Some Statistical Aspects of a Cooperative Study

LLOYD A. KNOWLER, Ph.D.*

The National Institutes of Health, and in particular the National Institute of Neurological Diseases and Blindness, are to be commended for sponsoring cooperative studies which permit many members of the medical profession to work together in studying important and complex diseases. It is hoped that opportunities such as this one will increase the probability of a breakthrough in the treatment of each disease or at least of gaining information which will be useful in sharpening and modifying present procedures to achieve better results.

Why Collect Data?

It is only natural to ask ourselves the question, "Why collect data?" Perhaps we would answer that the principal objective is to draw an inference, to render a judgment, or to make a decision. We realize that the solution of many, if not most, of our problems eventually depends upon numerical data—difficult though it may be to reduce those problems to numerical terms. Many of us have a greater degree of security and of comfort when we have unbiased numerical evidence to support ideas which we have formed from our experience. In scientific development it is necessary to refine, to alter, and to accept new approaches and methods as they are established, especially if the new approaches and methods are improved ones which lead to more favorable results. We must be willing and eager to accept modifications in order that we make progress.

Reliable Data

Cognizance of rules established in the discipline of statistics is essential to a scientific endeavor which includes in any considerable degree the marshalling of numbers of facts if serious error in the use of those facts is to be avoided. Good data are, of course, essential to any scientific endeavor, but the scientist must use sound statistics to make the maximum use of his data. The present study does involve numbers in varying quantity concerned with distressingly complex variables in the underlying problem. The importance of having close cooperation with a statistician was recognized at the outset.

Cooperative Study

Many persons believe it is desirable to have a cooperative study in many of the medical problems today—some believe it is essential. It is hoped, and anticipated, that results of the working together of so many persons from different disciplines will provide useful information which might never come from separate units.

A cooperative study may be desirable for one or more of the following reasons:

1. Cases may be so few in number that any one center would have an insufficient number to warrant any valid conclusion or it would take so long for one center to accumulate cases that the normal medical improvements from the beginning to the end of the sequence would mean that the data would not be comparable;

2. The population or universe from which the cases arise would be broadened;

3. Any differences in personnel and/or facilities would tend to be balanced; or

4. Funds and/or resources to make a study possible might be more adequate.

It may be that this general study demonstrates the feasibility of overcoming some or all of the obstacles indicated by these points, and indeed it may be considered as one of the pioneer studies of such broad scope that it "reaches around the earth."

Statistical Inference

Statistics has been thought of as the collection, tabulation, analysis, and interpretation of data. In making a judgment or rendering a decision based on the data, one becomes involved with statistical inference, which may be of two parts: estimation and tests of hypotheses. In regard to estimation and tests of hypotheses, one might immediately raise these basic questions:

* Professor of Mathematics, University of Iowa, Iowa City, Iowa.
1. What is the current status of a disease with respect to natural history, background reports, and current modes of treatment;

2. What would be the best methods of treatment among those which are available, having certain characteristics or conditions given; and

3. How can the disease be prevented?

Scientific Method

A scientific method may be outlined in many ways. Perhaps it would be in order to consider the following way:

1. Conduct a survey.
2. State a hypothesis. Also, perhaps set up one or more alternate hypotheses.
3. Test the hypothesis.
4. Revise the hypothesis; maybe an alternate hypothesis becomes the revised hypothesis. Set up alternate hypotheses.
5. Test the revised hypothesis.
6. Repeat if necessary.

Phases of a Study

In a study of infrequent events which by necessity need to be recorded in relatively small numbers at various centers from time to time, it is probably desirable to examine the first of the above points, that is, to make a study concerning the present status of a disease. In so doing it is natural that a team of investigators would attempt to secure information concerning every aspect of the problem. It is obvious that this information should be secured in the best possible manner and with accuracy. This is even more important when it is realized that it is not feasible to repeat a comprehensive study at frequent intervals, if at all. This is the attitude which has prevailed during the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage. This does not rule out the possibility, however, of maintaining a continuous investigation. Neither does it rule out the possibility of creating special studies—in fact, questions will probably be raised and problems encountered which will call for special studies, especially if a high rate of mortality is associated with the disease.

In connection with the first phase of this study it was proposed that some guidelines might be established to determine the treatments which might give the greatest promise of being most effective, or at least which might justify giving them further consideration. In order that such guidelines be established, one facet of this initial survey is to examine results by a case matching procedure. Of paramount importance is an estimate of the probability that a patient will survive one year, two years, three years, and so forth, under each of the three primary modes of treatment being considered, where, to the extent feasible, patients with similar conditions are matched. Also of considerable importance is an estimate of the condition of the survivors at the end of such intervals. It was anticipated that it might be possible only to establish guidelines to be followed by a special study designed to give more definitive answers to such questions.

Secondly, in analyzing the data it is possible that certain hypotheses will be formulated such that two or more treatments are assumed to be equally effective. The testing of these hypotheses may reveal which of several modes of treatment offers a patient the greatest probability of a good result, that is, it may be possible to designate which of several alternative modes of treatment for a patient with a particular condition results in the highest probability of survival for a certain length of time. It is hoped that the second phase of this study, the current special study referred to as the Comparative Study of Treatments for Intracranial Aneurysms, will shed some additional light on this problem.

As stated in the Plan for a Comparative Study of Medical and Surgical Treatments for Bleeding Intracranial Aneurysms, a principal objective of the special study is to provide an answer to the question, "Which of the alternative modes of treatment under study offers a patient with a single intracranial aneurysm that has bled during the previous three months the highest probability of good results in terms of survival, duration of acute illness, residual neurological deficits, and capacity for self-care and gainful employment?"

A sequential plan of analysis was adopted in order to terminate the study as soon as a sufficient number of cases has been ac-
cumulated to render a decision, where each treatment is being compared with each and every other treatment. It is necessary that the status of every patient be reported accurately and promptly, and that any change in the status be reported in the same manner.

A third phase of the study to be taken up when a more extensive accumulation of data has taken place will be the analysis of the material with the view of discovering means of prevention of the disease (Point #3 under Statistical Inference). In the last analysis a substantial contribution into this portion of the study would be the most valuable of all.