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Ethics and the Wrong Answer

Proper concern for the protection of human subjects participating in trials of new drugs, vaccines, concentrated immunoglobulins, and the like and the principle of informed consent should be and have become paramount considerations in planning and carrying out such studies. Indeed, the pendulum has swung so far that it sometimes may seriously prejudice the ability of the study to yield the correct result. One is thus on the horns of a dilemma. Is it ethical to do a study on human subjects with a design such that one may come up with the wrong answer or no answer? Is it fair to the participants? Is it fair to those who subsequently become the recipients or victims of what becomes a prescribed but useless prophylactic or therapeutic measure? Once a large-scale field trial has yielded a conclusion, right or wrong, and become official and sacrosanct, how many potentially better studies will not be carried out because of it? How much of a false sense of security will it give patients, their families, and society? Suppose the conclusion was reached because of inadequate controlled experimentation.

The validity of clinical experimentation in this field for evaluating the safety and clinical effectiveness of new drugs and biologics is almost always dependent upon the nature of the control groups of individuals. Of course no one would propose that a useful therapy be withheld from control patients while testing some new drug.

Examples of the problem are most readily found in trials involving immunization against various diseases. Valid experimentation necessitates the use of a control group of individuals who receive a placebo. The placebo material injected should be innocuous and is obviously chosen so that it will have no adverse or beneficial effect. One then evaluates, during a given interval, the incidence of the disease in the group receiving the vaccine and that receiving the placebo. In such experiments participants are generally assigned to a vaccine or placebo group on a random basis and should be informed of the probability that they may be in the placebo group; depending on the number of groups, this probability is usually 50, 33, or 25 percent. They have a right not to participate. If they so choose they remain at risk to exactly the same degree as if they were in the placebo group. Indeed, whenever possible one chooses a placebo which is known to be of value against some other infectious disease so that they derive some benefit from their participation.

Unfortunately, there is a growing deliberate tendency to design experiments in which the controls do not include a true placebo. A recent example is the use of only two groups in studies of the prophylactic effect in serum hepatitis (hepatitis B): one group receives hyperimmune gamma globulin prepared from donors selected for their antibody content and the other receives normal gamma globulin prepared from the population at large. Both preparations contain antibody to the virus, and if both groups turn out to have the same incidence of hepatitis, one will not know whether both immunoglobulin preparations were protective or whether both were useless. The assumption in the experimental design was that the hyperimmune gamma globulin would be better than the normal because it contained more antibody. Because the optimum dosage in man is not known, and if the result with both products turns out to be the same, they could have been equally good or equally bad. A true control group would have permitted a decision.

The protean nature of clinical trials does not permit a general solution to such issues. While it is manifestly desirable that every participant derive some direct benefit, this must not be a sine qua non and become the basis upon which poorly designed investigations are planned, justified, and carried out. Large numbers of individuals have always been and will be motivated to participate in such studies for the benefit of all and without any direct reward. Whenever receiving a true placebo does not adversely alter the risk compared to nonparticipation in the trial, such a group should be included. This is a small but important aspect of the total problem.—ELVIN A. KABAT, *Professor of Microbiology and of Human Genetics and Development, Columbia University, New York 10032*