

Ethical Considerations in Human Experimentation\*

G. A. Andrews

From: Proceedings of the 12<sup>th</sup>  
Annual Bio-Assay  
and Analytic Chemistry  
Meeting.  
Gatlinburg, TN  
Oct 13-14, 1966.  
Sponsored by ORAU, ORNL,  
ORADP and OR-Y-12.

During the past three or four years scientific journals and popular magazines have contained an increased number of articles about the ethics of human experimentation. Most of the writers "point with alarm" expressing concern that investigators, in their zeal, are being careless of the rights of the patient who serves as an experimental subject. This concern has been precipitated by publicity given to certain research activities. The Congressional investigators of the drug industry revealed some serious abuses. When the experimental injection of cancer cells into aged patients in a New York charity hospital received widespread condemnation in print, organized medicine felt the need to go on record as disapproving the method in which the study was carried out.<sup>1,2</sup> The attention given to this problem has been greatly accentuated by Dr. Henry K. Beecher, of Harvard Medical School, who has written extensively about it.<sup>3,4</sup> In my opinion, Dr. Beecher, like most men aroused in an intensely emotion-laden mission, has on occasion made misleading and exaggerated statements.<sup>5</sup>

Although there is recent emphasis on this problem, it is quite erroneous to suggest, as some lay science writers have, that it was largely neglected in the past and that until recently investigators have given little thought to the ethical aspects of human experimentation. Furthermore, it is incorrect to assume that, because a publication of scientific data makes no reference to consent from experimental subjects, such consent was not obtained.

Nevertheless, it is widely recognized that a serious problem does now exist and we may well seek the reasons for it. One is, obviously, the great increase in research of all types that is now being done and the corresponding increase in possible abuses. With this has come the growth of institutions and, in some projects staffed by a large group of physicians, a reduction in personal contacts between the individual physician-investigator and the patient. With the progress of medicine away from simple trials of therapy toward a search for basic knowledge, we find that a larger share of the investigations are concerned with studies not directly related to a practical trial of therapy; thus the subject may have little to gain directly. There is, or is believed to be, a growing intensity of competition among investigators, a desire for recognition, and a desire for academic posts that are filled on the basis of research achievement. Thus we have the opportunity for the investigator to let selfish interests

\*From the Medical Division, Oak Ridge Associated Universities, Inc., Oak Ridge, Tennessee, operating under contract with the United States Atomic Energy Commission.

predominate over his concern for the experimental subject. Whether or not such a trend exists, there is no doubt that the public has decreasing faith in the nobility of motives of physicians, and that patients are showing an increasing tendency to sue their physicians for malpractice, real or alleged. (Incidentally, except in connection with the trials of new drugs, there have been few if any lawsuits against physicians on the basis of acts performed in the course of clinical experimentation.) Quite different from the unduly ambitious investigator is the one who with completely unselfish motives becomes so fervid in his desire to help mankind that he uses poor judgement in relation to the risk to the individual patient-subject.

Whatever the reasons and explanations may be, there is no doubt that some experiments not ethically justifiable have been performed in recent years. Yet, an unresolved question is, How extensive is this problem? It is a truism that in all large fields of human endeavor one could, with careful search, find some examples of unsavory conduct. There is always the danger that a worthwhile activity will be discredited or destroyed because some publicity seeker dramatizes the exceptional, evil cases and gives the impression that the practices represented are typical. A balanced assessment of the whole field - "...on the one hand this is good, while on the other hand the weaknesses are..." - never attracts the attention that the muck-raking approach can yield.

No one really knows how much of experimental medicine is open to challenge on ethical grounds; certainly this cannot be clearly evaluated without more intimate knowledge of what goes on than can be obtained from the published scientific literature. Furthermore, to put the findings in perspective one might need to compare them with some other activities; for example, the ethics of behavior toward patients of physicians not engaged in research. Lacking the hope of any such informed appraisal we must rely upon opinions. My own is that we are not facing an appalling situation but that we have a clear need for improvement.

In considering codes of ethics for investigators we need to be conscious of the various relationships that may exist between the investigator and the person who is the subject of the experiment. Subjects of experiments may fall in the following categories (and possibly others):

1. Independent normal volunteer (paid or donating service),
2. "Volunteer" who is in employ of laboratory, in military service, or in prison,
3. Self-experimenter,
4. Patient volunteers -
  - a) Research directed toward diagnosis or therapy needed by subject,
  - b) Research directed toward advances in diagnostic or therapeutic methods in general, or toward basic scientific advancement, unlikely to be helpful to the volunteer,
  - c) Subjects serving as controls,
5. Healthy person taking new preventive material (i. e., vaccine) that may be potentially useful to him,
6. Tissue donor; research directed toward direct benefit to another person, related or unrelated.

This list clearly shows that ethical aspects of research vary greatly from experiment to experiment. No simple set of rules can deal specifically with all possible situations, but some rather general codes have been presented that give

useful guidelines. For background, the ancient Hippocratic Oath, and the interesting writings of Claude Bernard, in the middle of the last century, may prove useful. Relatively recent, carefully elaborated statements include the Nuremberg Code (1947),<sup>1</sup> the Declaration of Helsinki (World Health Organization) 1964,<sup>7</sup> and the statement by the British Medical Research Council, 1964.<sup>8</sup> Of these, the last seems to me the most useful because it attempts to cope in some detail with the subtleties involved. Beecher<sup>4</sup> has also stated general principles.

Among the considerations that are important in these codes and in our thinking about the subject are the following:

Informed Consent - Great emphasis is placed on the effort to have the subject truly understand the meaning of the experimental procedure in which he is to participate. Those who have dealt with this problem in practice realize that it is an ideal to be aimed at rather than an objective that can be achieved. Even a relatively simple experiment may be quite beyond the ability of the average patient to evaluate. Risks are never known with great accuracy, and the patient often decides on the basis of some intentional or unintentional signal from the physician he trusts, even if the experiment is being done by another physician.

Nevertheless, consent can be clearly given or refused, and it is important to have it documented. Whether it will often be really informed consent is another matter.

The Quality and Competence of the Research - The more hazardous the procedure, the more important it is that adequate preliminary work (i. e., animal experiments) be done, that relevant previous publications are known and considered, and that suitable precautions are taken. The potential value of the research must be thoroughly evaluated. Often the participation of a group of investigators is needed, as is the evaluation by independent physicians having no direct interest in the research and enlisted specifically as the protectors of the patient's welfare.

In our culture the supremacy of the rights of the individual is much stressed. Thus we are reminded that we must not take the responsibility of sacrificing, even to a small extent, one person's rights for the sake of helping many people even to a great extent. I am in agreement with this principle; I do not always find it easy to interpret in relation to specific research situations.

While performing a valuable service, those who have sounded the alarm about improper research practices need to be on guard against making unfair judgements and impairing research progress. They should remember that hindsight is a dangerous thing. For example, five years ago one could say, with a good deal of experimental data in support, that when cancer cells were taken from one person and injected into another, genetically different person, they would never survive and produce clinical malignancy in the recipient. Now there are reports of rare but definite exceptions to this rule. This new information may tempt us to change our evaluation of the ethical soundness of some previous research. It has been quite rightly pointed out, however, that research is either ethical or not at its inception.

Those who establish controls on any human activity often assert repeatedly that they do not wish or intend to restrict productivity. It should be clear, however, that denial of intent to restrict research accomplishments does not indeed prevent the

impairment in productivity that may result when the fears engendered in administrators lead to new regulations. One might concede that some restriction on achievement is a fair price to pay for increased protection to experimental subjects; if so we should pay it knowingly.

I have not attempted to even suggest the positive benefits that may accrue to the person who volunteers as an experimental subject. This is a topic that deserves much more attention than it has received in recent publications.

It is worthwhile that we have had our attention directed to the ethics of human experimentation. The main responsibility for dealing with it should be in the hands of the investigators, and future standards will depend largely on their integrity and conscientiousness. Scientific journals can perform a useful service by requiring that manuscripts indicate the nature of consent obtained from experimental subjects. It is to be hoped that if scientific administrators feel impelled to react to recent criticism with increased restrictions, the new rules will be carefully planned so as not to unduly inhibit good, desirable, ethical research.

#### REFERENCES

- 1a. E. Langer, Human Experimentation. Cancer Studies at Sloan-Kettering Stir Public Debate on Medical Ethics, *Science*, 143: 551-553 (1964). (This includes the Nuremberg Code.)
- 1b. E. E. Mandel, Experimental Cancer Cell Implants in Patients, *Science*, 144: 486 (1964).
2. E. Langer, Human Experimentation: New York Verdict Affirms Patient's Rights, *Science*, 151: 663-666 (1966).
3. H. K. Beecher, Experimentation in Man, American Lecture Series, A Monograph in American Lectures in Medicine, Publication No. 352, Charles C Thomas, Springfield, Illinois, 1959.
4. H. K. Beecher, Some Guiding Principles for Clinical Investigation, *JAMA*, 195: 1135-1136 (1966).
5. H. K. Beecher, Ethics and Clinical Research, *New Engl. J. Med.* 274: 1354-1360 (1966).

6. Claude Bernard, *An Introduction to Study of Experimental Medicine*, MacMillan Company, New York, 1927, pp. 101-102.
7. Human Experimentation, Code of Ethics of the World Medical Association (Declaration of Helsinki), *Brit. Med. J.*, 2, 177 (1964).
8. Responsibility in Investigations on Human Subjects, *Brit. Med. J.*, 2: 178-180 (1964).