Controlled Trials and Escape Clauses

To the Editor:

The report of intravenous propranolol in acute myocardial infarction by Cairns and Klassen (Chest 1981; 79:277) might have been valuable had the design of the study been appropriate, i.e., including random allocation of patients to treatment and control (placebo) groups. Cobbled into the end of the text is an escape clause of the kind now commonly seen in reports of uncontrolled surgical trials; it acknowledges "... the need for a large scale, randomized double-blind controlled trial." Preceding this is the admission that "the non-random allocation and absence of double-blind placebo controls permits bias in treatment allocation." Right on. But if the authors were truly convinced of this, and these statements were in their original text, why did they not design their trial correctly or did the two citations result from the notation currently found on almost all papers, "revision accepted"?

The authors are cardiologists of great skill and intellect and have undoubtedly carried out a careful investigation, but one that by being inadequately controlled, was flawed from the outset. Had they taken twice the time and studied, say, 24 patients, approximately half of them randomized to a control series, we might have had a definitive study suggesting (or establishing) beneficial effects of propranolol on CK release and establishing (or negating) reduction by propranolol of determinants of myocardial oxygen consumption. Perhaps the authors will themselves now undertake the "large scale randomized double-blind controlled trial" that they propose. Unfortunately, the history of uncontrolled "pilot trials" is such that this tends not to happen and other investigators may now be discouraged.

It is scientifically correct and ethically necessary to randomize an investigation from the first patients (allowing, in a flexible design, for possible modifications based on cumulative experience). On first introducing any trial treatment we cannot predict its precise early effects and we are in absolute ignorance of all late effects—good and bad. Hypothetically, for example, reducing infarct size might leave more living but injured tissue that could generate lethal late arrhythmias; other late effects could not be appreciated without appropriate control patients. Scientifically, all patients recruited for any trial should include appropriate concurrent control patients and ethically all patients should be randomized to have a 50-50 chance not to get a trial treatment that might be harmful in the long run.

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To the Editor:

Dr. Spodick raises the issue of the desirability of random allocation of patients to control and treatment groups in the assessment of a new treatment. We agree with him entirely that such a study design is required to provide definitive proof of the efficacy of the proposed treatment. However, we do not agree that randomized allocation is required when a treatment is being undertaken for the first time. When there is uncertainty as to the likely benefit of the treatment, the special circumstances which may determine outcomes, and the likelihood and magnitude of side effects, a small pilot study is of considerable value in guiding investigators in the design of definitive trials of the treatment. At the time the present study was conducted, no study had been published to define the effects of large dose intravenous propranolol in the attempt to limit human infarct size. The accumulation of 12 patients who met the appropriate admission criteria, who agreed to enter the study, and for whom appropriate hemodynamic monitoring facilities were available, required many months at the two centers. A randomized allocation of patients would have provided only half the number of treated patients in the same time, and would not have yielded as much information.

The statement, "These findings, in conjunction with data from other studies, indicate the need for a large scale, randomized, double blind controlled trial of the effect of intravenous propranolol on acute myocardial infarction size in man," was in the original manuscript. Similarly, we acknowledged that "the non-random allocation and absence of double blind placebo controls permits bias in the treatment allocation" in the original manuscript. We chose a cohort analytic design recognizing its deficiencies, but also its advantages over designs employing no comparison group, literature comparisons, or before-after comparisons. We contend that pilot studies such as this one, and that of Cold et al (Am J Cardiol 1976; 38:689-95) were important prerequisites to definitive trials of intravenous propranolol therapy of patients with acute myocardial infarction. We now know that with appropriate precautions the drug can be safely given in large intravenous dosage to patients with acute myocardial infarction. We know that hemodynamics are favorably altered acutely and that there are some suggestions of beneficial effects on infarct size. Data are now available from a number of human studies indicating that infarct size reductions are likely to be modest with any pharmacologic intervention. This evidence, plus knowledge that infarct size is highly variable, indicates that a definitive randomized trial will require a large number of patients to ensure that appropriate limits for α and β errors can be set. Such numbers are not available in a single institution and therefore the study must be multicentered. Such a trial of intravenous propranolol is currently in progress under the sponsorship of the NHLBI. A definitive answer as to the efficacy of propranolol in infarct size reduction should emerge from this trial, as it could not possibly from an initial small pilot study. In fact, most large trials have been preceded by small pilot trials.

We are in complete agreement with Dr. Spodick that definitive results are likely to emerge only from randomized treatment allocation study designs with double-blind outcome assessments. We have the greatest respect for his advocacy of the randomized trial design. However, we do not agree that there is no place for pilot trials to be conducted and reported when knowledge about a drug’s effects in a given setting is at a preliminary stage.

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