms
Risk-factor analysis
Range-of-normal determinations
Screening procedures
Diagnostic evaluations
Prognostic estimations
Pharmacokinetics
Therapeutic safety and efficacy
Quality control in data
Quality assurance in health care

This approach allows different types of research to be considered according to the general goals (and often according to the particular specialties) for which the research is employed. It has the advantage of providing a general outline within which eclectic issues can be considered. The main disadvantage is that no classification is provided for the different methods that can be used to assemble the people who compose the groups under investigation.

2.1.3. *Group-oriented Arrangement*

In the *group-oriented* approach, the research is catalogued according to the methods that created the particular composition of the groups of people under investigation. This classification would include groups organized as follows:

Randomized clinical trials
Surveys of therapy
Longitudinal cohort studies
Cross-sectional population surveys
Retrospective case-control studies
Other types of case-control studies
Hybrid arrangements of cases and controls

The group-oriented approach has the advantage of arranging the research according to the methods used for assembling the people under study. The disadvantage is that the goals of the projects are not noted.

2.1.4. *Architectural Arrangement*

An orientation toward both goals and groups can be achieved with the *architectural* classification, which will be employed here. The architectural approach is particularly powerful because the same kind of intellectual appraisal can be used to "dissect" the structure of several different types of research. An architectural arrangement also encourages the development, formation, and application of basic scientific principles and standards that are not readily perceived when the research is classified eclectically or when it is classified separately, according to goals or groups.

There are two main reasons for using the word *architecture* rather than *design* as a title for this approach. The first reason is that the word *design* has often become attached to the word *experimental* as a label for the plans of an investigation. Because most research in clinical epidemiology depends on observational data, not on experiments, the term *experimental design* is not only erroneous but can also be misleading if the premise of an experiment makes the investigator (or reader) neglect the many forms of bias that can distort the results of nonexperimental studies.

The second reason is that the word *design*, emanating from the world of art, carries no demands for reality or for function. An artist's design, like an abstract theoretic model, can be attractive and esthetically appealing, but it need not serve a real function or even correspond to any natural realities. An architect's structure, on the other hand, must have more than a design. The constructed entity must perform specific functions and must be adapted to the realities of nature. The word *architecture* is therefore used to describe the effort to create and evaluate research structures that have both the reproducible documentation of science and the elegant design of art.

2.2. BASIC AXES OF RESEARCH ARCHITECTURE

Before the architecture of research is discussed, the word *research* itself requires some attention. Because almost any thoughtful act of human scholarship can properly be regarded as research, the word is almost impossible to delineate, and the domain of research has almost no boundaries. A well-studied single patient, described in an enlightening case report, is an act of research; such a study (under certain circumstances) can even be the result of a designed experiment. Regardless of the purpose or structure of the work, the word *research* can properly be applied to systematic plans for discovering facts or principles in any field of knowledge. In most of the research to be considered here, the field of knowledge is clinical medicine, and the plans and discoveries refer to what is found medically in a group or groups of people.

The architecture of clinical research can be catalogued according to several separate axes of classification. Although each of these axes will be discussed later in greater detail, they are outlined in this section to help set a general framework for future discussion. The axes are based on ideas that refer to the purpose of the research, the type of agents under study, the allocation of agents, the number of temporal states, and the components of groups of data. Since these ideas must receive names to allow them to be discussed, the reader should be prepared to encounter some new terms or unfamiliar uses for old terms.

2.2.1. *General Purpose: Descriptive or Comparative*

The general purposes of research can be descriptive or comparative; the comparative purposes can be divided into evaluation of cause-effect relationships or of the quality of processes.

2.2.1.1. DESCRIPTIVE RESEARCH

Descriptive research provides collections of data that are used for purely descriptive reasons and sometimes as a background for policy decisions. No comparisons are conducted to draw conclusions about efficacy, quality, or any other accomplishments associated with the entities under study.

Descriptive studies are often used in health services research to provide information about costs and apparent needs for medical care. Thus, the individual capacity, clinical services, and expenses of maintenance might be described for the nursing homes in a particular geographic region. In clinical work, a frequently reported type of descriptive survey is a collection of data showing the spectrum of characteristics (such as age, symptoms, laboratory data, and so on) for a group (or series) of patients with a particular disease. Another kind of descriptive clinical survey is used to demarcate a range of normal for laboratory measurements or other data in a selected group of people. These descriptive clinical surveys often serve as reference background for discussions at medical conferences and for decisions about individual patients. A case report of interesting events noted in one or several patients is another commonly published type of descriptive study.

The results found in descriptive research are sometimes used later for comparative purposes. For example, the outcome of treatment A in a group of patients reported as a case series from one institution may later be compared with the results of treatment B reported in a case series from a different institution. Data assembled descriptively during the decennial census tabulations are also often used later for diverse forms of comparative research.

2.2.1.2. CAUSE-EFFECT (IMPACT) RESEARCH

In *cause-effect research*, specific comparisons are performed to draw conclusions (or obtain ideas) about the impact of a particular agent in producing certain changes. Studies of prevention, therapy, etiology, and pathogenesis of disease are almost always concerned with the effect of a causal agent.

No single word is readily available to replace the cumbersome *cause-effect* phrase as a label for this type of research. The word *analytic*, which is sometimes used by epidemiologists, has too many other connotations. The word *causal*, if used alone, may suggest research confined to etiology (i.e., cause) of disease, although studies of therapy are also concerned with the causal action, i.e., effect, of pharmaceutical substances, surgical operations, and other therapeutic interventions. If a single-word alternative is desired, perhaps the best term is *impact*. Thus, we can say that *impact research*, in contrast to the *process research* discussed in the next section, is concerned with the effects produced by an etiologic, pathogenetic, prophylactic, therapeutic, or other causal agent. In impact or cause-effect research, we focus on the changes that occur as outcomes after the intervention of the agent under scrutiny.

2.2.1.3. PROCESS RESEARCH

In *process* research, the comparison is concerned with the quality of either the product or the performance of a particular procedure. The procedure is not checked for any cause-effect impacts. We examine a product or a performance, not a change. Examples of process

research for quality of a *product* are investigations of quality control in laboratory measurements; observer variability among clinicians, radiologists, and pathologists; the efficacy of diagnostic markers (such as the VDRL test for syphilis); and the construction and evaluation of new forms of clinical questionnaires and indexes. Examples of process research for quality of a *performance* are the evaluation of a physician's clinical competence and the diverse types of audit that constitute the research called *quality of care.*

2.2.2. *Types of Agents: Procedures or Maneuvers*

In both the cause-effect and process forms of comparative research, a particular agent is under investigation. In both forms of research, the basic event under scrutiny can be outlined as

$$\text{INITIAL STATUS} \xrightarrow{\text{AGENT}} \text{SUBSEQUENT EVENTS}$$

In cause-effect research, the agent is the intended or suspected cause of the effect noted as subsequent events. In process research, the subsequent events represent the performance or product of the agent under evaluation.

To have a suitable nomenclature for labeling these activities, we can use the term *agent* as a general title for the particular active entity under investigation. We can then give separate names to the agents employed in process research and in cause-effect research.

2.2.2.1. PROCESS PROCEDURES

For process research, the word *procedure* has already been used and seems quite satisfactory as a name for the investigated agent. With this label, the foregoing diagram would be drawn as follows for process research:

$$\text{INPUT} \xrightarrow{\text{PROCEDURE}} \text{OUTPUT}$$

The process would be represented by a combination of *procedure* and *output.* Thus, the process of measuring serum cholesterol consists of a chemical procedure that yields a numerical result for the level of serum cholesterol. The process of delivering health care for a patient with a sore throat consists of a procedure of clinical reasoning that yields a set of actions taken as diagnostic tests and therapy.

2.2.2.2. CAUSE-EFFECT MANEUVERS

For cause-effect research, an optimal word is difficult to find, because so many different kinds of entities can be contemplated as agents. A single word is particularly desirable for describing these entities, because the architectural model for cause-effect research provides a unified approach that encompasses both the traditional etiologic studies of epidemiology and the traditional therapeutic studies of clinical medicine.

The phrase *causal agent* is the most direct title for this idea, but it is not a single word and it could create confusion when applied to agents that do not etiologically cause disease. For example, if we want to study the prevention of poliomyelitis or the remedial treatment of congestive heart failure, it would seem strange to refer to the Sabin vaccine or diuretics as causal agents. A substitute term that might be used is *effector,* particularly because it suggests the idea of producing a change in the initial state of the recipient. A disadvantage

of the word *effector,* however, is that certain agents contemplated as effectors may not actually produce an effect or change.

Of the available alternative terms, the most desirable seems to be *maneuver.* Despite the etymologic disadvantage of the meaning "to work by hand," the word maneuver does carry the connotation of an intention to produce change, and it seems generally better than either causal agent or effector. We shall therefore use *maneuver* as the name for the particular etiologic, therapeutic, demographic, or other entity that is contemplated, suspected, demonstrated, or intended to be responsible for producing a particular effect.

There are many different kinds of maneuvers, and they often lend their names to the research topics under study. The maneuver can be an allegedly noxious substance—such as atmospheric pollution, contaminated shellfish, cigarette smoking, a high-fat diet, or a slothful life style—that is believed to contribute, etiologically or pathogenetically, to development of a disease. It can also be a therapeutic entity—such as a medication, surgical operation, psychiatric technique, or physical substance (such as oxygen)—that is believed to exert a prophylactic or remedial action in disease.

The maneuver can even be a demographic attribute—such as race, gender, economic status, or educational background—that is regarded as affecting intelligence, economic achievement, or susceptibility to disease. Thus, if we state that women are more likely than men to develop urinary tract infections, the maneuver is the female gender. The maneuver can also be the personnel or fiscal system involved in purveying medical care. For example, in a clinical trial testing whether nurse practitioners are as capable as family physicians in providing primary medical care, the work of the nurse practitioners constitutes the principal maneuver under investigation.

With this concept, the basic architecture of a cause-effect study can be outlined as

$$\text{BASELINE STATE} \xrightarrow{\text{MANEUVER}} \text{OUTCOME}$$

The term *baseline state* rather than *initial state* is used here to help denote the differences, to be discussed in detail later, between the people whose initial state is contemplated for study and those who are actually entered into the research.

2.2.3. *Allocation of Agents: Experiment or Survey*

The word *experiment* is another term that is difficult to define. It is often used for any activity that is novel, regardless of whether the work has a planned comparison. For example, the first time that a newly developed drug is given to a human being, the work would probably be called an experiment, even though no controls or comparative groups are under study.

In common scientific usage, the term *experiment* is used for a planned cause-effect study in which the action of a particular maneuver is contrasted with the results of a comparative, or control, maneuver. Thus, a randomized controlled trial of therapy is an experiment; so is a physiologic study of the comparative urinary effects of saline infusion versus sulfate infusion in a healthy volunteer. The label of experiment could also be applied to a planned comparative investigation in process research. For example, to test observer variability among radiologists in the diagnosis of pulmonary embolism, we might arrange a special study in which a series of deliberately selected films are submitted (and later resubmitted) for blind, independent readings by each of the participating radiologists.

For many aspects of research architecture, the term *experiment* can be applied to a comparative study in which the investigator governs the allocation of the compared agents,

assigning them according to a prearranged plan. This type of plan is used in many process studies of quality control or observer variability. In experimental research with therapeutic agents, the plan of allocation usually involves a randomized assignment of the maneuvers under comparison.

The investigator's ability to allocate the agents under comparison is one of the hallmarks that distinguishes an experiment from a *survey*. The latter term is customarily used for research projects in which the agents under comparison were not assigned according to an investigative plan. For example, in process research, data obtained under ordinary conditions of clinical practice may later be collected for an investigation of diagnostic markers. This type of study is a survey, not an experiment, because the investigator did not formally plan the strategy and sequence of arrangements for exposing each patient to the compared procedures, which are the diagnostic marker tests and the standard methods used to establish the diagnosis.

In studies of therapeutic agents, most of the published research has been conducted as surveys, not as experimental clinical trials. In regular clinical practice, treatment is assigned according to the individual patient-based judgments of the treating clinicians. At some point thereafter, an investigator may collect a series of patients who received treatment A and compare their results against those found in a series of patients who received treatment B. This type of survey has been the conventional method, before the advent of clinical trials, by which doctors evaluated the efficacy of therapy. Surveys of therapy are still commonly used today, however, and they are often the only method by which certain types of treatments can be evaluated.

Studies of etiologic agents have almost all been conducted as surveys, not as experiments, because such maneuvers as cigarette smoking, high-fat diet, and slothful living were self-selected by the recipients, not imposed by an investigative plan. Similarly, descriptive studies of natural growth and development in healthy people and of the clinical course of a disease are conducted as surveys, because the natural maneuvers were not deliberately assigned in a research plan.

2.2.4. *Temporal Direction: Cross-Sectional or Longitudinal*

The data that describe a group of people can represent observations made at one or more than one point in time for each person. For example, we can examine a group of people and summarize their average weight at the time of the examination. We can re-examine that same group of people a year later and note the average amount of weight they have gained (or lost) during the interval. We can continue re-examining these people annually for the next 10 years and determine the trend shown in their average weight during that decade. In each of these instances, the results could be reported in a single summary expression that cited average weight, average gain, or average trend. Nevertheless, despite the single summary expression, the results would cover a different number of temporal states. In the first instance, we needed to examine each patient once; in the second instance, we needed to follow the patients to note their condition at the time of a second examination a year later; in the third instance, the temporal data would extend through the initial state of each patient and a re-examined state at each annual interval in the subsequent decade.

As a name for studies in which the data for each person represent essentially one point in time for that person, we can use the term *cross-sectional*. The data in such studies do not refer to any changes that may occur subsequently. The idea of cross-sectional applies to a single temporal condition, regardless of the particular calendar dates on which the data were obtained for each person or each group. Thus, we might cross-sectionally

note the presence or absence of retinopathy in members of a group of diabetic patients who were individually examined on different dates in the diabetic clinic. We also obtain cross-sectional data when we note, as a diagnostic test, a patient's response to some injected substance, such as ACTH. Although the response occurs after the ACTH injection, the data are cross-sectional because the injected substance is used to reveal the patient's condition, not to change it.

To refer to studies in which the people are followed forward in time, i.e., information regarding their condition is being obtained and analyzed at one or more subsequent occasions, the best word is *serial*, but *longitudinal* has already become well established for this purpose. Although not an optimal term, because it refers to geography rather than time and because an alternative argument could be offered for *latitudinal*, the use (or abuse) of *longitudinal* will be continued here to spare the reader any additional linguistic problems. To illustrate usage, in the first paragraph of this section the study of average weight at a single examination was cross-sectional. The studies of average weight gain and time trends in weight were longitudinal.

The word *cohort* is commonly used as a name for the group of people who are followed forward in a longitudinal study. In its original epidemiologic definition, a cohort consisted of a group of people who were all born in the same year or period of years,[1] but the word is too valuable to be so restricted. In contemporary usage, a cohort consists of a group of people followed longitudinally forward in time from some mutually common event, such as birth, entrance into college, exposure to an etiologic agent, establishment of a diagnosis, or receipt of treatment for a disease. Cohort is now used so often for this purpose that it regularly appears as an adjective, with *longitudinal studies* being called *cohort studies*.

Longitudinal (or cohort) research is usually much more difficult to do than cross-sectional research. After a single examination of each person, the investigator has the data needed for a cross-sectional study, but a longitudinal study carries the extra burden of making arrangements to follow each person and collect data at stipulated intervals thereafter. Most forms of descriptive research are cross-sectional, but descriptive studies of the natural history or clinical course of different medical conditions are longitudinal. For example, research conducted to indicate the post-therapeutic outcome of a group of patients with cancer is longitudinal; research that describes the presenting manifestations of the patients at the time treatment was instituted is cross-sectional. Some studies have both cross-sectional and longitudinal components. Thus, the spectrum-of-disease surveys that were noted earlier often contain cross-sectional descriptions of the condition of the patients on admission to the hospital, and longitudinal descriptions of what happened afterward in the patients' clinical courses.

Because cross-sectional investigations are so relatively easy to do, they are often used for cause-effect studies of the etiology of disease. For example, to investigate longitudinally whether reserpine therapy causes breast cancer, we would have to do an enormous study, assembling thousands of reserpine takers and thousands of non–reserpine takers, following both groups for many years to determine the subsequent occurrence (or nonoccurrence) of breast cancer in the two groups. To investigate this same question cross-sectionally, we could get an answer much more quickly and from much smaller groups of people. We would do a retrospective case-control study, assembling about 100 to 200 cases of people with breast cancer and a similar number of controls without breast cancer. We would ask the members of each group about their previous exposure to reserpine and then compare the rates of exposure in the two groups.

The simplicity of this case-control approach has made it highly appealing to epidemiologists interested in studying etiology of chronic disease, but the inversion of customary scientific logic in the retrospective architecture creates many problems that will be discussed

later. The point to be noted now is that research studies can contain longitudinal or cross-sectional data and that cross-sectional studies are often used as a substitute for longitudinal research.

2.2.5. *Components of Groups: Homodemic or Heterodemic*

When data are summarized in a quotient, such as a mean, proportion, or rate, the numerator and denominator of the quotient may come from the same group or from different groups. In all forms of laboratory research and in all forms of research with which most clinicians are familar, the same people who are counted in the denominator are also accounted for in the numerator. For example, if we say that the one-year survival rate of a group of people is 60% (9/15), the numerator has accounted for the one-year survival status of all 15 people who appeared in the denominator: 9 were alive and 6 were dead. If we say that the group had a mean survival time of 14.7 months, everyone is also accounted for. The numerator used to calculate this mean contains the sum of values for survival time of each person, and the denominator consists of the 15 people in the group.

The name *homodemic* (i.e., the same people) refers to the type of research data in which each person who appears in a denominator is also cited in the numerator. This type of information is so expected and so common in scientific research that its absence warrants special attention. Many quotients cited in public health epidemiologic research are *heterodemic* (different people). The same individuals who appear in the denominator are not necessarily all accounted for in the numerator. For example, when we see a statement that the mortality rate for people in the city of New Haven in 1970 was 11 per thousand, the components of this rate are a denominator of 137,707 people, determined during the census tabulation of 1970, and a numerator of 1530 deaths that were reported to the state health department. The 137,707 people who appear in the denominator are not individually accounted for in the numerator. We did not check each person's status at the end of the year and determine whether that person was alive or dead. Some of the denominator people may have moved away, so that we have no idea of their status, and some of the numerator people listed among those who died may not have been present (or alive) in New Haven when the census was taken.

The formation of a heterodemic quotient, using data from two different sources and comprising results from two different groups, is a common tactic in classical epidemiology. The tactic provides all of the general population rates of mortality, nativity, fertility, and so on, for which epidemiology is traditionally famous.

One quick way to determine whether a particular project (or set of data) is homodemic or heterodemic is to ask what is the basic unit of investigation in the research. In homodemic research, the basic unit is a person. All the pertinent data describing that person can be recorded in a single medium of storage, which can be a questionnaire, case report form, punched card, magnetic tape, or other format. The investigator assembles the results of the research by processing the data stored in the format for each individual person, and all the pertinent information under analysis is located in those individual formats.

In heterodemic research, the basic unit is a group of data collected by or submitted to commercial organizations, health agencies, or governmental institutions. These different groups of data provide numbers for the sales of products, indexes of commodity consumption, and occurrence rates of disease that are usually associated to form the heterodemic statistics. In such studies, all the pertinent information under analysis could not be recorded in a *single* format for each individual person.

2.3. SEQUENCE OF PRESENTATION IN TEXT

Each of the basic features just described— in purpose, agents, allocation, temporal states, and group components—could be used as the main axis on which to build a further discussion of investigative methods. Because the rest of the methodologic decisions usually depend on a project's purpose, the comparative and descriptive goals of research will be the first topics to be presented for additional discussion.

Regardless of whether a comparative study is concerned with evaluating a process or an impact, certain basic scientific principles can be stipulated for the comparison. The next chapter will be devoted to these principles, which apply to any type of comparative research.

2.4. SYNOPSIS

Of the diverse classifications that might be used for medical research, the architectural arrangement has the advantage of allowing the goals of the research and the component parts to be noted simultaneously. The architectural arrangements can be catalogued as follows: the purpose of the research can be descriptive or comparative; the agents under study can be processes evaluated for quality or maneuvers evaluated for cause-effect impacts; the allocated agents may be investigated in an experiment or survey; the temporal status of the observations can be cross-sectional or longitudinal; and the groups under investigation can have homodemic or heterodemic components.

Despite the different goals of process research and cause-effect research, both activities involve acts of comparison for which certain basic scientific principles can be established. The principles will be discussed in the next chapter.

EXERCISES

Exercise 2.1. For the impending 20th postgraduate reunion of college classmates, an epidemiology-oriented member of the class has obtained suitable consent to do the research studies described in the list that follows. Please classify each of these studies as cross-sectional or longitudinal and as homodemic or heterodemic.

2.1.1. From responses to questionnaires sent to all members of the class, a profile of the class will be prepared, showing current average income, marital and family status, and "happiness quotient."

2.1.2. From data on file at the college, the income status of each graduate's family when she or he began college will be related to the graduate's current income level.

2.1.3. The subjects in which each graduate began to major in college will be related to the family's income level when the graduate entered college and also to the graduate's current income level.

2.1.4. The subjects in which each graduate majored in college will be related to any deaths noted in the class since graduation.

2.1.5. The current income level of the graduates will be related to whether they actually attended the 20th reunion and also to their later presence or absence at the 30th reunion.

2.1.6. From data supplied by the college, the proportion of each appropriate

class attending alumni reunions during each of the past 10 years will be obtained and will be related to the gross national product during each year.

Exercise 2.2. The material that follows contains excerpts of summaries for 11 research projects published in clinical literature. On the basis of the descriptions contained in these summaries, classify each project as impact (i.e., cause-effect), process, or descriptive; experiment or survey; cross-sectional or longitudinal; and homodemic or heterodemic.

2.2.1. *Human Placental Lactogen: The Watchdog of Fetal Distress.* Human placental lactogen measured in the last trimester of pregnancy has been used as a screening test to indicate fetal distress, neonatal asphyxia, or dysmaturity after an apparently normal pregnancy. There is a 56% chance of perinatal complications if the hormone concentration has been in the fetal danger zone (more than two standard deviations below normal) on at least one occasion.

2.2.2. *Epidemiologic Evidence for Two Types of Trigeminal Neuralgia.* Patients with trigeminal neuralgia and healthy control subjects were compared to determine whether several risk factors for trigeminal neuralgia were related specifically to the anatomic divisions of the trigeminal nerve. The vertical location of the pain was strongly related to age at diagnosis. Non-Jewish religion was primarily a risk factor for trigeminal neuralgia of the lower face (any third-division involvement), whereas non-drinking and non-smoking were risk factors for trigeminal neuralgia of the upper face (no third-division involvement). The epidemiologic evidence suggests that different etiologic mechanisms may operate for trigeminal neuralgia of the lower face and upper face.

2.2.3. *Fibrinolytic Activity and Postoperative Deep-Vein Thrombosis.* Ninety-five patients undergoing gynecologic operations were studied in a double-blind trial to assess the effects of phenformin and ethylestrenol, given for four weeks, on the incidence of postoperative deep-vein thrombosis (DVT). Forty-five patients received phenformin and ethylestrenol and 50 patients received placebo preparations. Although phenformin and ethylestrenol produced a significant shortening of the dilute blood clot–lysis time, there was no difference in the incidence of DVT in the two groups of patients.

2.2.4. *Leukocyte Electrolytes in Cardiac and Noncardiac Patients Receiving Diuretics.* In 18 patients with heart disease receiving diuretics and digitalis, the sodium and water content of leukocytes was significantly increased. The content of potassium and its concentration in cell water were significantly reduced, indicating an absolute intracellar potassium deficiency. Leukocyte sodium content exceeded potassium content in two cases. Ten patients without heart disease who were receiving diuretics had normal leukocyte sodium and water content. In this noncardiac group, leukocyte potassium content averaged 353 mEq. per kg. dry solids compared with a mean of 377 mEq. per kg. dry solids in 59 control subjects, but this difference did not achieve significance. However, a few noncardiac patients taking diuretics had very low leukocyte potassium content. The results suggest that the intracellular electrolyte abnormalities in the cardiac patients were associated more with the heart disease than with its treatment, although diuretics may increase the potassium deficiency.

2.2.5. *Are There Safer Hypnotics than Barbiturates?* The mortality associated with prescribing barbiturates and nitrazepam has been compared. Because deaths from poisoning are enumerated annually by the National Center for Health Statistics, the deaths associated with barbiturates or nitrazepam can be determined from this list. The number of prescriptions issued annually for these substances was estimated from a random sampling of pharmacists who kept special files of data. For a six-year period, the numbers of deaths in which these drugs were implicated and the death rate per million prescriptions for each drug were respectively 12,354 and 133 for barbiturates and 90 and 13 for nitrazepam. The evidence suggests that nitrazepam is a safer drug than barbiturates.

2.2.6. *Antenatal Diagnosis of Neural-Tube Defects Using Cerebrospinal Fluid Proteins.* Diagnosis of an anencephalic fetus has been confirmed by immunologic detection of β-trace protein of cerebrospinal fluid in amniotic fluid. In 75 control amniotic fluid samples, a precipitin reaction to β-trace protein could not be demonstrated. It is suggested that this method may serve as a reliable specific index of neural-tube defects.

2.2.7. *Urea Treatment of Skin Malignancies.* One hundred twelve patients with basal or squamous cell skin carcinomas were treated with urea. During the first two years,

treatment consisted of injections of urea solution around the lesion, and 73% of the patients definitely benefited. In the third year, treatment was modified by combining injections of urea with scraping off and treatment of the traumatized surface with urea powder. In this way, definite benefit reached 91%. Despite very good results with the conventional therapeutic methods, urea treatment is thought to be valuable because of its simplicity, superior cosmetic results, and absence of side effects.

2.2.8. *Mortality and Anemia in Women.* Mortality over a three-year period has been related to hematocrit readings in 18,740 women examined in several hematologic surveys. There is evidence of a small increase in mortality in anemic subjects and of a distinct increase in mortality in subjects with hematocrit levels above about 46%. In the more anemic women, a higher than expected proportion of deaths were due to neoplasms, but there was a clear deficiency in the proportion of deaths due to cardiovascular disease.

2.2.9. *Variation in the Interpretation of Radiographic Change in Pulmonary Disease.* Series of chest films from five patients being treated for tuberculosis or sarcoidosis were presented in the correct chronologic sequence to a panel of five interpreters. Several weeks later, the panel read the films again, but this time the chronologic order had been reversed without the knowledge of the panel. As an earlier study had shown for pneumoconiosis, the assessment of radiographic change in tuberculosis and sarcoidosis was influenced by the assumed chronologic sequence of the serial films.

2.2.10. *Liver Scans and the Detection of Clinically Unsuspected Liver Metastases.* To determine the value of radioisotope liver imaging in the preoperative assessment of patients with treatable cancer, liver images were obtained in 46 patients with carcinoma of the large bowel who did not have hepatomegaly. At operation or necropsy, eight (17%) were proved to have hepatic metastases, and liver scans detected seven of these. The technique gave a correct answer in 44 patients, giving an overall accuracy of 95%. This evidence implies that liver imaging is useful in the preoperative assessment of patients with cancer, even if the liver is clinically normal.

2.2.11. *Plasma-Prolactin in Human Breast Cancer.* Plasma prolactin was assayed in 115 patients with breast cancer and 115 matched controls. Mean plasma prolactin levels were 6.0 ± 3.7 ng. per ml. and 5.9 ± 2.9 ng. per ml., respectively. Plasma levels in 64 members of nine families with a high frequency of breast cancer were irregularly distributed, with a mean prolactin level of 10.4 ± 8.1 ng. per ml. Statistical evaluation demonstrated that breast cancer patients and controls may be regarded as one population but that the prolactin levels in the high-risk group represent a different population ($P < 0.0004$).

Exercise 2.3. An investigator coming to you for help in planning research wants to test the idea that breast feeding in infancy helps prevent schizophrenia in later life. Without evaluating the worthiness or importance of the research, without worrying about the determinations of *breast feeding* or *schizophrenia*, and without concern for the feasibility or validity of any project you may design, name and briefly outline three different architectural structures that could be used for this research project.

Exercise 2.4. In a group of patients with omphalosis who were admitted to the clinical research center and who gave informed consent for the research, the investigators are testing the effect of a sodium sulfate infusion on renal blood flow. After baseline measurements of renal blood flow, each patient is randomly assigned to receive either a sodium sulfate infusion or a normal saline infusion. After the infusion, renal blood flow is measured again. After resting for two hours, the patient then receives another baseline measurement of renal blood flow, following which the alternative agent is infused (i.e., those who previously received sulfate get saline and vice versa). After this second infusion, renal blood flow is measured again and the investigation is concluded. Classify this research according to the format used in Exercise 2.2.

Exercise 2.5. A practicing physician, who specializes in the care of patients with diabetes mellitus, has assembled data about the effects of different forms of treatment on the patients seen in his practice. He prepared a report of his results and submitted

it for publication, but the work was rejected by the *Journal of Prestigious Medicine* because the treatments were not compared in an experimental trial. Having read the description of an experiment in the fourth paragraph of Section 2.2.3, the physician now claims that his work is really experimental.

He says that he has made advance arrangements for collecting high-quality data in each patient, and he has a specific advance plan for assigning treatments. He assigns diet alone to diabetic patients who fulfill certain stipulated criteria, oral hypoglycemic agents to patients who fulfill other criteria, insulin for yet other criteria, and so on. His devoted patients accept all of his recommendations, carry them out with a high degree of compliance, and appear faithfully for his frequent examinations during long-term care. He has tabulated the data for development of vascular complications in the treated groups, and he has drawn conclusions about the merits of the treatment associated with the lowest rate of complications.

He is incensed by the rejection of his careful experimental studies and he wants you, as a clinical epidemiologist, to help compose the letter with which he will protest the unjust criticisms received from the *J. Prest. Med.* What would you advise him to do?

CHAPTER REFERENCE

1. Frost, 1939.