4 Controlled comparison

'HISTORICAL CONTROLS'

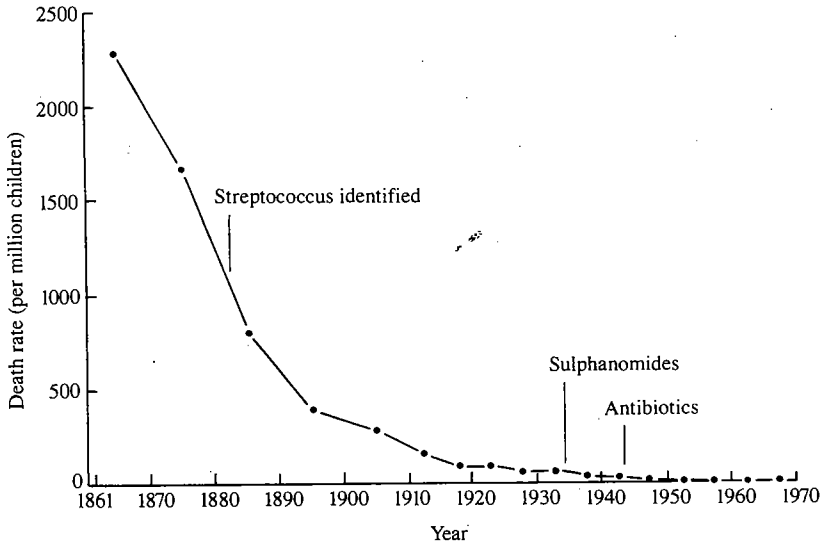
Most established treatments in the medical armamentarium were introduced without undergoing a formal test by concurrent comparison. The traditional approach has been to use the experience of the past as the basis for judging the effects of an innovation; 'historical controls' have served as the standards for comparisons. In recent times, physicians are becoming aware of the problems associated with retrospection, for it assumes that all important determinants except the new treatment under study have remained unchanged. Moreover, it assumes that all important determinants affecting outcome are known, so that the validity of the 'everything is the same' premise may be verified. The magnitude and complexity of these problems have grown as the pace of change in the modern world has quickened. Marvin A. Schneiderman of the National Cancer Institute, in the title of a review of the pitfalls in interpreting retrospective experience, asked (in exasperation), 'Looking backward: is it worth the crick in the neck?'

> 'And all our yesterdays have
> lighted fools the way to dusty death.'
> Shakespeare (*Macbeth*)

Changing course of illness

Major alterations in the 'natural' course of an illness may come about because of temporal changes in a variety of influences acting singly or in combination. These may include progressive alteration in social circumstances, the general health and nutritional status of patients, the degree of exposure to or inherent change in a pathologic agent, the criteria for diagnosis of the disease, the severity of the disorder, and the non-specific supportive care of patients, to name a few of the many variables that may change the course and final outcome of disease.

Trend of scarlet fever mortality



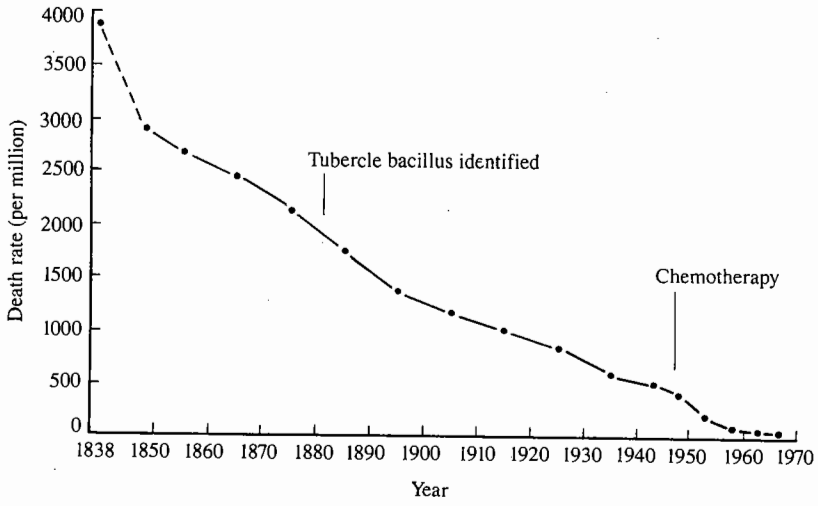
Death rates from scarlet fever among children under age 15, England and Wales (Redrawn from McKeown's figure.)

Trend of mortality in scarlet fever The rapid decline in deaths caused by one form of streptococcal infection, scarlet fever, is a striking example of the problem in interpreting the effect of a medical innovation at a particular moment in history. Thomas McKeown, the British epidemiologist, has shown that approximately 90 per cent of the fall in the scarlet fever death rate among children took place before the first use of what came to be known as the 'miracle drugs' in 1935. And it is difficult to be sure whether or not the rate of change since then has been influenced by modern antibacterial treatment.

Trend of mortality in tuberculosis Pulmonary tuberculosis in England and Wales fell steadily in the 19th and the first half of the 20th century, McKeown found. During this period many forms of treatment were used with apparent success, but the claims are now considered to have been exaggerated (treatment with gold salts, for example, was found to be worthless after it had been prescribed widely 'with good results' for over 15 years).

When the antibiotic agent, streptomycin, became available in 1946, members of the Medical Research Council in Britain were wary of scattered reports indicating that the new treatment was effective against the ancient

Trend of pulmonary tuberculosis mortality



Death rates from pulmonary tuberculosis, all ages, England and Wales. (Redrawn from McKeown's figure)

disease. They knew that the 'natural' course of the respiratory form of tuberculosis was so variable and unpredictable it would be difficult to evaluate any mode of treatment. (The situation was in marked contrast to the one in which the infection involved the central nervous system; meningeal tuberculosis was uniformly fatal. Here the past was a reliable standard of comparison. It was merely necessary to treat a group of proven cases; if *any* recoveries took place this would be clear evidence that the new treatment was responsible for the unprecedented success.)

The multicenter randomized controlled trial organized in 1946 (p 37) set out to compare results of the standard treatment for pulmonary tuberculosis (bed rest) with the experimental regimen (bed rest and streptomycin). At the completion of the study it was found that mortality was lower among patients who received the new drug. The need for a concurrent control group in this landmark trial was underlined by the finding that impressive clinical improvement occurred in some of the patients treated by bed rest alone. Moreover, the limitations of streptomycin treatment also became apparent. The new drug was toxic to the auditory nerve, and tubercle bacilli quickly developed resistance to its antibacterial action. Although the trial results suggested that the new treatment would accelerate the decline in mortality rate from the respiratory form of tuberculosis, it was also clear that a search for more satisfactory agents was urgently needed.

Demographic changes

Distortions in experiences may be introduced, as we have seen, by changes in the way patients are distributed throughout the medical system. Selective forces acting systematically, over time, on populations as a whole (such as changes in patterns of fertility) may also produce elusive changes in the types of patients available. Under these circumstances, it is difficult to evaluate the relative contribution of medical efforts, compared with intandem effects of social and demographic changes.

Shifts in high-risk births For example, beginning in the 1960s, there was a systematic shift in the distribution of births in the United States. The proportion of births among women in high-risk categories (that is, those with characteristics associated with high mortality in the offspring) began to decrease, and women with favorable outcome indicators accounted for a larger share of total births. A survey by Naomi M. Morris and her colleagues at the University of North Carolina noted the decline in infant mortality for the years 1965–72 and estimated that 27 per cent of the fall could be accounted for solely by the shifting proportions of characteristics in the pregnant population. The change was ascribed to 'family planning' (not family planning *services* necessarily, but individual decisions and behaviour concerning age at first pregnancy and number of pregnancies).

During the same years, projects were established in a number of American cities to provide special prenatal and infant care. The success of these intensive efforts was measured by a fall in infant mortality rate. But, as the analysts pointed out, some of the improvement was related to more favorable distributions of the inherent characteristics of childbearing women. Even under the most generous assumptions, only a small fraction of the decline in infant mortality seen in the country as a whole could possibly be attributed to the effectiveness of the well intentioned efforts to provide coordinated special care to a relatively small number of mothers and infants.

Conflicting effects of interventions

A major problem facing physicians is that of untangling multiple and, at times, opposing effects of their interventions. Unexpected harmful consequences of untried treatments are an ever present danger, and these may be difficult to detect when there is no concurrent control group of patients who receive the standard treatment.

Antibacterial treatment to prevent infection When antibacterial drugs became available after World War II, they were used with some encouraging results in newborn infants, but the record was disappointing in babies born

prematurely who were at highest risk. The spotty results were thought to be related to the fact that early signs of bacterial invasion were difficult to recognize in the small babies.

Beginning in the late 1940s, premature infants were given antibacterial drugs to *prevent* infections, and survival seemed to improve following the introduction of this form of routine care. Almost five years elapsed before it was found, by means of a randomized controlled trial, that the new practice was not always benign. One established treatment regimen, penicillin plus sulfisoxazole, was found to have its intended effect of preventing fatal infections—but the beneficial action was irrelevant. In the formal trial, mortality rate after the second day of treatment was much higher among infants who received this established regimen that had been used widely with complete confidence. A non-infectious, often fatal, form of brain damage (known as kernicterus) was found nine times more often among babies who succumbed after the accepted treatment than among concurrent controls treated with a newly proposed drug to stave off infection.

The fatal side effect of the established treatment was unsuspected and had been completely overlooked before the formal trial. An increase in kernicterus-related deaths during the years of penicillin/sulfisoxazole treatment was hidden among other fatal conditions (often multiple in the same baby) found commonly at the time of autopsy examination. (It was later discovered by Gerald B. Odell, then at Johns Hopkins University, that sulfisoxazole 'released' the protein-bound yellow pigment, bilirubin, in the blood of jaundiced newborns; the toxic pigment was then free to enter and fatally damage the brain of a treated baby.)

A biblical comparative trial involving children

The prophet Daniel conducted a trial of a vegetarian diet (a pottage of leguminous plants and water) as compared with a daily provision of the king's meat which was offered to a group of well-favored children 'such as had ability in them to stand in the king's palace.' At the end of ten days on the experimental diet, 'their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the king's meat.'

Daniel 1:11–15

RANDOMIZED ALLOTMENT

The sulfisoxazole incident is not unique. It is a tragic reminder of what is, in fact, the rightful burden of all innovation: How can the risk of introducing a new treatment be limited? Despite the most extensive pre-clinical study, the first human application of a powerful treatment is a blind gamble. The possibilities of gain and loss must be undertaken without fore-knowledge of the probable odds. How is the 'impossible' decision made to choose between the accepted standard treatment and the proposed improved approach when a fellow human being must be assigned to one of the two (or more) treatments under test?

John Wesley draws lots to seek guidance concerning marriage (March 4, 1737)

'Having both of us [Mr Delamotte and himself] sought God by deep consideration, fasting and prayer, in the afternoon we conferred together but could not come to any decision. We both apprehended Mr Ingham's objection to be the strongest, the doubt whether she was what she appeared. But this doubt was too hard for us to solve. At length we agreed to appeal to the Searcher of Hearts. I accordingly made three lots. In one was writ, "Marry": in the second "Think not of it this year". After we had prayed to God to "give a perfect lot", Mr Delamotte drew the third, in which were the words, "Think of it no more". Instead of the agony I had reason to expect I was enabled to say cheerfully "Thy will be done". We cast lots again to know whether I ought to converse with her any more, and the direction I received from God was "Only in the presence of Mr Delamotte".'

(Quoted from Wesley's journal by F.N. David of the University of London)

Allegory of Fortune
Fortune is often portrayed on a ball or a wheel, often with a blindfold. The wheel is usually introduced in pictures as a symbol of uncertainty or insecurity. In this painting by Leombruno (16th century), the goddess is characterized as inconstant, dangerous, and delicately balanced (*Dea varia, lubrica et fragilis*).

Limiting risk by lot

A solution is to be found by turning to one of the most venerable practices in the long history of humankind: in the face of an irresolvable dilemma the gods are consulted for guidance. Sortilege, or divination by lots, is the time-honored and eminently fair method used to guide choices under conditions in which there is paralyzing uncertainty. Many variations in detail have been used, but the general procedure is fairly uniform; the question is posed, the lot is cast, and the decision is made. The method, it has been noted, does not give the god, or more specifically the goddess of fortune, much scope for self-expression, but at least it produces an unequivocal directive. And in medicine, I must add, the method protects patients from the consequences of the all too human frailties of their caretakers.

Randomization

The ancient method of divination by lot is formalized in the present-day method of randomization of treatments. The procedure was invented (p 11) to ensure that compared treatments will be assigned to patients in such a way that all possible allocations are equally likely within the constraints of the experimental design. (One such restriction is used in a method called 'balanced' randomization in which the numbers of assignments are equalized in small blocks of consecutive patients.)

Advantages of random allotment The essential weakness of before-and-after design is overcome in a randomized clinical trial. Both standard treatment and new treatment groups are observed concurrently, thus eliminating the 'time bias' of historic controls. And random allotment eliminates the physician's bias in the assignment of treatments. It has been pointed out, for example, that biased assignment of patients is particularly likely to occur in selective comparisons of medical versus surgical treatments; often only low risk patients are considered to be candidates for operations whereas many more candidates are judged suitable for medical treatments.

The precaution of random allotment ensures that neither personal idiosyncrasies nor lack of balanced judgment enters into the formation of different treatment groups. It removes the unfairness that may arise when treatments are prescribed on the basis of unjustified guesses. Of course, the protective plan may be foiled if patients are enrolled only on condition that they receive a specified treatment (or if they are removed when the goddess of fortune decides against one of the prejudged alternatives). A decision to participate must be made before the treatment assignment is disclosed if a patient is to be shielded fairly when taking a risky step into the unknown.

Another advantage of random assignment is that the method tends to balance treatment groups in respect to relevant determinants of outcome, whether or not these factors are known. (Such blind faith is related to our convictions about the behavior of random processes: rain drops *do* tend to fall equally on exposed squares of paper). And, finally, randomization guarantees the validity of the statistical tests of 'significance' that are used to compare treatments.

The latter arguments deserve special emphasis because the need for the treatment-by-lot step in bedside studies is often misunderstood. For example, comparisons of treatments using concurrent controls often are thought

'Balanced' randomization sequences

Balanced randomization should be considered when enrollment in a trial takes place slowly over a period of months or years because temporal changes in severity of illness are not uncommon. The object of the approach is to ensure fairly equal matching of numbers in treatment groups at all times in the course of a prolonged trial. For example, two treatments (A and B) may be assigned in a restricted form of randomization that enforces equal numbers at the enrollment of every sixth patient. All of the 20 possible sequences of 3A's and 3B's are given number designations as follows:

Number	*Sequence*	*Number*	*Sequence*
00–04	AAABBB	50–54	BAAABB
05–09	AABABB	55–59	BAABAB
10–14	AABBAB	60–64	BAABBA
15–19	AABBBA	65–69	BABAAB
20–24	ABAABB	70–74	BABABA
25–29	ABABAB	75–79	BABBAA
30–34	ABABBA	80–84	BBAAAB
35–39	ABBAAB	85–89	BBAABA
40–44	ABBABA	90–94	BBABAA
45–49	ABBBAA	95–99	BBBAAA

Number category 00–04 indicates that the compared treatments will be given to six consecutive patients in the order AAABBB, category 05–09 designates the order AABABB, and so on. A series of two-digit numbers are then obtained from a random number table and these determine the sequence of six treatment blocks in the trial. Each treatment assignment is placed in an opaque envelope and these are arranged in a long series according to the treatment order in consecutive blocks. The envelopes are sealed and the face of each envelope marked with a number to indicate the order in which the envelopes are to be opened as consecutive patients are enrolled and treated. When six patients are enrolled, the numerical balance between treatment A and treatment B is equal, and the equality is maintained with the enrollment of the twelfth, eighteenth ... patient.

Since the assignment for the last person entered in each block can be determined before the envelope is opened, the ideal of 'masked' treatment decision is not met completely. The potential for such disclosure can be reduced by varying the size of consecutive sets. A random order of block size makes it very difficult to determine the next assignment in a series.

to be impractical because it is virtually impossible to assemble two groups of patients that are matched exactly in every clinical detail. When R.A. Fisher introduced the element of randomization in experimental design, he explained that it is pointless to insist that all conditions in compared groups must be exactly alike because the list of possible factors that might influence the outcome can never be exhausted: *the number is unknown.* Random assignment of treatments serves as the fundamental safeguard under these conditions of uncertainty about risk variables. Although the groups compared are never perfectly matched for 'all important determinants,' the process of randomization fulfills the requirements of the logic of chance.

Laws of chance operate On the assumption that the results are governed by the laws of chance, we may ascribe a probability distribution to the difference in outcome *expected* between groups receiving equally effective treatments. Any *observed* difference may now be described in the terms of 'betting odds' used by gamblers. As has been emphasized by David P. Byar of the National Cancer Institute, it is the process of randomization that generates the 'statistical significance' test (p 127), and this process is independent of prognostic factors known or unknown. The validity of 'significance' levels based on randomization does not require the unachievable assumption that the treatment groups are exactly matched.

Stratification and sensitivity Contrived efforts to achieve near equality in compared groups are often made before randomization by subdividing eligible patients into subgroups of individuals who resemble each other in respect to their known prospects for illness outsome. The ideal sought by the tactic, called prognostic stratification, is to reduce the variability of outcomes and increase the sensitivity of a trial. It is less likely that a specific effect will be overlooked when comparisons are made between individuals under similar risk. For example, the gradient of birthweight-related risk of RLF was so steep that infants enrolled in the national study were divided into three risk strata (by birthweight) and random allotments of treatments were carried out among babies within each stratum.

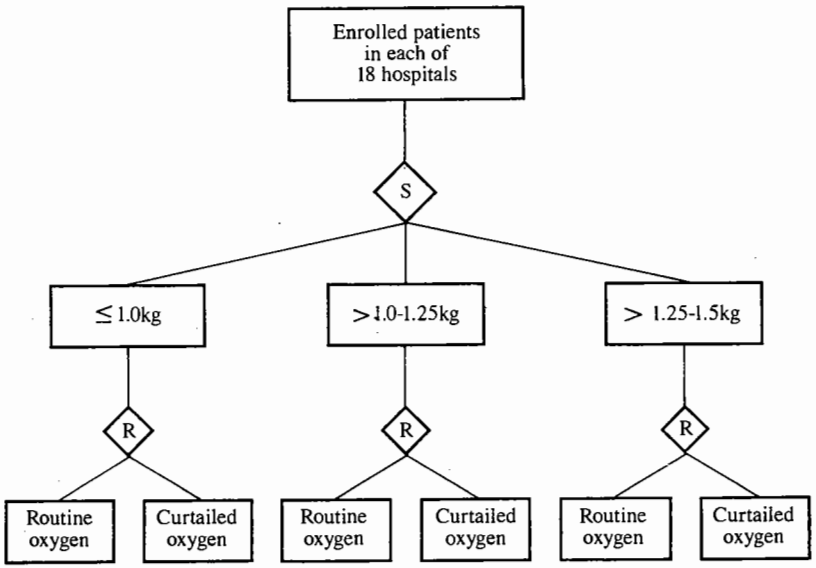
Practical limits of subgroups As a practical matter, the number of prognostic characteristics that can be considered is severely limited by the inherent diseconomy of scale in the problem. The addition of each extra variable means that the number of mutually exclusive subgroups will increase geometrically. For example, two variates require four subgroups, three require eight and so on. Many enrollees are needed if each of the subgroups is to have enough members to provide a reasonable contrast. As a result, the number of prognostic categories for assignments in clinical trials is usually scaled down to take into account only the most important

determinants thought to have a bearing on the outcome of the study. Sometimes, a summary prognostic index based on several characteristics may be used as a single variable for assignments. This may achieve a reasonable balance among the separate factors on which the index was formulated.

There is some disagreement about the need for stratified entry in large single center trials; in the alternative approach, prognostic stratification is carried out only at the time of analysis of results. In multicenter trials, the characteristics of patients in each hospital are likely to vary in ways which may affect outcome. Thus, it is advisable to consider each center as a replication of the trial and to randomize accordingly; stratification by hospital is a minimum subdivision in collaborative studies.

Random allotment within prognostic strata

The randomized clinical trial of two oxygen-management regimens was conducted in 18 hospitals throughout the United States. All premature infants who weighed 1.5 kilograms or less and who survived 48 hours, born in or brought to the cooperating hospitals, were admitted to the study. A Coordination Center in Detroit, Michigan was notified by telegram of the enrollment of each infant and assignments were made as follows*:



S: babies grouped into three prognostic strata according to birthweight (under 1.0 kilogram, 1.0 to 1.25 kilograms, and 1.25 to 1.5 kilograms)

R: random allocations to oxygen management regimens (routine oxygen treatment or curtailed oxygen administration)

At the end of the trial, outcomes in each of the oxygen management subgroups were added for a final comparison of results.

* Allocation in the trial was more involved than indicated here because of a two-stage design (p 177), but the principle of random allotment within subgroups was preserved.

A caveat Having made the arguments for the importance of the 'casting of lots,' I must now pass along Feinstein's warning against undue reverence for randomization as a panacea for the cure or prevention of all intellectual maladies in planning clinical studies. Obviously, it would be misleading to imply that distortions do not occur with random allotments. The laws of chance require that gross imbalances, like all improbable events, must occur in the long run.

ALLOCATION IN PILOT TRIALS

Pilot observations of the results of a new treatment (to determine the dosage and other details of administration) are usually carried out in selected patients. Randomization starts only after these initial explorations have been completed in enough people to allow a formal trial to be carried out without changes in a prescribed regimen.

Randomize the first patient

The standard approach has been challenged by Thomas C. Chalmers, of the Mount Sinai School of Medicine, who has proposed that randomization should begin with the first patient. He argues that the limitation-of-risk rationale for random allotment can be defended when there is no hint about relative efficacy and toxicity of a new drug (or procedure): this innocent state exists in its purest form at the time the first patient is to be treated. What the clinical investigator is doing in an uncontrolled pilot trial, he continues, is asking certain patients to forego their right to the standard accepted therapy and be treated by a procedure that has not yet been developed sufficiently to warrant its comparison with that standard treatment. Chalmers' arguments are logical and quite practical: a stepwise approach, ending in a final version of the randomized trial, can be carried out with due regard for the rights of patients and the requirements of the rules of evidence. But it must be firmly resolved that the investigative efforts will not end with pilot observations.

Uncontrolled pilot studies

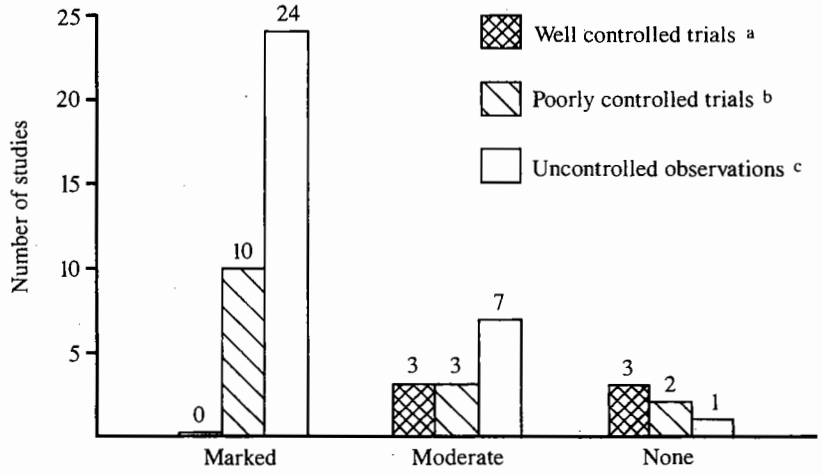
Preliminary results of success or of failure are frequently misleading when initial observations are conducted without concurrent controls. If the pilot experience fails to demonstrate the hoped-for effect, efforts are often abandoned before a potentially useful intervention is given a fair trial and the preliminary results are rarely reported. On the other hand, if the initial results indicate a positive effect, the results are published and the investigators become so convinced of the value of the intervention that they are unwilling to conduct a critical trial to determine the limits of applicability of the new treatment.

It has become customary in preliminary reports to include a paragraph advising that controlled studies should be carried out to confirm the initial observations. Such trials, however, are rarely, if ever, conducted by the original, enthusiastic innovator. The report of encouraging results has a ripple effect; others are emboldened to conduct uncontrolled explorations of the hopeful approach and a critical test is delayed.

The history of a surgical procedure to prevent bleeding from varicosities of the esophagus complicating cirrhosis of the liver is an example of a frequently seen relationship between the design of studies and expressed enthusiasm for new treatments. After 15 years of controversy concerning the treatment to prevent esophageal hemorrhage, a large-scale randomized clinical trial was conducted by a cooperative group of Boston hospitals. No

Design of studies and expressed enthusiasm

'... nothing improves the performance of an innovation as much as the lack of controls.' Hugo Muench



*Enthusiasm for a surgical treatment purported to reduce the risk of esophageal hemorrhage in cirrhosis of the liver (53 studies of the procedure reviewed by John P. Gilbert and his associates at Harvard University).

[a] Well controlled: a study in which assignment to treatment groups is in random order and the patient is accepted for study before the treatment is known.

[b] Poorly controlled: a study in which there is selection of patients for the treatments to be compared according to clinical judgment, and comparison is made with the whole group or the unselected group; or a study in which the controls are historical and originate in a different time or place.

[c] Uncontrolled: no attempt is made to compare the patients receiving the treatment in question with a group not receiving this treatment.

evidence of a beneficial effect of the surgical procedure could be detected. I will return to the issues raised by pilot observations in chapter 9 (The Stopping Rule).

Two definitions

Quasi-Experimental Design
The phrase 'quasi-experimental design,' according to D.L. Sills in the *International Encyclopedia of the Social Sciences*, refers to the application of an experimental mode of analysis and interpretation to bodies of data not meeting the full requirements of experimental control. The circumstances in which it is appropriate are those of experimentation in social settings—including planned interventions—where complete experimental control is not possible. When properly done, when attention is given to the specific implications of the weaknesses of the design in question, quasi-experimental analysis can provide a valuable extension of the experimental method.

True Experimentation
The core requirement of a true experiment lies in the experimenter's ability to apply experimental treatments in complete independence of the prior states of the persons under study. This independence makes the resulting differences interpretable as effects of the differences in treatment. The independence of experimental treatment from prior status is assured by randomization in assignments to treatments. Where innovations are to be introduced throughout a social system and where the introduction cannot in any event be simultaneous, a use of randomization in the staging can provide an experimental comparison of the new and the old, using groups receiving the delayed introduction as controls.

NON-RANDOM ASSIGNMENT

The term 'quasi-experimental' has been used to describe non-random methods for assigning compared treatments. In the simplest of these, standard treatment and new treatment are assigned alternately as patients appear for enrollment. This systematic method (and variations, such as assignment by alternate day, by odd or even hospital chart number, and so on) offers no protection against the introduction of personal biases that might interfere with the basic goal of comparing like with like. For example, physicians may deliberately 'steer' patients into a preferred group when they know the schedule of assignments. Moreover, even when they conscientiously try to avoid influencing assignments, they may unwittingly do so when they decide whether or not their patients are qualified for enrollment in the trial. If these decisions are made when they know which treatment the patients are to receive, it is difficult to avoid selective recruitment. The result is a systematic sorting of patients that may have a much greater influence on outcome than the treatments under test.

ADAPTIVE ALLOCATION PROCEDURES

A number of assignment schemes have been developed that use information obtained during the course of a clinical trial to determine the treatment prescribed for the next patient who is enrolled. Some of the approaches seek progressive improvement in the balance of numbers and prognostic characteristics, others adjust allocations according to the responses to previously assigned treatments in the hope of winning in what might be considered a game against nature.

Marvin Zelen of Harvard described a game-like design that uses the 'play the winner rule', well known in gambling. A success of one treatment in a comparative series generates a future trial of the same treatment with a new patient; a failure generates a future trial of the alternative treatment. In practice, the first treatment is assigned by the toss of a coin. If the response is successful the 'winning' treatment is offered to successive patients until a failure occurs. At that point the alternative treatment is used for the next candidate. When a failure is encountered on the alternative, the next patient receives the original 'winner' and so on.

Another adaptive plan, known as the 'two armed bandit' method, begins by assigning treatments in random order. As the trial proceeds, information is gained about the probability of success for each treatment. The new data is used to adjust the ratios of assignments, so that a progressively higher proportion of newly enrolled patients receives the currently 'better' treatment.

Shortcomings of adaptive designs

The general aims of adaptive strategies for treatment assignments cannot be faulted. They are used to increase the chance that more patients will be assigned to the superior treatment as the trial progresses and to shorten a trial in which some patients are exposed to an inferior treatment. Unfortunately, there are a number of practical difficulties that limit the usefulness of the approach. In chronic disorders, for example, there may be a long delay (years) between treatment and outcome. Moreover, the response used to judge the 'winning' treatment may be misleading if unexpected serious complications turn up later (for instance, liberal oxygen treatment was found to improve the respiratory performance of premature infants while long afterward the link between the intervention and RLF was uncovered). Finally, a serious limitation of adaptive schemes arises from the shaky assumption that patients admitted throughout the study are homogeneous in characteristics which affect the outcome of treatment.

Dilemmas of allocating untried treatments

Undoubtedly, there will be continued efforts to seek improvements in the designs for allocating treatments in clinical trials. And there is no reason to

expect that a single approach will be suitable for all clinical studies. It is unrealistic to ignore the fact that some doctors and their patients are unwilling to submit treatment decisions to the luck of the draw. Nevertheless, the random assignment format remains the most powerful one available for comparisons of treatments. And, I wish to re-emphasize, the dilemmas for each individual patient enrolled in a randomized trial and for the community as a whole are resolved by one of the fairest risk-limiting practices used by human societies. The democratic aspect of this approach to containment of hazards was demonstrated in the randomized clinical trial of sulfisoxazole treatment of babies. It was shocking to find the fatal complication in those who were enrolled in the trial, but the new information was obtained by a strategy that spared half of the participants from exposure to the unsuspected hazard of the previously 'accepted' treatment and would spare the lives of future babies.

The modern version of sortilege affirms an ancient observation: Man has one thing in view, Fate has another.

> 'Cry and howl, son of man ...
> Because *it is* a trial ...
> Thou therefore, son of man, prophecy, and smite
> thine hands together ...
> Go thee one way or other ... withersoever thy *face* is set.
> I will also smite mine hands together and I will cause
> my fury to rest: I the LORD have said *it*.'
>
> *Ezekiel* 21:12–17