CONSIDERATIONS IN THE PROTECTION OF HUMANS AS SUBJECTS OF RESEARCH[1]

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The need to protect human research subjects without obstructing potentially vital research has been with us ever since human civilization began. The following piece describes development and implementation of protective measures currently employed in the United States.

Introduction

The histories of medicine, medical law, and medical research, all begin approximately 2,500 years before the dawning of the Christian era. In 1750 B.C. the Code of Hammurabi proclaimed that a physician who performed a new operation and caused the death of his patient should have his right arm removed. A little over a century later, Persian law repeated the penalty, but allowed the physician to go free if he had previously performed the operation on no less than three unbelievers. Although this undoubtedly made medicine safer for most Persian citizens, all worshipers of Zoroaster, it undoubtedly increased the risks for worshipers of other gods such as Baal and Moloch.

Throughout subsequent history there have been repeated instances of the use of certain segments of the population as research subjects. In 1756, in England, during the reign of George II, six condemned criminals who had not had smallpox were forced to lend themselves to vaccination trials. Later, since these criminals were adults and vaccination was to be practiced on children, half a dozen "charity children" belonging to the St. James parish were experimentally inoculated, all without injury. Just a little over 10 years later, in 1767, the English courts introduced the doctrine of "informed consent" into the practice of medicine, if not into that of medical research. The doctrine, in essence, stipulates that a patient must be given a fair and reasonable explanation of what is to be done to him, the nature of the accompanying risks, and the probable benefits.

The doctrine was first applied to the field of medical research in the case of *United States vs. Karl Brandt, et al.*, heard before the Military Tribunals at Nuremberg, Germany, following the destruction of the Nazi Government in 1945. In the judgment on this case the Tribunal listed principles to be observed in permissible medical experiments. These principles, which constitute what has become the "Nuremberg Code," state, in brief, that:

- The voluntary consent of the subject is absolutely essential.
- The experiment should be based on the results of previous animal experimentation and on a knowledge of the natural history of the problem, so as to insure that the outcome of the experiment will be fruitful.
- The experiment should avoid all unnecessary risk and suffering.
- The degree of risk should never exceed that determined by the humanitarian importance of the problem.
- The experiment should be terminated at the request of the subject, or whenever the risks, in the opinion of the experimenter, have become excessive.

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This document, conceived in the aftermath of the Nazi terror, was never widely adopted as an international guide to medical research. It is not applicable to research that does not involve supposedly competent adults, and does not clearly relate to research in a clinical setting. In 1964 the World Medical Association adopted the so-called "Declaration of Helsinki" which has been widely adopted as the standard for performance of medical research.

The Research Review Committee

Background

At about the same time, both the British Medical Research Council and the U.S. Public Health Service reached the conclusion that static codes and medical practice laws could not be relied upon as sole guarantors of research subjects' rights. During discussions in both countries, it was agreed that a decision to depart from standard and accepted medical practice in a systematic program of clinical investigation should require the approval of the investigators' peers and associates. To this end, we have established committees in our research institutions to pass judgment on all research proposals.

This judgment does not bring into question the integrity, competence, or good faith of any investigator. On the contrary, in the absence of these qualities in the investigator the review is meaningless. No amount of careful review and counsel by his peers can prevent a dishonest or unscrupulous investigator from disregarding the rights of his patients. As in every country, the remedy for such disregard lies in the judicial system.

What peer review can do is to extend the knowledge of the investigator, and to make him more aware of potential scientific, ethical, and moral pitfalls. It is one of the unhappy truths of this age that our ability to acquire new knowledge has greatly exceeded our ability to absorb, digest, and utilize it. The competent surgeon attempting a new procedure can, in our opinion, profit from the advice of his fellow surgeons, physiologists, psychiatrists, pharmacologists, and other scientists. In some especially difficult areas, such as transplant surgery, complex problems (related to life and death, the cause of death, or the psychological impact of carrying within you a dead donor's beating heart) may make the advice of priests, lawyers, and experts in other nonscientific fields extremely valuable.

Since 1937 the Public Health Service has employed a peer review system in the United States to study applications made for research support grants by the nation's universities and laboratories and, to a lesser degree, by the universities and laboratories of other nations. This peer review is discipline-oriented: Surgeons review surgery proposals; pathologists, pathology proposals; radiologists and radiation physicists, proposals in radition. Only 2 per cent of the thousands of proposals reviewed in any one year raise questions about undue risk of injury. Likewise, only a very small percentage raise ethical questions.

For many years, after a particular application was approved and a grant made, the investigator was left free to pursue his research goals unhindered by further advice from our reviewers. In 1966, after several demonstrations of poor judgment on the part of investigators, leading to extensive public criticism and law suits against investigators, hospitals, and the Government, we decided to extend the peer review system into the institutions themselves.

The Review Committee Today

At the moment more than 650 United States institutions have established internal review committees to oversee research actively in progress inside their walls. Although these committees were originally established to review only work supported by the U.S. Public Health Service, they now review practically all such research.

Typically, a university will have more than one committee. One will serve the behavioral

sciences, one the biological sciences, and one the medical school. Other committees or subcommittees may be established, depending on the relative degree of independence of schools of dentistry, public health, etc. The medical school committees are usually the most active and the most immediately concerned.

The university committee's membership varies, but it usually includes representatives of all major departments and the hospital administration. The nursing and chaplain's services are often represented as well. In the United States, because of the large number of existing religious sects, the religious representation may be supplied by a priest, a rabbi, a protestant minister, or a nondenominational ethicist or philosopher. Legal consultation or representation must be available to the committee.

The committee is required to review each proposed project to:

1) ensure that adequate personnel and facilities are available to deal with any probable emergencies during the experiment;

2) ascertain that the balance between risks and benefits, both to the subject and to the population at large, justify the research; and

3) make certain that adequate, appropriate, and legally effective informed consent will be obtained. The rigor of such consent must reflect the magnitude of the risks to be accepted by the subject.

Since the laws of the several states of the United States vary, even with regard to the practice of medicine, and since our richly varied population includes culturally diverse groups such as Spanish-speaking residents along the east coast and the Mexican border, French-speaking residents in Louisiana and the eastern Canadian border, and Oriental residents on the west coast, the committee is also asked to ascertain the acceptability of the project in terms of institutional practices, local standards of medical practice, applicable law, and local community considerations involving matters such as speech and religion.

When we make grants to overseas institutions we employ much the same standards. Such grants are, unhappily, less frequent today than they used to be, and we do not require a very complex committee–just a small one suited to the size of the project. We do, however, expect the committee to abide by the standards of medical practice of the institution involved, to use applicable law (which usually reflects traditions other than those of English common law), and to take into account community attitudes relating to morals and ethics which may be quite different from our own.

Thus the local review required for institution grantees is broad, and is concerned with local problems. The review conducted in Washington is in-depth and applies only the collective standards of the reviewers. These reviews are not interchangeable. We cannot be aware here of all the problems and considerations that affect individual schools, nor can an individual school assemble a committee with the in-depth competence of our national committees. Both reviews are considered necessary to represent the public interest.

The mechanism is not without its problems. It takes time. It may create personal stresses. It tends to be conservative. It cannot possibly reflect all shades of thought at any one time. Nor does it provide any guarantee against lawsuits or against public or political dissatisfaction with the outcome of a particular experiment.

Nevertheless, the improvement of health has and will depend in large measure upon medical research. And public confidence in research depends to a large degree upon public appreciation that this research is receiving careful scientific scrutiny and that its conduct is characterized by professional self-discipline. As noted by the British Medical Research Council in its 1962-1963 report, "Mistaken or misunderstood investigations could do incalculable harm to medical progress. It is our collective duty . . . to see that this does not happen . . ."[3]

[3]Unpublished report.

SUMMARY

The need for preventing harm to human subjects of medical research without preventing medical research has been with us ever since human civilization began. The present article describes the development of non-judicial measures designed to help meet this need in the United States.

Since 1937 the U.S. Public Health Service has employed internal committees to study university and laboratory applications for research support grants, using what is called a "peer review system." That is, surgeons would review surgery proposals; pathologists, pathology proposals; etc.

In 1966, following a period of extensive public criticism, the Government extended this peer review system into the individual institutions concerned. Under this arrangement, a committee at the institution proposing the research reviews each project to ensure that adequate personnel and facilities are available, to ascertain the balance between risks and benefits, and to make certain that proper consent of the research subjects will be obtained. This is then followed by a similar review at the national level. A comparable two-tiered system is employed in the case of U.S. Goverment research grants going to institutions outside the United States.