

3. Dingfelder JR. Primary dysmenorrhea treatment with prostaglandin inhibitors: a review. *Am J Obstet Gynecol.* 1981; 140:874-9.
4. Eglinton G, Raphael RA, Smith GN, Hall WJ, Pickles VR. Isolation and identification of two smooth muscle stimulants from menstrual fluid. *Nature.* 1963; 200:960, 993-5.
5. Pickles VR, Hall WJ, Best FA, Smith GN. Prostaglandins in endometrium and menstrual fluid from normal and dysmenorrhoeic subjects. *J Obstet Gynaecol Br Comm.* 1965; 72:185-92.
6. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol.* 1971; 231:232-5.
7. Schwartz A, Zor U, Lindner HR, Naor S. Primary dysmenorrhea: alleviation by an inhibitor of prostaglandin synthesis and action. *Obstet Gynecol.* 1974; 44:709-12.
8. Budoff PW. Treatment of dysmenorrhea. *Am J Obstet Gynecol.* 1977; 129:232.
9. Budoff PW. Use of mefenamic acid in the treatment of primary dysmenorrhea. *JAMA.* 1979; 241:2713-6.
10. Pruss TP, Gardocki JF, Taylor RJ, Muschek LD. Evaluation of the analgesic properties of zomepirac. *J Clin Pharmacol.* 1980; 20:216-22.
11. Cooper SA. Efficacy of zomepirac in oral surgical pain. *J Clin Pharmacol.* 1980; 20:230-42.
12. Baird WM, Turek D. Comparison of zomepirac, APC with codeine, codeine and placebo in the treatment of moderate and severe postoperative pain. *J Clin Pharmacol.* 1980; 20:243-9.
13. Stambaugh JE, Tejada F, Trudnowski RJ. Double-blind comparisons of zomepirac and oxycodone with APC in cancer pain. *J Clin Pharmacol.* 1980; 20:261-70.
14. Mayer TG, Ruoff GE. Clinical evaluation of zomepirac in the treatment of acute orthopedic pain. *J Clin Pharmacol.* 1980; 20:285-91.
15. Lewis JR. Zomepirac sodium: a new nonaddicting analgesic. *JAMA.* 1981; 246:377-9.
16. Henzl MR, Massey S, Hanson FW, Buttram VC, Rosenwaks Z, Pauls FD. Primary dysmenorrhea: the therapeutic challenge. *J Reprod Med.* 1980; 25:226-35.
17. Ruoff GE, Andelman SY, Cannella JJ. Long-term safety of zomepirac: a double-blind comparison with aspirin in patients with osteoarthritis. *J Clin Pharmacol.* 1980; 20:377-84.
18. Honig S. Preliminary report: long-term safety of zomepirac. *J Clin Pharmacol.* 1980; 20:392-6.
19. O'Brien CP, Minn FL. Evaluation for withdrawal symptoms following chronic zomepirac administration. *J Clin Pharmacol.* 1980; 20:397-400.

SPECIAL ARTICLE

THE ETHICS OF THE RANDOMIZED CLINICAL TRIAL

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THE ethics of medical experimentation on human subjects has attracted much attention in recent years. There has, however, been rather less attention paid to the special ethical problems and dilemmas posed by the randomized clinical trial.

The sheer number of such trials, the risks and costs that they involve, and the dangers that are posed both by permitting and by restricting their use would seem to warrant further ethical analysis of the randomized clinical trial.

This article attempts to distinguish some of the major ethical problems posed by the randomized clinical trial, to set out some of the principal considerations that militate in favor of and against permitting such trials, and to suggest some tentative ethical criteria for medical researchers involved with them.

THE AMBIGUITIES OF MEDICAL EXPERIMENTATION

There is a sense of the term "experimentation" in which it would be true to say that physicians have been experimenting on their patients since time immemorial. From earliest times, when a patient has presented unusual symptoms or a condition that fails to respond to conventional treatment, doctors have experimented with new therapies. This ad hoc, empirical approach to medical knowledge — trying out new treatments and procedures and then carefully observing the results — was the dominant method in Western medical science until well into the present century. Physicians were able to learn from their patients while they were

treating them, with little or no conflict of values and obligations.

There are medical scientists who appear to believe that nothing has changed notably with the introduction of the randomized clinical trial:

Medical experimentation on human beings, in its broadest meaning and for the good of the individual patient, takes place continually in every doctor's office. Hence the general question of human experimentation is one of degrees rather than of kind. Deliberate experimentation on a group of cases with adequate controls rather than on individual patients is merely an efficient and convenient means of collecting and interpreting data that would otherwise be dispersed and inaccessible.¹

Against this claim, I would contend that modern clinical investigation is an altogether different sort of enterprise from the medical experimentation of previous times. What is now referred to as medical experimentation involves the designing of procedures that systematically manipulate subjects, and the use of controls for the purpose of gaining knowledge.

The employment of properly controlled clinical trials in medical experimentation has been of vital importance in the progress of medical science. But this new form of experimentation has also generated some of our most difficult and perplexing moral dilemmas.

CONFLICT OF OBLIGATIONS

When a physician, responsible for the medical treatment of a particular patient and bound by a moral oath (typically, some contemporary version of the Hippocratic oath) to hold the interests of that person as paramount, enrolls the patient as an experimental subject in a clinical trial, the physician inevitably puts himself in the morally ambiguous position of having

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two distinct and potentially conflicting roles. In his traditional role of healer, the physician's commitment is exclusively to his patient. By contrast, in his modern role of scientific investigator, the physician engaged in medical research or experimentation has a commitment to promote the acquisition of scientific knowledge.

Since each of these roles — that of scientist on the one hand and personal physician on the other — defines itself by reference to a different primary purpose, the possibility of conflict is an ever-present danger.

One should note in passing that this is not, of course, the only conflict of obligations faced by the physician. The physician's obligation of confidentiality to his patient may conflict, for example, with his legal obligation to report gunshot wounds or certain infectious diseases. This example is but one of many possible value conflicts, all of which arise from the fact that the physician has a plurality of responsibilities — to society, to future generations, to the legal system (the state), and to his own career and self-interest — in addition to his obligation to his patients. These responsibilities and obligations will, on occasion, run afoul of each other and even when there is no outright conflict, there may be difficult tensions.

Having drawn a clear-cut distinction between therapy and experimentation, one must admit that in practice this distinction is often blurred by the large number of gradations between the experimental and the therapeutic ends of the spectrum. A good deal of research is carried out by physicians on subjects who are simultaneously patients — their own or those of some other doctor. In many cases the patient himself is intended to benefit directly from the experiment; that is part of its purpose, but not its whole purpose. One of the essential aims underlying so-called therapeutic experimentation is to contribute to medical knowledge. In pursuit of this objective, procedures may be undertaken that are not strictly necessary for the treatment or cure of a particular patient. Systems of treatment are chosen partly with a view to curing the patient and partly with a view to testing new procedures or comparing the efficacy of various established procedures. The patient who is also a research subject may thereby be exposed to added hazards, discomforts, or inconveniences. Despite these disadvantages, it will sometimes be to the direct and immediate benefit of a patient to become a research subject. For example, by agreeing to participate in an experiment, a patient may gain access to a new and promising drug that is being tried out in a limited way. Alternatively, or additionally, the patient may benefit indirectly by receiving especially careful attention and care from an elite group of highly trained specialists.

The point that needs to be emphasized, however, is that regardless of whether a patient benefits from agreeing to become a research subject, the physician who attempts to combine the traditional role of healer with the modern role of scientist places himself in a situation that contains a potential conflict of values. His commitment can no longer be exclusively and un-

equivocally to promote the interests of his patient. He is fortunate indeed when his scientific and personal obligations overlap or coincide, but when they conflict, as they often must (for reasons explained below), serious ethical dilemmas must be faced and priorities assigned.

THE NEED TO SACRIFICE INDIVIDUALIZED TREATMENT

The first of the special moral problems raised by the randomized clinical trial is the potential conflict between the goals of therapy and the goals of experimentation. Although a patient who has been enrolled as a research subject in a randomized clinical trial may benefit from the therapeutic effects of the treatment being tested, the fact that the treatment cannot be entirely tailored to that patient's special needs seems to violate the physician's obligation of unqualified fidelity to his patient's health. Fried asks the key question in this regard: "[i]s it ever likely to be the case that in a complex medical situation the balance of harms and benefits discounted by their appropriate probabilities really does appear on the then available evidence to be in equipoise? Or even approximately enough in equipoise to make the argument go through?"²

The morally troubling doubt concerns the likelihood that physicians may be able to recruit a statistically significant number of volunteers for randomized clinical trials only by neglecting the particular circumstances of individual patients. When all the patient's circumstances, including his attitudes and value system, are brought into the equation, it seems doubtful that the risks and benefits of the treatment alternatives will often be in perfect (or even rough) equilibrium.

Consider for illustrative purposes the situation facing a woman with breast cancer who is being asked by her physician to participate in a randomized clinical trial designed to test the relative efficacy of radical as opposed to conservative mastectomy. It is likely that one would find considerable variations in the priorities assigned by the women involved to such factors as the prolongation of life and esthetic disfigurement. Some patients would have, as their overriding priority, the reduction of the risk of mortality. Others would opt as strongly for the procedure involving the least disfigurement. Still others would adopt intermediate positions, trading off risks and benefits or harms according to their concept of self and self-image.

Here is the dilemma: if the physician recommends that his patient enter a randomized clinical trial as a research subject without a detailed inquiry about whether this would be the best plan from the patient's point of view — taking all the patient's relevant attitudes and values into consideration — then the physician would seem to be guilty of sacrificing the interests of the patient to the interests of science or humanity. On the other hand, if the physician conducts such an inquiry, there is the risk of introducing bias into the selection of subjects or eliminating too many from the study.

There might seem to be a quick and easy solution to this dilemma. After all, it is the patient who must give informed consent to becoming a research subject. The physician's role is merely to explain the nature of the experiment and to offer a recommendation. The difficulty with this as a solution, however, is that it flies in the face of sociologic data indicating that patients generally rely heavily on the advice of their physicians with respect to value trade-offs.³ This is especially the case when the patient is acutely ill. Such patients are typically in a weakened physical state, perhaps in pain or drugged, often emotionally upset, and likely to feel dependent on and submissive toward those charged with their care and treatment. This submissive deference can be easily exploited (consciously or unconsciously) by physicians who are engaged in scientific research and who solicit patients to participate in a research program. Although there may be no question of force, fraud, or deceit, the circumstances surrounding serious illness may be thought to constitute a kind of duress.

What are the implications of all this for the physician-researcher who wishes to recruit his (or a colleague's) patients for a randomized clinical trial? The physician's traditional obligation of unqualified fidelity to his patient's well-being may be somewhat compromised by his desire, as a clinical investigator, to enlist the cooperation of patients as participants in a randomized trial. Unless the trial includes an adequately large sample of research subjects, its scientific value will be undermined. But close attention to the individual circumstances, attitudes, and values of each patient-subject may create a major obstacle to the recruitment of such an adequate sample.

The moral question at issue, then, is this: When, if ever, is it morally justifiable to sacrifice the patient's right to completely individualized treatment for the benefit of scientific progress? The dilemma that must be confronted arises from the fact that the moral point of view requires that "therapeutic" measures be investigated thoroughly before they become widely used and, at the same time, places serious obstacles in the path of those who would carry out such investigations. To the extent that formal design is sacrificed to individually tailored treatment, scientific rigor will be lost. This course, too, has ethical costs: a therapeutic trial that is inconclusive owing to a poor design will yield questionable results, possible harm to future patients, and a need to repeat the entire experimental process with a new set of subjects and proper controls.

This point was made concisely by Sackett in the *Journal*:

The intervention trial of greatest benefit to patients satisfies three objectives: validity (its results are true), generalizability (its results are widely applicable), and efficiency (the trial is affordable and resources are left over for patient care and for other health research). The first objective, validity, has become a nonnegotiable demand; hence the ascendancy of the randomized trial.⁴

One clear tenet of what we might label "the ethics of design" is that by ensuring validity a properly de-

signed experiment will protect us from a false conclusion of efficacy or failure.

Even here, however, there is a troubling dilemma, for our desire to avoid false conclusions of efficacy may come into conflict with a second desire: to provide the medical community with promising early results of uncontrolled clinical trials. By a happy coincidence, the same issue of the *Journal* cited above, in which scientific validity is declared by Sackett to be a "non-negotiable demand," contains two letters on the same subject, one upholding and one challenging the position expressed by Sackett.

Hollenberg, Dzau, and Williams had published what they considered to be "promising" results of an initial, open, uncontrolled trial of a new therapy.⁵ The ethics of conducting such uncontrolled studies and publishing the ensuing results was challenged by Sacks, Kupfer, and Chalmers.⁶ Sacks declared that the therapeutic study conducted by Dzau and his colleagues should not have been approved by an ethically vigilant human experimentation committee or carried out by ethically conscientious investigators, and that its results should not have been submitted for publication nor, once submitted, published.

The argument in support of these conclusions, briefly, is this: that without adequate controls, the results of such a study lack validity; that to report merely anecdotal experience from uncontrolled and unblinded studies is to risk seriously misleading other investigators and their patients about the effectiveness of a new drug for a life-threatening condition; that once investigators become convinced or persuaded, on scientifically invalid grounds, of the efficacy of a drug, they will then mistakenly consider themselves ethically bound to administer such a drug to their patients and will, accordingly, be unable to enroll their patients in a properly randomized trial; and finally, that when sick patients are placed at risk in the course of experimentation with new drugs, such risks cannot be justified unless rigorous scientific design ensures statistical validity.

Dzau and his colleagues rejected these conclusions, and counterposed an alternative set of values that may override a mechanical insistence on employing randomized clinical trials for all therapeutic research. Their argument can be summarized as follows. It is unethical to undertake the enormous cost and demands of a large, controlled clinical trial until one has collected "some preliminary evidence of efficacy"; moreover, it is impractical to carry out full-scale randomized clinical trials without such preliminary data because of the difficulty of recruiting patients in the absence of favorable preliminary indications; and, when preliminary uncontrolled trials produce dramatic evidence of therapeutic benefit, the medical community is entitled to receive notice of this evidence so that it can consider enrolling appropriate patients in subsequent controlled trials. From this it follows that it is not only ethically permissible but ethically mandatory that such uncontrolled studies be undertaken and that

their results, at least in certain circumstances, be published.

I do not believe that this conflict of values can be easily resolved, but it can perhaps be reduced to some extent by the introduction of some additional restricting qualifications. The availability of resources will inevitably operate as a constraining factor, but every clinician is under an obligation to conduct therapeutic trials with as much statistical and methodologic rigor as possible. Patients who are invited to participate in clinical trials should be apprised (at least in some general manner) of the degree of rigor built into the experimental design. When an uncontrolled clinical trial produces results so dramatic and noteworthy that it is deemed essential to present preliminary data to the medical community, those who release such speculations are under a stringent obligation to issue clear and unmistakable warnings about the unproved status of their results. The advantages to the medical community of receiving such early notice must be set against the dangers that either the medical community itself or the general public (which is usually less sophisticated in these matters) may place unwarranted and potentially harmful constructions on the data.

One is faced here with the need for some kind of judicious balancing act. Broad guidelines appear to be more appropriate than rigid rules. Risks and benefits must be weighed and assessed on a case-by-case basis. Both the costs of undertaking scientifically ill-founded studies and the harm from publishing unreliable speculations are worryingly high. But any blanket prohibition against such research and publication would itself impose an unnecessarily high cost — namely, the loss of certain very considerable benefits, at least in some circumstances.

INFORMED CONSENT

Closely related to the foregoing is a moral problem, raised by randomized clinical trials, that involves the requirement of informed consent. The patient who is invited to become a research subject is clearly entitled to know that he is taking part in an experiment; and he has a right to know that he may decline to participate. He is clearly entitled to know also that the treatment used in his case is one whose efficacy has not yet been established. The issue becomes more problematic, however, when one asks whether the patient also always has a right to be informed that his therapy is being selected by a randomizing device.

There is some reason to fear that such full disclosure would be an insuperable obstacle to recruitment of volunteers in sufficient numbers and would thereby make it impossible to perform further randomized clinical trials. Since such trials are of great importance to medical advances, it might be contended by some researchers that when there is nothing to choose between the treatments, the patient-subject need not be informed of the method (randomization) by which his particular treatment will be chosen.

It is ethically unnecessary to disclose the fact of randomization, so the argument goes, so long as the patient knows everything a reasonable person would need to know to reach a decision. To resolve this issue one must decide whether the fact of randomization is "materially relevant." This is a requirement both of law and of morality. But how are we to interpret the requirement in this instance?

Every potential research subject is legally and morally entitled to undertake his own evaluation of the risks and benefits and to bring to bear his own attitudes and values in reaching a decision. He is entitled to have the opportunity to view himself and to be viewed by the investigator as a joint venturer or a partner in the enterprise, rather than as raw material. (Some physicians would insist that this should also be the norm, the paradigm, for the nonexperimental doctor-patient relationship.) Consent makes this relationship possible, and represents the duties of fidelity and loyalty owed to each other by researcher and subject.⁷

Of course, the moral legitimacy of an experiment requires more than simple consent. If a person agrees to become a research subject without first having been given adequate information in a form that he can understand, then he has not really had an opportunity to decide his own fate. He has been used as a guinea pig, treated as an object or thing, rather than as a person or co-adventurer.

Since the purpose of the doctrine of informed consent is to make meaningful the research subject's right to autonomy, the patient is entitled to receive all the information relating to his choice that will facilitate his deliberations. All risks potentially affecting the decision must be unmasked.

Those who favor withholding from patients the information that, once they become research subjects, their treatment will be chosen according to a randomizing formula rather than according to the individual judgment of their physician can argue that no disclosure is necessary because there is nothing material to disclose. So long as no "better treatment" is known — and this will be the case until the results from the experiment are in — the patient cannot legitimately complain. No material information has been withheld.

Against this view, I would argue that information is material and ought to be disclosed, even if it would not influence a reasonable person, when it is known that it would (or might) influence the potential subject. It seems likely that many patients would be influenced by knowing that selection of treatment was to be randomized. Indeed, it is because of the fear that many patients would be (unreasonably) influenced that some investigators would like to withhold the information. Whether or not it is rational for potential subjects to be influenced by such information (and I agree that it is not entirely rational), it is their right to have it. To withhold from the subject information relating to the process by which the treatment method is to be selected would be, in effect, to usurp the subject's right to

autonomy. I conclude, therefore, that it is unethical to solicit consent from prospective subjects for a randomized clinical trial without informing them of the manner in which their treatment will be selected.

THE PROBLEM OF TREATMENT PREFERENCE

It is widely accepted that physicians have an ethical obligation to provide the best treatment available for their patients and that this obligation generally overrides such competing goals as the desire to promote scientific knowledge. The recruitment of patients as research subjects for randomized clinical trials is nevertheless held to be morally permissible because, before such trials are completed, we do not actually know which is the best treatment. Consequently, the randomized clinical trial is not inconsistent with the physician's duty to provide the best possible treatment for his patient.

There is, however, a difficulty with this line of reasoning. It is true that before scientific testing of various treatment alternatives is completed, physicians cannot know which is the best treatment for any given patient. But it is also true that most physicians will have from the outset some sort of treatment preference based on incomplete scientific evidence. Such a treatment preference (for conservative as opposed to radical mastectomy, let us say) on the part of the physician falls well short of knowledge and might even be labeled a bias or hunch. The point is, however, that physicians will seldom be truly indifferent to the alternatives being tested. If the physician informs the patient of an intuitive preference, is it likely that the patient will then consent to participate in a clinical trial in which, because of the randomized nature of treatment selection, he may receive a treatment different from the one preferred by the physician? Will the patient readily distinguish a merely intuitive preference on the part of the physician from a scientifically based preference? The fear harbored by many medical scientists is that once patients learn that the physician has a preference with respect to available treatments, they will decline to participate in any clinical trial in which an alternative treatment may be substituted. The adverse effects of such reactions on medical experimentation are potentially severe.

At this point in the argument, one may opt for any of several alternative ethical positions. One could, for example, reject the initial assumption that physicians have an absolute ethical obligation to provide the best treatment for their patients. One could, that is, invoke such competing values as the advancement of medical knowledge and the benefit of humanity (including future generations) to justify withholding from patients the information that their doctor has a treatment preference. In support of this position, it might be noted that for the many centuries before the advent of the randomized clinical trial, a period in which medical progress depended on ad hoc clinical judgments, medical interventions were typically inefficacious when

they were not positively dangerous to the health of the patient. If a study of the history of medicine reveals anything, it reveals that clinical judgment without the check of scientific controls is a highly fallible compass.

A critic may object, however, that the utility of the randomized clinical trial is not really in dispute. One could readily concede that the preference of a physician, unsupported by adequate scientific evidence, is relatively unreliable, but one might nevertheless insist that patients are entitled to know of such preferences (accompanied by appropriate warnings as to their merely intuitive nature). For a physician to withhold such information would be to violate his patient's right to the best possible care. This is an important right, a fundamental part of the implied contract between doctor and patient. It would be quite wrong to violate it lightly. But this is not necessarily to confer on it an absolute status. There may be circumstances in which other, competing values are entitled to an even higher priority. The truly difficult task for society, in cooperation with medical scientists, is to identify such circumstances with sufficient care so that what should be an unusual and infrequent violation of a basic right does not expand to become a common and frequent occurrence.

A FURTHER PROBLEM

Let us suppose that a physician has obtained consent from his patient to participate in a randomized clinical trial. The contract for experimentation is based, at least in part, on the patient's understanding that the physician has no present treatment preference. Let us further suppose, however, that as the early data from the trial become available for interpretation, a trend seems to be developing that favors one treatment over another. Is the physician then morally obligated to withdraw his patient from the trial? If not, is the physician morally obligated to convey this information to the patient so that the patient can choose whether to continue or to withdraw?

From the medical researchers' point of view, such withdrawals, if they were to become numerous, could well vitiate the scientific value of their work. The medical scientists might argue that it would often be scientifically inappropriate to rush to judgment on the basis of early data. Long-term as well as short-term effects may be important, and in any case, proper treatment decisions should not generally be based on a single clinical trial, however rigorous and well conducted. Moreover, such decisions should not generally be based on incomplete early data. Efficacy and safety can be adequately assessed only on the basis of a large body of data and only by those with proper scientific training. Again, the history of medicine provides us with innumerable cases of hasty judgments that were later modified or reversed in the light of subsequent studies and clinical experience.

The conclusion of this line of reasoning is that physicians should not, in general, withdraw their patients

from clinical trials because of a treatment preference based on incomplete data, nor should they inform their patients that they have changed from being indifferent to the method of treatment to having a preference. Patients are not in a good position to assess the strength of the scientific evidence, and numerous patient withdrawals would have potentially disastrous effects on medical research.

One must, I think, concede the force and plausibility of this line of argument. But its conclusion is worrying. Can it really be proper for physicians to permit patients committed to their care to receive treatment that appears — on the basis of the available evidence — to be less than the best? What does this do to the physician's oath, "The health and life of my patients shall be my first consideration"?

Such a practice, if it were to become widespread, would represent an important shift from a patient-centered to a social-welfare-centered ethic. Perhaps such a shift is overdue and should be welcomed. Critics of the medical profession have been suggesting for some time that modern medicine is too individualistic. A wider social focus might be considered ethically preferable.

Those who would accept such a change of ethical orientation by the medical profession ought nevertheless to be concerned about the element of betrayal of trust that is involved. The implicit contract on which the doctor-patient relationship now rests commits doctors to place the highest priority on their patients' health and to provide patients with all the information they need to give informed consent. To sacrifice (or to risk sacrificing) the patient's best interests by withholding from him information that might well lead to his withdrawal from a randomized clinical trial violates that contract.

On the other hand, perhaps there are ways to avoid such a violation of trust. The patient could be informed from the outset that one of the ground rules of a particular randomized clinical trial required that the physician not act on trends emerging from incomplete data, not even to apprise the patient of such early results. The patient would then be in a position to take this into account in making the decision to become a research subject. Having been given this information, the patient would not be able to complain later that he had been duped or deceived. The advantages of participation in randomized clinical trials might still outweigh those of refusal, so the interests of science would be protected equally with the right of the patient to know where he stood.

CONCLUSION

In this discussion I have canvassed arguments relating to a number of ethical problems associated with randomized clinical trials. Several conclusions have emerged, albeit tentatively, from the discussion.

The physician who enlists his patient in a randomized trial faces at least the possibility of a conflict of obligations. In many cases the tension between the physician's traditional role as healer and his modern role as scientific investigator can be resolved without serious cost either to the patient or to science. In other cases, however, the tension may reach the level of outright contradiction. The Hippocratic principle of exclusive commitment to patient welfare, with its corollary of totally individualized treatment, may sometimes properly be modified so as to permit randomized clinical trials to proceed with a statistically significant sample of subjects. The circumstances in which it is ethically permissible to abrogate the Hippocratic principle are in need of careful definition.

It is generally unethical to solicit consent from prospective subjects for a randomized trial without telling them how their treatment will be selected. It may, in some circumstances, be ethically permissible for a physician to withhold the information that he has an intuitive treatment preference. But again, some carefully worked out criteria are needed to define when it is and when it is not appropriate to withhold such information from the potential research subject.

Finally, the physician whose judgment concerning competing treatments undergoes a change in the course of a randomized clinical trial may keep his patients in the trial and may withhold the interim adverse data from the patient, but only if the patient has given antecedent consent to such a procedure. Without the patient's consent, such a practice would constitute an unethical violation of the patient's rights and would risk undermining the trust on which the doctor-patient relationship rests.

REFERENCES

1. Shimkin MB. The problem of experimentation on human beings. I. The research worker's point of view. *Science*. 1953; 117:205-7.
2. Fried C. Medical experimentation: personal integrity and social policy. In: Beam AG, Black DAK, Hiatt HH, eds. *Clinical studies*. Vol. 5. New York: Elsevier Press, 1974.
3. Gray BH. Human subjects in medical experimentation: a sociological study of the conduct and regulation of clinical research. New York: John Wiley, 1975.
4. Sackett DL. The competing objectives of randomized trials. *N Engl J Med*. 1980; 303:1059-60.
5. Hollenberg NK, Dzau VJ, Williams GH. Are uncontrolled clinical studies ever justified? *N Engl J Med*. 1980; 303:1067.
6. Sacks H, Kupfer S, Chalmers TC. Are uncontrolled clinical studies ever justified? *N Engl J Med*. 1980; 303:1067.
7. Ramsey P. The patient as person: explorations in medical ethics. New Haven: Yale University Press, 1970.