Preface

There is no question that medicine has made unprecedented strides in recent years, but an increasing number of voices now ask, Where is medicine going? The goal was stated succinctly in 1952 by Nobel laureate MacFarlane Burnet:

> The aim of medicine in the broadest sense is to provide for every human being, from conception to death, the greatest fullness of health and length of life that is allowed by his genetic constitution and by the accidents of life.

In reviewing the historic development of medical research as a means to further this end, he found evidence that scientific investigation in this field had, indeed, grown out of human need. But he expressed concern that the activity (i.e. the systematization of methods for the most effective satisfaction of human desires) might lose contact with social aims.

In the years since Burnet's thoughtful analysis, a powerful new methodological tool in medical research has been perfected—the randomized clinical trial. This development grew out of an earlier refinement, random order of assignments, in biological experiments on conditions undergoing concurrent comparison. The new strategy, first in preclinical and later in bedside experimentation, led to a leap forward that has been compared, by Mervyn Susser of Columbia University, to the abrupt advance following the invention of the microscope. But unlike other tools in medical research, the use of the randomized clinical trial requires the full co-operation of relatively large numbers of human beings. The nature of this investigative 'instrument' links it inextricably with social considerations.

In the period immediately after World War II, many new treatments were introduced to improve the outlook for prematurely-born babies. (These infants accounted for the largest number of deaths in the days and weeks after birth.) Over the next few years it became painfully clear that a number of changes in caretaking practices had produced completely unexpected harmful effects. The most notable of these tragic clinical experiences

was an 'epidemic' of blindness, retrolental fibroplasia, in the years 1942–54. The disorder was found to be associated with the way in which supplemental oxygen had come to be used in the management of incompletely developed newborn babies. The twelve-year struggle to halt the outbreak provided a sobering demonstration of the need for planned evaluation of all medical innovations before they are accepted for general use. One observer noted that when the value of a treatment, new or old, is doubtful, there may be a higher moral obligation to test it critically than to continue to prescribe it year-in, year-out, with the support merely of custom or wishful thinking. Formal strategies for clinical testing evolved to fulfill this newly-prominent obligation.

During this period of 'awakening' (in the early 1950s) I began to use the (then) recently developed format of the randomized clinical trial as a tool for evaluating some of the many new treatments for premature infants in The Babies Hospital at Columbia University. I was soon convinced of the utility of the schematic approach, despite the practical difficulties. Repeated experience provided impressive demonstrations of the intrinsic caution and fairness of this approach: scientific *and* democratic principles proved to be complementary (not antithetical!). I fully expected that the new techniques would be accepted rapidly, but my prediction was quite wrong. As the years have rolled by, opposition to pre-planned human experimentation has increased. The objections are in complete disaccord: some have argued that the rigorous demands of randomized trials delay the introduction of urgently needed treatments to relieve suffering; others have accused investigators of proceeding too rapidly (i.e. by exposing patients to unproven 'experimental' treatments). The incongruity of these positions and the rising clangor of the debates have convinced me that there is an alarming and ever-widening communication gap which separates medical inquirers from the rest of society. The message that must be widely broadcast is this: observation and experiment are fundamentally different kinds of operations.

The way in which doctors set out to apply the experimental format in the design of human studies is set out in the pages which follow. In this volume, I have leaned heavily on my own experiences with treatment trials involving newborn babies. I must explain that the examples in this field of medicine are by no means unique. I believe, however, that studies involving helpless neonates call attention to some of the most difficult stumbling blocks which stand in the way of widespread acceptance of the need for planned studies. Additionally, there is a need to be more critical about the quality of evidence in matters relating to infants and children than in any other province in medicine. If evidence misleads in the case of interventions for adult patients—particularly those beyond the age of reproduction—the long-term global consequences of error are relatively trivial. Since ours is

the only species on the planet which has achieved rates of newborn survival which exceed 90 percent, it seems to me we must demand the highest order of evidence possible before undertaking widespread actions that may affect the full life times of individuals in the present as well as in future generations. Here a strong case can be made for a *slow* and *measured* pace of medical innovations. (Premature dissemination of a new medical technique, before evaluation by carefully designed clinical trials, has been likened by Eugene Braunwald of Harvard University to a genie who has escaped from a bottle—it is virtually impossible to undo the confusion resulting from such unrestrained therapeutic exuberance.) Finally, I have focused on a relatively few examples of medical problems (repeated reference is made to the retrolental fibroplasia experience) in the hope of lightening the semantic burden for the non-medical reader who must cope with unfamiliar medical terms and concepts in addition to those concerned with research methodology—the central issue in this book.

The philosophic outlook called 'critical rationalism' is the epistemological underpinning of the scientific attitude. A fundamental insight of this view of the world is that we can learn from our mistakes. Critical examination of knowledge claims is the only way we have of detecting our blunders and harnessing them for useful purposes. I have emphasized this outlook which is the root premise for the kind of experimentation seeking to discriminate between possibilities. In addition I have stressed the design of clinical experiments and the logical foundation of statistical methods rather than the arithmetic operations used in the analyses of outcomes in clinical trials. Workable clinical experiments simply cannot be designed with lofty detachment from the frustrating details of the real world. In the pages of this book, I have made an effort to dispel the simplistic notion that the use of scientific rules of evidence in human experimentation implies that there is a fixed set of directions that may be applied mechanically to test a given question. The disturbing assumption of such a myth is that if you go through the motions attributable to science, then science will result. (Such operations, sociologist Erving Goffman once pointed out, are reminiscent of the experiments children perform with toy sets: 'Follow the instructions and you can be a real chemist, just like the picture on the box.')

The phrases 'dramatic breakthrough', 'miracle drug', 'life-saving discovery', and the like are often applied to the results of medical research; there is, consequently, an understandable belief that only money and national resolve stand in the way of any rapid solution to major medical problems. It may come as a rude shock to read my account of a catalogue of obstacles that must be overcome to make very modest gains in improving the outlook for most of our afflictions. It would be well, I suggest, for those who are impatient with the fact that a medical millennium is

nowhere in sight to keep in mind the advice of workers in fireworks factories:

> It is better to curse the darkness
> than to light the wrong candle.

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