effect of a surgical procedure performed within the chest (Cobb et al., 1959). Nonetheless, it would have been inappropriate to do anything other than place the patients' welfare first, even though that forced some of the goals of the studies to be compromised.

Clearly, this lack of blinding of subjects and investigators will prove more important in the interpretation of some outcomes (e.g., chest pain) than of others (e.g., mortality). If possible, of course, it is better to keep both subjects and investigators ignorant of the treatment status, as this will minimize the possibility of actions on the part of either group that could bias the results. When complications of disease or therapy arise that necessitate knowledge of the specific therapy to which the patient has been assigned, this information usually can be given to one or more physicians external to the study who can decide on the proper course of action. If the therapy under study is a drug, the blinding is generally done by preparing a placebo identical in appearance to the active agent. However, one study in which the identical appearance of drug and placebo was achieved but blinding was not is instructive to review here:

> *Example:* In the early 1970s, healthy adults were enrolled in a randomized controlled trial in which they were asked to take vitamin C (3 g/day) or a lactose placebo for 9 months, during which time the incidence of colds was monitored (Karlowski et al., 1975). Because some subjects indicated that they had bitten into and tasted the preparation that they had been given, the investigators asked all subjects at the conclusion of the study to guess the group to which they had been assigned. Of the 102 who attempted a guess, 79 were correct (77%). Eleven percent more of the subjects given a placebo had 2 or more colds during the follow-up period than did those given vitamin C. However, an even larger difference was associated with a subject's believing he or she was assigned to a particular group: 36% of subjects assigned to receive vitamin C had 2 or more colds, twice the incidence in persons who, though they actually were taking placebo, thought they were taking vitamin C. A similar difference was found for persons who received the vitamin but believed it was a placebo—the proportion of this group with 2 or more colds was higher than that among persons receiving placebo (67% vs. 47%). Because a subject's suspicion of the group to which he or she had been assigned so strongly influenced the results, and because a subject's suspicion was much more often right than wrong, the validity of the vitamin C-placebo comparison was seriously compromised.

Among those 2-arm randomized trials in which no untreated or placebo group is included, there are some in which the goal is to determine whether the treatments being compared are equally effective. This goal may be sought once one of the treatments has been shown to be effective and when a second treatment—not yet similarly evaluated—has potential advantages in terms of ease of administration, cost, or the incidence of adverse effects. In such

Jones B, Jarvis P, Lewis JA, et al. Trials to assess equivalence: The importance of rigorous methods. *Br Med J* 1996;313:36–39.
Karlowski TR, Chalmers TC, Frenkel LD, et al. Ascorbic acid for the common cold: A prophylactic and therapeutic trial. *JAMA* 1975;231:1038–1042.
Koster RQ, Dunning AJ. Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction.

Contents

Monographs in Epidemiology and Biostatistics
Volume 36

CLINICAL EPIDEMIOLOGY

The Study of the Outcome of Illness

Third Edition

Noel S. Weiss

OXFORD
UNIVERSITY PRESS
2006