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HISTORICAL AND ETHICAL CONSIDERATIONS IN INVESTIGATIONS INVOLVING HUMAN SUBJECTS[1]

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"If the study to which you apply yourself has a tendency to weaken your affections, and to destroy your taste for those simple pleasures in which no alloy can possibly live, then that study is certainly unlawful, that is to say, not benefitting the human mind."

Mary Shelly
1818

Research involving human subjects plays an indispensible role in the discovery and development of new drugs. The term, "discovery" is not to be misconstrued. I am not suggesting that humans can be used in initial screening efforts with new drug candidates. However, it is important to remember that certain drugs (or their uses) have been serendipitously discovered during clinical investigations. Several examples of such discoveries are well documented in the literature.[2,3]

In recent years, increasingly stringent regulations have been promulgated regarding the use of human beings in all types of research. Stricter regulations have resulted from abuses in the past and a growing federal bureaucracy. While academicians must "publish or perish," it appears that many of our colleagues in Washington have adopted a similar mandate. Seriously, however, there is no question that many governmental officials involved with regulations regarding human subject research are trying to constructively address perceived problems or potential concerns. Many such concerns emanate from the public in the form of complaints to the DHEW Office for the Protection of Research Risks.

This paper was developed to provide historical and ethical perspectives on current regulations pertaining to the use of human subjects in research. It is hoped that it may serve to bring the reader to the point where he/she may better understand the reasons for regulations and perhaps, constructively criticize new regulations and amendments as they are developed.

HISTORICAL PERSPECTIVES

The Magna Carta, sealed in 1215 A.D. by King John, has been characterized as the earliest and perhaps most significant document in all of history that relates to the freedom of mankind and the origins of the Western legal system. While the Magna Carta principally guaranteed political rights, it served as an important (and somewhat ironic) precedent for the American Declaration of Independence and United States Constitution. As will be noted

later, the Constitution is inexorably tied to the rise in Western Individualism in the 19th and 20th centuries.

Roots of concern for humans used in research can be traced to German literary movements in the late 18th and early 19th centuries, and English Romanticism which blossomed during the first half of the 1800's. One of the more famous German Romantics, E.T.A. Hoffmann, produced a series of Kunstmärchen (art fairy tales) which later became known as the "Tales of Hoffmann."[5] In the German Kunstmärchen, according to Kent and Knight[5], "....the uncanny, the mysterious, the horrible, the grotesque, and prosaic merge with startling and deceptively simple ease." One of Hoffmann's most famous tales, "Der Sandmann" ("The Sandman"), records the story of a young college student, Nathanael, who falls in love with the beautiful Olympia. However, Olympia turns out to be an automaton; the creation of the mad Professor Spalanzini and the Disney-like creator, Coppelius who have deceived the unsuspecting young man. Upon discovery of the evil trickery, Nathanael ultimately goes insane and dies in a futile attempt to kill Coppelius.

Dr. Joseph Brady, a Professor at Johns Hopkins University, who served on the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, suggests[6] that Hoffmann's "Der Sandmann" is a portent of the deceit that would blemish some of the human investigations witnessed in the mid-twentieth century.

The antecedent concern for human investigations both from the perspective of the subject and the investigator is probably best

exemplified through Mary Shelly's, "Frankenstein."[7] The story resulted from an impromptu competition devised by the poet Shelly, Lord Byron, his secretary Polidari and the author during a wet summer holiday in Switzerland. What resulted, is a tale that has intrigued innumeralable readers and twentieth-century movie-goers.

Mary Shelly typifies the liberal rationalist's view of man's innate goodness, and the ability of man to improve and control his/her conditions. However, Shelly warns that power can rise above reason. For the scientist Frankenstein,[7] his months of research and hard work in the laboratory were at the expense of his family and human feeling (see quote before introductory paragraph). Thus, Frankenstein, because of his unruly "progeny," is at once, creator and slave to his creature. This is an outstanding literary precedent to the concept of what we now commonly refer to as a risk/benefit ratio.

The Frankenstein myth is a romantic version of the Faust legend and expresses an awareness of the duality in man. This same theme subsequently appears in Oscar Wilde's "Dorian Gray," Robert Louis Stevenson's, "Dr. Jekyll and Mr. Hyde," and Edgar Allan Poe's, "Wilkinson."

Evolution of Ideas and Attitudes in the Middle and Late 19th Century

As the 19th century progressed, a rise in Western Indivfdualism occurred. This has been characterized by Professor Brady[6] as an, "...autonomous challenge to previous paternalistic practices which were previously assumed to be beneficial to the individual."

Simultaneously, scientific rationalism developed and a shift in the notion of medicine and the physician as strictly providers of primary care. There was an emerging sense that the physician had the responsibility of developing knowledge for the benefit of others. However, as early as 1865, the famous French physiologist, Claude Bernard expressed ambivalence over the seemingly contradictory interest of human experimentation and the maintenance of human dignity.[1]

Events of the 20th Century

Historically speaking, the so-called Tuskegee (Alabama) study was one of the first investigations where clear violations of human rights were documented.[10] In the 1930's, the U.S. Public Health Service began a study of the long-term effects of syphilis. Two groups of Black males were used. One group had syphilis while the control group was diagnosed as being disease free. Both groups were appropriately treated for all ailments except syphilis. The study extended into the 1960's; well after various penicillins were available to cure the venereal disease. Though revelations of the Tuskeegee Study in the 1970's received much attention in the media, its influence on legislation was added to that of a number of other events occurring during the period 1940 to 1970.

After World War II, descriptions of Nazi experiments[11] with human beings shocked and horrified the world. The relevations brought out during the Nuremberg trials resulted in a death sentence for seven defendents, four of which had been trained as physicians. More importantly, the United States Military Tribunal formulated a

set of guidelines for conducting medical experimentation. These proposed rules laid the foundation for many subsequent agreements and regulations and are provided verbatim[11] for the reader's interest.

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent, should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be make know in him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   The duty and responsibility of ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurably by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur: except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment, the human subject

should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment, the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

After the war and on into the 1950's, the World Medical Association and medical societies in the United States and the United Kingdom adopted codes of ethics similarly worded to those of the Nuremberg recommendations.[12] Despite these commitments and the requirement of consent forms mandated by the 1962 amendments to the Food, Drug and Cosmetic Act of 1938, serious violations of human rights continued in biomedical experimentation on into the early 1960's.

In 1966, Beecher[13] published a landmark paper in the New England Journal of Medicine. Beecher[13] documented 22 examples of studies published in reputable medical journals which revealed serious breeches in ethics. In the author's words, "Evidence is at hand that many of the patients in the examples to follow never had the risk satisfactorily explained to them, and it seems obvious that further hundreds have not known that they were the subjects of an experiment although grave consequences have been suffered as a

direct result of experiments described .... Included in the Beecher article[13] were the famous (or infamous) Willowbrook Study and what has become known as the New York Jewish Chronic Disease Hospital Case.[14] In the Willowbrook study, hepatitis was induced in mentally defective children in which a mild form of hepatitis was endemic. While the parents gave consent to an intramuscular injection or oral administration of the virus, they were not informed of the appreciable hazards involved.

In the Jewish Chronic Disease Hospital case, live cancer cells were injected into 22 human subjects as part of a study of immunity to the disease. The subjects apparently were just told that they ....."would be receiving some cells....," the word cancer was not used.

Beecher[13] also reviewed a number of incidences of unethical conduct in clinical studies involving drugs and the evaluation of drug-treatment. In one case, the relapse rate in typhoid fever was studied in patients treated in two different ways. At the time, chloramphenicol was recognized as an effective treatment of typhoid. A subject pool of 408 charity patients was selected. Of this group, 251 were treated with chloramphenicol while 157 were symptomatically treated but did not receive chloramphenicol. The chloramphenicol-treated group had 20 deaths (7.97%). In contrast, the group deprived of test drug suffered 36 deaths (22.9%)

A second drug study cited by Beecher[13] involved investigation of the hepatotoxicity of triacetyloleandomycin. At the time, spotty

evidence of hepatic dysfunction had emerged and a study in 50 patients, ages 13 to 93 was carried out. The patient population included mentally defective children and juvenile deliquents who were inmates in a children's center. According to the investigators, ... "By the time half the patients had received the drug for four weeks, the high incidence of significant hepatic dysfunction.... led to the discontinuation of administration to the remainder of the group at three weeks." However, it is noteworthy that the investigators reported 54% of the patients revealing abnormal excretion of bromsulfophthalein after only two weeks! Eight patients were subjected to one or two liver biopsies and one-half of this group was further subjected to a "challenge" dose of the drug. Besides the obvious lapses in ethical judgment related to continuing with the drug treatment, it is important to emphasize that liver biopsy per se held an estimated 2 to 3 per 1000 chance of death at the time!

Beecher concluded his study with two important judgments:[13]

1) "Ordinary patients will not knowingly risk their health or their life for the sake of 'science.' Every experienced clinician investigator knows this. When such risks are taken and a considerable number of patients are involved, it may be assumed that informed consent has not been obtained in all cases.

   The gain anticipated from an experiment must be commensurate with the risk involved.

2) An experiment is ethical or not at its inception; it does

not become ethical post hoc - ends do not justify means. There is no ethical distinction between ends and means."

In the same year that the Beecher article was published (i.e. 1966), the National Institutes of Health began requiring the establishment and functioning of Institutional Review Boards (IRB's) for grantee institutions. In the early 1970's, revelations of the Tuskeegee study prompted passage of the National Research Act in July of 1974. This act created the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research and help promulgate a set of regulations that are currently supposed to be followed in the conduct of human investigation.[15]

The National Commission, before being disbanded, issued the so-called "Belmont Report" in 1978.[16] This document served as the basis for a proposed new set of regulations (published in 1979) which are currently under review. Overall, the regulations presently in force define informed consent procedures, mandate the composition and function of the IRB, and set out requirements for consent forms. The new regulations, if adopted, may provide for expedited review of certain types of innocuous research (primarily in the social-behavioral sciences) and more carefully define the roles of investigators and IRB's in the evaluation and implementation of human subject research.

Before leaving this section, it is important to recognize that many highly ethical drug studies were conducted after World War II. Furthermore, the risks in drug research should not be overemphasized.

For example, Zarafonetis et al.[10] recently reported on the incidence of clinically significant adverse effects in Phase I investigations. Their report involved evaluation of 805 protocols with 29,162 participants and over 614,000 subject days. The studies were performed during a period of twelve years prior to 1977 and involved 64 significant medical events, of which 58 were characterized as adverse drug reactions. Thus, the incidence of adverse drug reactions in Phase I trials may be only about 0.2%. Furthermore, individuals close to the regulatory process[5,6] report a lack of reports of horrific or malevolent practices in modern biomedical research. However, even Beecher[13] did not indict the medical and pharmaceutical establishments for malevolency. Rather, he pointed to benign neglect and occasional over zealousness in achieving research goals as leading causes of situations where the rights or health of patients have been compromised. Clearly, there is cause to take extraordinary care to prevent repetition of the types of violations of human rights that have occurred in the past thirty years even though they have been in the minority.

ETHICAL PRINCIPLES

The United States Constitution and our legal system serves as a guardian of the powerless and the compromised individual. Regulations currently guiding the conduct of human investigations are principally oriented towards protection of human participants. In the following paragraphs, consideration is given to the ethical principles that should undergird research with human subjects.

Boundaries Between Practice and Research

Occasionally, the terms practice and research are confused, partially because the two can occur simultaneously. The term "research" indicates ...."an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby develop or contribute to generalized knowledge...."[16] Furthermore, research usually involves use of a formal protocol (in which the hypothesis is stated) including the procedures to be followed.

Practice may include departures from usual clinical procedures; however, the deviations from standard practice should not be radical and are for the exclusive benefit of the patient being treated. Extraordinary departures from standard practice or objectives that are set to develop knowledge for broader benefit than a single individual, tend to transform practice into research. Certainly, research and practice can be carried out concomitantly. As a general rule, if an activity contains any element of research then it should come before an investigational review board.

Basic Ethical Principles

There are three basic ethical principles that are of greatest importance in evaluating research involving human subjects. These are, respect for persons, beneficence, and justice.[16]

Respect for Persons

The term, "respect for persons" embodies the concepts that 1, individuals should be treated as autonomous beings, and 2, people with diminished autonomy are entitled to extraordinary protection.

In his paper on privacy and research, Kelman[19] uses the term "self-presentation" as the right to exercise control over oneself. The concept of self-determination is also apropos.

An autonomous person is one who is capable of developing personal goals and voluntarily progressing towards these self-initiated objectives. To show "respect for persons" is to honor the opinions and choices exercised by the individual. Violation of this respect is manifest when individuals are denied the right of making informed judgments. Thus, the concept of informed consent is intimately tied to respect for the individual.

Implicit in the notion of "respect for persons" is the idea that extraordinary care must be exercised in cases of individuals who are compromised in any way in making free judgments. The elderly client of a nursing home may gain the feeling that lack of participation in a clinical study may decrease the level or quality of subsequent care. Indigent patients may find themselves in parallel situations.

Beneficience

In the context of human subject research, beneficience pertains fundamentally to the maxims, 1, do not harm, 2, maximize possible benefits and minimize possible harms. Thus, it is incumbent on investigators not only to respect the decisions of subjects and to protect them from harm, but also to secure their well-being.[16]

The concept of beneficience is embodied in the Hippocratic Oath and was first extended by Claude Bernard[9] into the realm of research.

Over 100 years ago, Bernard stated that one should not injure persons regardless of the benefits that might come to others. Of course, it is impossible to eliminate risks in many clinical studies. However, the principle of beneficience demands that investigators and other pertinent members of their institution give sufficient forethought, planning, and effort to minimizing risks.

Justice

The concept of justice pertains to "fairness in distribution" or "what is deserved." Justice, in various social contexts, has been defined in terms of 1, to each person an equal share, 2, to each person according to need, 3, to each person in proportion to his/her effort, 4, to each person according to merit or overall contribution to society.[16] In research, justice pertains to subject selection. Are subjects being studied or engaged in a study merely because of their ready availability, their compromised position or manipulability rather than their true suitability for the investigation? For example, justice was certainly violated in the Tuskegee study!

Taken in broader perspective, justice can be thought of in terms of the beneficiaries of publicly supported research. Justice demands that no group be selectively chosen to suffer the risks of research who will not ultimately benefit from results.

In summary, "respect for persons" relates to informed consent and the freedom subjects are permitted in choosing to participate in research. Beneficience embodies maximizing benefits and

minimizing harm in investigations. Justice involves equity in the selection of subjects for investigations.

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