1 'Knowing' in medicine

For countless ages, the ailing have turned to 'healers' who profess to know how to bring about relief and cures. The affected give little thought to the gnawing question, *How* do they know? Indeed, most of us, when ill, prefer to avoid raising such doubts for conscious consideration. Even a shaman who engages in deliberate deceptions has been known to turn to other shamans for treatment when he himself is sick. However, once the element of blind faith is set aside, the question of 'knowing' in medicine is not different from the general question, How do we know what we know about the natural world?

Knowledge grows by the solution of problems; the primitive approach to solutions is the trial-and-error method used by all living forms in the course of adaptation. Since the number of errors in random explorations is large, the crude method is slow and costly. The probings of humankind and of some animals gain in efficiency as they are guided by abstract reasoning. However, the major human advantage is that of time-binding; each generation can begin where the previous one left off. Unfortunately, the enormous power of this faculty is blunted when the received messages discourage fresh explorations. For example, at the time of a solar eclipse, some South Pacific natives blow whistles, shout, and beat drums to frighten the moon into disgorging the sun. When the intervention is challenged, the leaders reply, in effect, why change, it works.

A HERITAGE OF AUTHORITARIANISM

Uncritical reliance on past experience, *post hoc ergo propter hoc* reasoning, and veneration of dogma proclaimed by authoritative figures, were all embodied in a form of medical thought known as Galenism. Galen (AD 138–201) codified a system of medicine that endured without challenge in the Western world for about sixteen centuries. It was based on his vast experience as a physician in Rome, and on dissections and experiments in animals.

The general approach was teleologic: Nature acts with perfect wisdom, he held, and does nothing uselessly. Galen wrote extensively and made

statements with impressive self-confidence about virtually every medical topic. His words were regarded as immutable by worshipful followers.

When Andreas Vesalius, a 16th century Belgian physician, first dissected a human heart and did not find 'pores', said by Galen to perforate the septum separating the ventricular chambers, the Belgian assumed the openings were invisible to the eye. Some years later, with his faith in authority shaken, he declared dramatically that 'pores' did not exist. Vesalius' book describing dissections of the human body appeared in 1543. It undermined the foundations of Galen's pronouncements by showing that the long-accepted descriptions of human anatomy were incorrectly set down. The Galenists, who formed the majority of university physicians, vehemently denied the truth of the new statements.

Galen's erroneous views that blood flowed to and fro in a tide-like movement within arteries and veins were not upset until the 17th century. The announcement of the discovery of the circulation of the blood by an English physician, William Harvey, in 1628, met with violent opposition. Even when it was admitted, grudgingly, that Harvey might be right, a defender of the established view wrote that if the new findings did not agree with Galen, the discrepancy should be attributed to the fact that Nature had changed; one should not admit that the master had been wrong.

An aphorism ascribed to Galen reveals the kind of invulnerability claimed by physicians for hundreds of years:

> All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases.

GROWTH OF SCEPTICISM

Western medicine's progress from mystical certainty to scientific uncertainty began with the challenges to Galenism. And the spirit of doubt spurred an exponential growth in inquiry that has continued to the present day. In the short time since World War II, an enormous amount of descriptive information has been collected concerning the constituent parts of the human body down to the smallest subcellular and molecular units. Vital functions and specific disorders are now described in the mechanistic terms of biochemistry and physiology, and a powerful array of drugs and physical agents have been developed to modify physiological and pathological processes.

Much of this has come about as the result of ingenious technical developments which have permitted never-before-possible observations and measurements. But, more significantly, never-before-challenged hypotheses have been questioned and formal rules of scientific evidence have been applied with increasing frequency in tests of hypotheses.

I underline the importance of this shift in emphasis (from collecting observations to testing ideas) because there is a common belief that the scientific method is an engine-like operation for the assembly, classification, and interpretation of facts about the material world. In the pages that follow, I will dwell repeatedly on the limitations of the observations-only approach in medicine. Here I wish to point out the curious origin of the incomplete view of how we set out to make sense out of information. The roots extend back to the time of William Harvey in the ideas of one of his influential patients, Francis Bacon, a Lord High Chancellor in 17th century England.

The millenarian view

The notion that wholesale collections of observations about natural events can provide perfect knowledge about the world can be traced to an interpretation of biblical text. The inspiration came from the Book of Daniel, Chapter 12, in which the prophet described the final state of the world before the millennium. In Verse 4 it is foretold that at the time of the end '... many shall run to and fro, and knowledge shall be increased'.

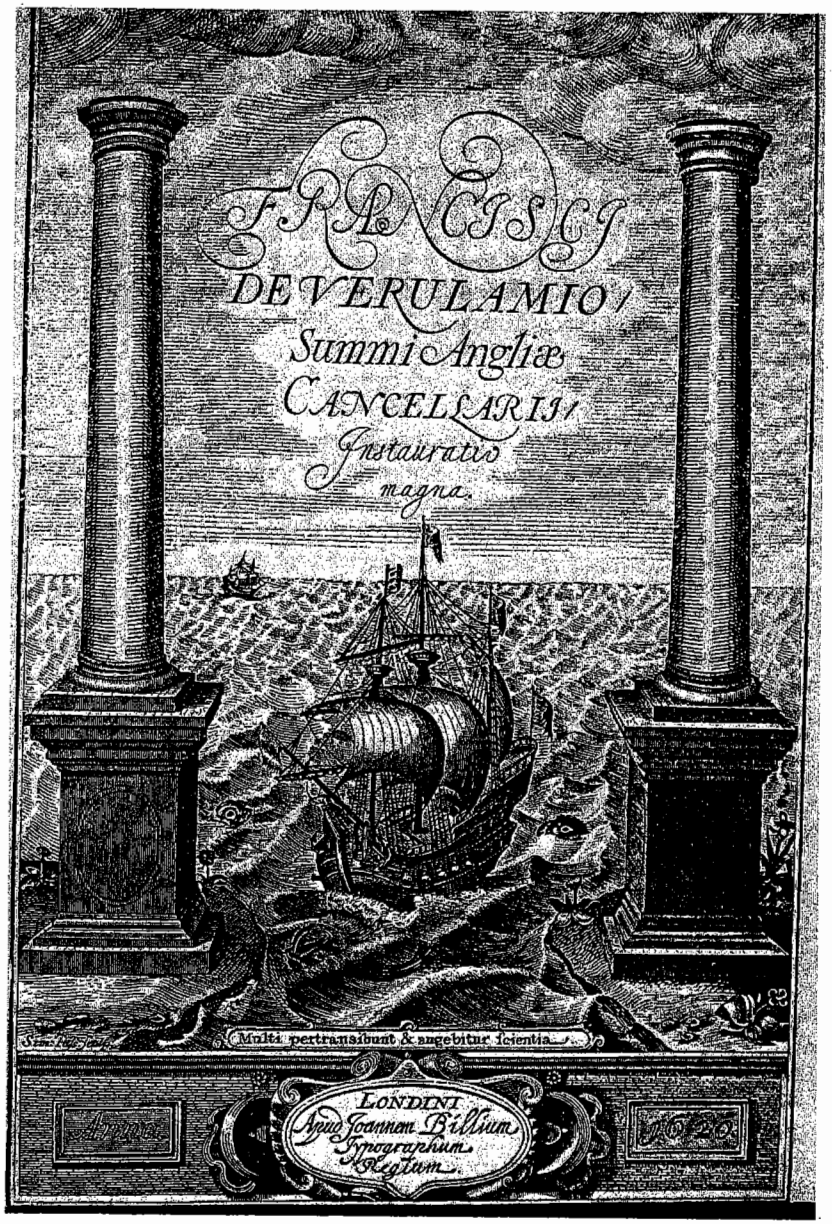
These lines of scripture, British historian Charles Webster has shown, played a surprising role in the development of science and medicine, for they were used by Bacon and his Protestant co-religionists to resolve a basic dilemma facing them in the early 1600s.

If Man originally fell owing to his pursuit of knowledge, how was it *now* possible for him to seek worldly enlightenment without falling from grace? Bacon argued that all knowledge must recognize and be guided by the primacy of religion. Probing what he defined as 'secondary causes' for utilitarian purposes would, therefore, incur no risk of transgression. Instead, these mundane explorations would glorify God and restore Man's dominion over Nature.

The notion of restoration was central to Bacon's thesis; the idea was to recapture intellectual attributes lost by Adam at the time of the Fall. The pursuit would hasten the coming of the millennium, a return to conditions of life associated with the Garden of Eden. According to the prophet Daniel, Man was destined to regain a position of dominance. Each step to increase knowledge was a move toward the millennial condition. Bacon proposed '... to extend the power and dominion of the human race over the universe'.

Bacon's inductive method

The project was set out in Bacon's book entitled *Instauratio Magna* which appeared in 1620. The great restoration of Man through science was to be accomplished through a new method of research called *Novum Organum* (also hailed as 'True Directions Concerning the Interpretation of Nature').



Title page of *Instauratio Magna* by Francis Bacon (first Baron of Verulam) published in 1620. The pregnant line from Daniel 12:4 appears here in Latin—*multi pertransibunt et augebitur scientia* ('many shall run to and fro and knowledge shall be increased'). Note the symbolism of the two Pillars of Hercules at the entrance to the Mediterranean Sea; these marked the farthermost limits of the habitable world in the minds of the ancients. Here Bacon indicates voyages of exploration beyond the time-honored limits.

The improved plan of discovery consisted of deriving laws from collections of observations—the method of induction. Bacon was convinced that a very diligent dissection of the world would provide the means for *completely* understanding it.

He also advised that observers invent experiences without waiting for Nature to act. And he argued that his scheme would have the effect of transferring the business of finding the pattern-of-particulars from the mysterious operations of the imagination to a logical procedure. It should be possible, therefore, to develop a mechanical course of action to discover laws governing any aspect of natural phenomena. He said, 'My way of discovering sciences leaves little to individual excellence, because it performs everything by the surest rules and demonstration.'

Bacon was certain the co-operative effort of large teams of researchers would lead to the speedy discovery of *everything there is to know*.

The spirit of Galilean experimentation

Galileo expert Stillman Drake has recounted the story of an argument concerning floating objects in water that began in the summer of 1611 at a small meeting in Florence. There was a discussion about condensation of matter by cold—ice was mentioned as an example. Galileo said ice is rarified water and merely appears to be dense. Since it floats, he argued, ice must be lighter than water. A professor of philosophy explained the floating of ice by its broad and flat shape; it is unable to cleave the surface resistance of water and this keeps it afloat. The argument went on for months; finally, the opponents met to sign an agreement fixing the conditions of a contest which could be judged by referees.

The defender of the shape-theory planned to use pieces of ebony, some in the form of thin chips and some in spherical and cylindrical shapes. Since the flat pieces could be floated while the balls and cylinders would invariably sink, this was to be offered as experimental proof that shape was the only factor which determined the floating or sinking of bodies in water. Galileo, on the other hand, proposed that different shaped pieces of ice and of ebony should be submerged in water and then released.

The contest never took place because the shape defender never appeared at the appointed time. But the spirit of Galileo's approach is perfectly obvious. He proposed a critical experiment that placed the rarified water explanation at maximum risk—it was designed to allow observers to make a clear choice between competing theories concerning the floating of objects in water.

Galilean experimentation

Bacon's inductive approach was fundamentally different from the method of research clarified by his contemporary, Galileo Galilei. The Florentine astronomer and physicist recognized that there are usually competing explanations for a phenomenon and he tried to devise tests which could discriminate between possibilities. Bacon advised that experiments (invented

experiences) be carried out merely to increase the supply of observations for the engine of induction; Galileo's experimental design appealed to experience for the express purpose of testing some postulated law.

Most important, the critical methodology was open-ended; it discarded the millennial idea of completeness of observations and experience because no earthly criterion of 'completeness' could be envisioned. The deductions from a mathematical formula or an hypothesis were subjected to an ordeal (*il cimento*); if they failed the test, the experimenter devised fresh experiments in the light of what had already been observed.

This method of discovery depended (as it does today) on an essential element—the creative imagination of the experimenter. It was accepted that the concept of 'knowing' has a provisional quality; there is uncertainty about the durability of explanations. And it followed that there must be tentative acceptance of only those theories which have survived rigorous critical tests.

> 'The observer listens to nature; the experimenter questions and forces her to unveil herself.'
>
> Georges Cuvier

Endurance of inductivism

The founders of the Royal Society of London made it clear that they acquired the concept of a systematic investigation of the natural world from Bacon. But the Fellows of the Society changed over to the approach of Galileo, almost without comment on the difference between the two versions of the scientific method.

The curious thing about all of this is that inductive logic became established as a tradition in science. Despite the shortcomings recognized at the very start and criticism of this type of reasoning by philosophers from David Hume to Karl Popper, the idea persisted that knowledge grows by collecting facts on a grand scale. What is even more amazing about the durability of inductivism is the clear evidence that it was not used by those who made the most important advances in science and medicine. (Harvey was not influenced by his patient; he said of Bacon, 'He writes Philosophy like a Lord Chancellor.')

Biologist Peter Medawar examined the paradox in which researchers pay lip reverence to a style of investigation which they do not use and cannot authenticate from their own experience. 'Sciences which remain at Bacon's level of development,' he pointed out, '... amount to little more than academic play.'

EXPERIMENTAL METHODS IN CLINICAL STUDY

Over 100 years ago the French physician and physiologist, Claude Bernard, recognized that developments in the basic sciences were gradually turning medicine 'toward its permanent scientific path'. Nonetheless, there was an unresolved problem; physicians were slow to adopt the method of investigation common to the sciences. He noted, for example, that they appeared unwilling to concede the important distinction between the analytic power of observation and that of experiment.

Bernard explained the principles that form the basis of experimental reasoning in his classic treatise, *An Introduction to the Study of Experimental Medicine* published in 1865. He stressed that 'Gaining experience and relying on observation is different from making experiments and [recording] observations.' And he made strong arguments for 'precise reasoning based on an idea born of observation and controlled by experiment'. Bernard called for a shift to critical (Galilean) methods in medical research.

His words had, and continue to have, a very wide influence on medical thought. Nonetheless, it would be misleading to ignore the fact that the resistance he sought to overcome has not yet disappeared. Medicine still struggles with a double standard of credulity in its search for understanding and effective action.

Faltering support for scientific rigor

Preclinical studies in laboratories are carried out under the watchful eyes of referees—tough critics who insist that rules of evidence be strictly observed. A constantly remodelled body of biomedical evidence has been assembled, and it serves as the fertile source of rational proposals for everyday applications in medical practice.

The next step, an experimental test of predicted effects of interventions in groups of patients, falters because of a block well known to Bernard. 'Many physicians attack experimentation,' he said, 'believing that medicine should be a science of observation, but physicians make therapeutic ex-

> **An eighteenth century controlled trial**
>
> 'On the 20th of May, 1747, I took twelve patients in the scurvey aboard the Salisbury at sea. Their cases as similar as I could have them ... Two of these were ordered a quart of cider a day. Two others took twenty five gutts of elixir vitriol ... Two others took two spoonfuls of vinegar ... Two were put under a course of sea water. Two others had each two oranges and one lemon given them each day ... The two remaining took the bigness of a nutmeg ... The consequence was the most sudden and visible good were perceived from the use of the oranges and lemons.'
>
> James Lind, 1753

periments daily on their patients so this inconsistency cannot stand careful thought. Medicine by its nature is an experimental science,' he continued, 'but must apply the experimental method systematically.'

The practical difficulties of carrying out this hundred-year-old advice are considerable. Unfortunately, there is no other way to obtain evidence of an order which approaches the rigorously objective kind we seek by scientific inquiry in all other areas of the material world. The rules of scientific evidence cannot be repealed by pleading hardship.

Impatience with delays

There are understandable, if not strictly logical, reasons for the reluctance to submit hopeful treatments to experimental tests in matters involving the well-being and the lives of our fellow humans. The slow, painstaking steps and the scepticism which underly the reasoning seem niggling in the face of suffering and rapidly progressing illness. After basic studies concerning isolated phenomena have been rigorously battle-tested, there is an understandable temptation to translate the hard-won information into practical action as quickly as possible. The powerful urge is given a boost by the machinery of present day mass communication which needs to be fueled by an endless flow of miracles.

It is probably unnecessary to seek further for an explanation of the ambivalence which characterizes attitudes toward the experimental approach in modern clinical research. For it is hard to deny that doubt is unwelcome at the bedside; we have a deep-seated yearning for magical cures.

Stepping into the unknown

Despite dramatic modern victories, failed innovations continue to outnumber successes in medicine. Moreover, the consequences of therapeutic error were relatively insignificant until the modern era. For example, when Galen advocated 'Mucilage of Holihock' for the cure of piles, few patients were injured.

Like weapons in the modern arsenals of war, therapies have become exceedingly powerful and the potential for harm on a very wide scale has escalated accordingly. Spectacular therapeutic disasters have made it clear that informal let's-try-it-and-see methods of testing new proposals are more risky now than ever before in history. Since there are no certainties in medicine, it must be understood that every clinical test of a new treatment is, by definition, a step into the unknown.

The community at large (and specifically lawyers, clerics, bioethicists, and legislators) has been poorly informed about the logical basis of the experimental approach and the inherent safety in this orderly, cautious methodology. Misconceptions abound and strong feelings have stood in the way

of improvement in understanding. In another context John Kenneth Galbraith, the economist, observed, 'Where reality does not accord with wish our practice is to devise a myth which then serves as a bridge between evidence that cannot be escaped and the belief which is sought.'

The high cost of maintaining the myths which have been devised concerning the subject of clinical experimentation has become substantial and the common good can no longer afford ignorance of this matter. The question, *How* do they know? cannot be avoided; it is a public issue.

An unwitting medical experiment

Doctor John Snow's observations on the occurrence of 286 instances of fatal cholera in districts served by two water companies during the 1854 epidemic in London.

Water company	*Fatal attacks of cholera to each of 10 000 houses*
Southwark and Vauxhall Co.*	71
Lambeth Co.**	5

* *Source*: water from the Thames at Battersea Fields, about half-a-mile above Vauxhall Bridge, containing 'hairs of animals and numerous substances which had passed through the alimentary canal.'

** *Source*: water works at Thames Ditton 'quite free from the sewage of London.'

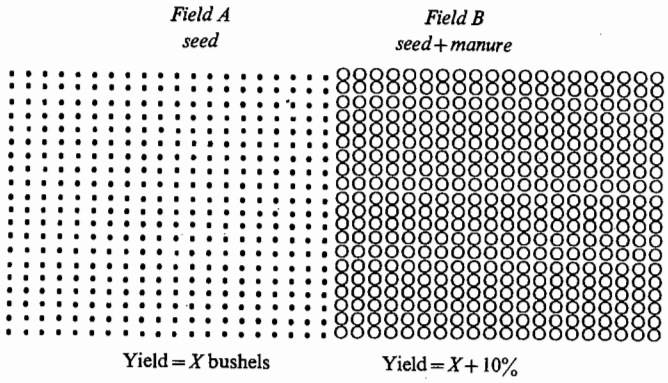
THE RANDOMIZED CLINICAL TRIAL

In this book I will focus on a special form of experimentation—the randomized clinical trial—which has been developed to test medical innovations. This alternative to time-honored methods of judging new treatments is the one evaluative strategy which requires the most understanding by the entire community. It cannot be carried out without widespread co-operation.

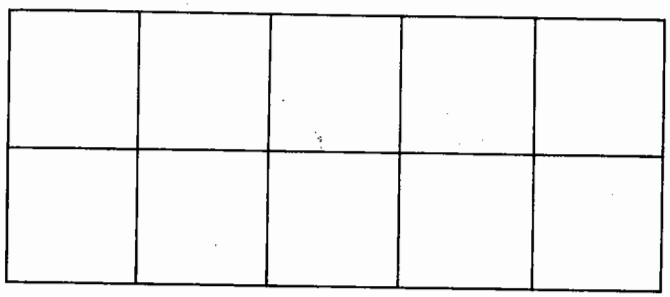
The details of how doctors perform the technical skills of their craft have little to do with the basic principles of the approach. No specialized medical knowledge is needed to follow the arguments. That is not to say that technological details of experimental maneuvers are not crucially important, but they are usually dwarfed by preceding matters related to straightforward reasoning, to the peculiarly human aspects of experiencing illness, and to the special problems associated with interpreting results in human beings in contrast to other species.

R.A. Fisher's arguments concerning the arrangement of agricultural field trials (1926)

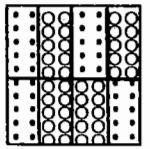
A field trial to test the effectiveness of manure might be conducted as follows:



Fisher asked, 'What reason is there to think that, even if no manure had been applied, the acre which received it would not still have given the higher yield?' If the experimenter could say that in twenty years' experience with uniform treatment the difference in favor of Field B had never touched 10 per cent, he could say, 'Either there is something in the treatment or a coincidence has occurred such as does not occur more than once in twenty trials.' The 1 out of 20 likelihood of a difference of this size is indicated very roughly by the experience in twenty successive trials. To determine the 1 in 20 expectation (referred to as the '5 per cent significance level') with any accuracy would require about 500 years' experience. Since the experimenter could not produce a record of 500 years' yields, the direct test of 'significance' was impractical. Nevertheless, Fisher argued, if the experimenter had only ten previous years' records he might still make out a case if he could claim that under uniform treatment the difference in yields had never come *near* to 10 percent excess yield in Field B. From the theory of errors the actual values for the ten years can be used to calculate how frequently a difference of 10 percent might be expected to turn up by chance in ten repeated trials under uniform treatment. Since the only purpose of the ten previous years' experience was to provide an estimate of the expected-by-chance frequency of occurrence of differences of various magnitudes, Fisher proposed a design for obtaining such an estimate from the actual yields in the trial year. He suggested a method of replication in which the test site is partitioned into blocks of equal size:



Each block is further subdivided into a number of plots of smaller size; and within each block (considered separately) the plots are assigned to the contrasting treatments in *random order*:



(○ yield) minus (• yield) = block difference

Each block now comprises one replication of the compared treatments. The block differences are used in place of the records of previous years' yields to provide an estimate of deviations. The validity of estimate is now guaranteed by the process of randomization, since each plot has an equal probability of treatment with or without manure. The likelihood of occurrence of difference in yields between the two treatments may now be estimated as before.

Evolution of the randomized trial format

Pioneering development in England The methodology of the randomized clinical trial is based on principles developed for agricultural research in Britain during the 1920s. R.A. Fisher, a pathfinding biometrist, introduced the concept of random allocation of treatments to subdivided plots of land. He adapted mathematical techniques (developed earlier by Karl Pearson and other workers at the University of London's Laboratory of Biometry, and by William Sealy Gosset who wrote under the pseudonym 'Student') which made it possible to calculate reasonable estimates of variability in yields attributable to chance in field trials.

The Fisherian principles of design and analysis were used in a landmark randomized clinical trial conducted in Britain following World War II to evaluate the streptomycin treatment of tuberculosis. The format of present day trials evolved from this experience and a series of British trials which followed. The influence of A. Bradford Hill, the statistician who played a leading role in the pioneering studies in the UK, and that of Donald Mainland of New York University, has molded the current form.

Methodological standards Until fairly recently, the mathematical strategies for statistical analysis of experiments received more attention than did the development of principles for examining the underlying conceptual basis of the design of trials involving free-willed doctors and their patients. In recent years, Alvan R. Feinstein of Yale University has examined, in minute detail, the logical 'architecture' of studies conducted under the uniquely distorted conditions encountered in medical settings. From his analyses, those of

David L. Sackett of McMaster University, and of Thomas C. Chalmers of Mount Sinai School of Medicine, a methodological discipline has been developed to help expose the multifold sources of bias which must be taken into account in planning clinical investigations.

Choice between observational and experimental studies in medicine

Observational studies	*Experimental studies*
Advantages	
1 Practicality -greater variety and larger scale of tests of hypotheses, as compared with experiments -few ethical objections, since interventions are not imposed by pre-planned design -relatively large number of participants can be recruited (especially if only past events are used) -duration of study is relatively short (especially when observations are in the form of existing records of past events) -relatively inexpensive in time and in personnel (especially when using existing records of past events)	1 Safety -relatively few individuals exposed to unpredicted risks in untried interventions 2 Vigor -capable of critical tests of limits of applicability 3 Precision -theorized causal factor can be defined and limited -exposure of test factor under control of experimenter -systematic distortions by extraneous factors may be minimized by design 4 Efficiency -relatively few observations needed to refute some hypotheses 5 Assumptions -random allotment of treatments is assured by design
Disadvantages	
1 Documentation -exposure to causal factor less certain 2 Specificity -isolating causal factor is difficult 3 Remoteness -causal factor and outcome tend to be separated at some distance in time and space 4 Time order -direction of relationship between cause and effect less certain 5 Systematic selection -availability of patients for treatments -allotment of treatments 6 Efficiency of statistical tests -lower than experimental designs	1 Impracticality -inborn attribute cannot be manipulated -predicted risk of intervention is too great -long term observation is difficult -relatively large number of participants needed to detect small differences 2 Reductionism -focus on one independent variable (*The* cause) excludes others from attention 3 Representativeness -difficult to recruit a truly random sample from 'universe' 4 Expense -relatively great in staff and organizational costs 5 Public acceptance -pejorative myths

(Based on arguments of epidemiologist Mervyn Susser)

Indispensable ordeals

Randomized clinical trials are not without serious limitations. Not the least of these are technical barriers and moral restraints which make it impossible, in some instances, to employ the resolving power of this approach. Other limitations will become obvious as I describe the concepts and operational details in the pages which follow. Nonetheless, this risk-limiting, humanized instrument is the sharpest tool which has been devised for evaluating the limits of applicability of new proposals. Donald S. Fredrickson, former Director of the National Institutes of Health, has pointed out that randomized clinical trials are *indispensable ordeals* in modern medicine.

Even when less powerful testing approaches must be used, the reasoning of the randomized trial lends itself as a guide for setting out specified elements of a clinical problem before we proceed. The analytic process begins by asking, What is the question?—the subject of the next chapter.

> 'All life is an experiment. It is an endless succession of changes and chances, of risks taken and hunches played, of lions bearded and gauntlets run ...'
>
> Oliver Wendell Holmes