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CONSIDERATIONS IN THE PROTECTION OF HUMANS
AS SUBJECTS OF RESEARCH

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CONSIDERATIONS IN THE PROTECTION OF HUMANS AS SUBJECTS OF RESEARCH*

The histories of medicine, medical law, and medical research, all begin approximately 2,500 years before the beginning of the Christian era. In 1750 B.C. the Hammurabi Code 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 Persian medicine safer for the greater number of its citizens, all worshipers of Zoroaster, it undoubtedly increased the risks for the worshipers of other gods such as Baal and Moloch.

Throughout subsequent history there has 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

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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.

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 Health Organization adopted the so-called "Declaration of Helsinki" which has been widely adopted as the standard of medical research conduct.

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 the sole guarantor of the rights of research subjects. In 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 requires the approval of investigators, peers, and associates. To this end, we have established in our research institutions, committees 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. The remedy for disregard lies in the judicial system in every country.

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 extremely difficult areas, such as transplant surgery, complex problems related to life and death, the cause of death, and the psychologic impact of carrying within you a dead donor's beating heart, the advice of priests, lawyers, and experts in other nonscientific fields may be of extreme value.

In the United States, the Public Health Service has, since 1937, adopted a peer review system to study applications for grant support of research by the nation's universities and laboratories and, to a lesser degree by the universities and laboratories of other nations. This peer review is essentially discipline oriented: Surgeons review surgery proposals; pathologists, pathology proposals; radiologists and radiation physicists, proposals in radiation. Only 2 percent of the thousands of proposals reviewed in any one year might raise questions of undue risk of injury. A very small percentage raises ethical questions.

When 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 systems into the institutions themselves.

At the moment more than 650 United States institutions have established internal review committees to review research actively

in progress within their walls. Although these committees were originally established to review only research 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 biologic 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 most active and of most immediate concern.

The committee membership varies but usually includes representatives of all major departments, and of the hospital administration and pharmacy. The nursing and chaplain's services are often represented. In the United States, because of the large number of existing religious sects, the religious representation may be by a priest, 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 the project to:

- 1) assure 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) 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 the composition of our population also varies and includes: Spanish-speaking residents along the east coast and our 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 consideration such as speech and religion.

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

Thus the review required for institution grantees is hard, and is concerned with local problems. The review conducted in Washington is in depth and applies only the collective standards of the reviewers. Since the membership lists of our review groups include names like Amador, Arias, Bilbao, Calarosa, Charache, Colon-Yordan, Cota-Rables, de Cordova, de Luca, Diaz, Eyzaguirre, Fernandez-Pabon, Garcia, and Gonzalez, it seems clear that the thinking of our Spanish and Portuguese-speaking colleagues does play some role in these matters.

These reviews are not substitutions. 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 in the public interest.

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

Nevertheless the improvement of the health of our people has and will depend in large measure upon medical research. However, the people's confidence in research depends to a large degree upon their appreciation of the careful scientific scrutiny of this research, and professional self-discipline in its conduct. 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 ..."