Human Experimentation and Research

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How do physicians find out what is a safe and effective treatment for sick human beings? One way is to consider the accumulated medical practice of the past. Usually by trial and error the physicians of the past determined what was effective for curing one or other disease condition of their patients. As a fact, errors were made but lessons were learned and passed on to the medical community. Some of these past researches were to a degree systematic, some were haphazard; much depended on the physician's previous training and experience. Generally, such attempts were motivated by the desire of the physicians to help their patients. Gradually, the *armamentarium* of the practicing physician was increased by the accumulation of experience throughout the world which was shared by word of mouth and by medical literature.

New medications and procedures are often (at least in the past) the result of serendipity (from Horace Walpole, *The Three Princes of Serendip*) and/or careful observation. Thus, for example, one version would be how *quinine* was discovered by the observation that Peruvian Indians drinking the water accumulated at the base of the cinchona tree. Another version, An Augustinian monk (friar) wrote in 1633 about the use of ground bark (of the cinchona tree) also called "Jesuit bark", mixed with water to treat fevers (from Goodman and Gillman, 4th edition, pp. 1115-1116). William Withering (1785) published a report on *Foxglove* in which he had noted that a woman was dispensing a brew made up of some 100 plants which was successful in the treatment of dropsy. Then he set out to discover which plant was responsible for its beneficial action and discovered that it was *Digitalis purpurea*. The immuno-suppressive drug, cyclosporine, was

discovered as a product of a fungus found in Norwegian arctic soil. Today it is now common practice of modern pharmaceutical companies to investigate native medicinal plants (known as herbal medicine) for their active medicinal components in order to identify them chemically, which then often permits synthesis of the active principle(s) and more effective clinical studies.

A more systematic approach was gradually introduced into finding better means of bringing new knowledge into the medical practice: *controlled* human experimentation. Of course, a sort of human experimentation has been going on for centuries. The concept of human experimentation was discussed in the writings of Greek and Roman physicians as well as in Arab medical writings. (See discussion by David J. Rothman, "Research, Human: Historical Aspects" in *Encyclopedia of Bioethics*, Revised Edition, (1995), Warren T. Reich (ed), vol. 5, pp. 2248-2258). Ethical concerns were not entirely overlooked. The Jewish scholar, Moses Maimonides (1135-1204) and the Franciscan philosopher, Roger Bacon (1214-1294), raised interest to the dignity of the human person who was the subject of medical attention (*Ibid*).

Among the first to use treated control groups in the testing of new treatments was James Lind, who in 1747 took 12 scurvy patients aboard his ship, divided them into six groups of two, and placed each couple on a different dietary regimen. The group which received oranges and lemons showed the most improvement (see Curtis L. Meinert with Susan Tomascia, *Clinical Trials*, New York: Oxford University Press, 1986, p.5).

The work of the English country physician Edward Jenner (1749-1823) included vaccination to protect the person from small-pox. Jenner was among the pioneers to have a notable impact on the practice of medicine (*Ibid.*). Claude Bernard, a French physician (1813-1878) and the French chemist, Louis Pasteur (1822-1895) are often credited to be among the first to develop a more scientific mode of medical experimentation and research.

However, it is only in the middle of this century that extensive government supported medical research became a major contributor to medical knowledge. This is not to ignore the significant contributions made by medical schools and universities supported by individual grants and private foundations. The occasion for the great spurt in medical knowledge and research was World War II and its medical

and surgical demands (*Ibid.*). However, in the rush to meet the pressing medical problems of war and wartime conditions, the ethical niceties —such as the need for obtaining informed consent from the human subject (*ibid.*)— were often ignored. [A trivial example would be my experience as a graduate student (1942) in Pharmacology. While in my lab, one of the senior professors came to me and said simply "stick out your arm," which I did without hesitation or question. On the bare skin of the under surface of my forearm he placed a drop of a clear liquid. He started his stopwatch and after precisely one minute he measured the erythema which had developed at the site of the drop (about 2 inches). Later, I learned that he was testing "blister gas," and I was an uninformed and to that extent a "non-consenting" subject. Recall that students are members of a consent-prone group, along with charity patients and others]. After the World War II (1946) medical research continued with increasing government funding, no doubt stimulated by the many successes which had been recorded resulting from the war-time research.

Because the primary focus of the early research on human subjects was the *scientific* aspect of the research, lesser attention was paid to the ethical aspects, particularly the rights of the human subjects of that research. Not that these were ignored; some researchers had a very high sense of what was ethically correct or wrong in human research. But there was very little official attention to the subject probably under the presumption that the individual medical researcher was ethically upright and could be depended upon to do the ethically right thing. In addition, ethics was often interpreted primarily to mean etiquette, a set of rules, written and unwritten, for many in the medical field, particularly outside of the Catholic community. This dictated the relationship that ought to prevail between and among physicians who proclaimed the priority of a patient's well-being among other concerns of the physician.

However, confidence in a code of honor in this kind of gentlemen's agreement among physicians that their knowledge and professional actions would be used only for the good of their patients, was shattered when the revelations of medical atrocities which occurred in the Nazi concentration camps (e.g., Dachau, Auschwitz, Buchenwald) and elsewhere, e.g. China, Japan, and even the United States (e.g., Tuskegee and untreated syphilitic patients) became known. The War Crimes Trial in Nuremberg (1946-1947) surfaced the horrifying de-

tails of the actions of some prominent Nazi physicians who sought new medical knowledge to help their own soldiers but by means which were simply immoral. These revelations led to formulations or codes, such as the Nuremberg Code (NC) for medical experimentation to protect the human subjects in medical experimentation. A number of other codes (such as the World Medical Association's 1964 Helsinki Declaration, revised at least three times since then) have been developed, which in part were refinement of the NC and in part additions and changes in the light of new experience and new areas of research such as genetics, DNA, etc.

The Nuremberg Code set the stage for the subsequent codes which were developed for the purpose of protecting the human rights of human subjects in clinical research. The very first provision of the Code's ten provisions was: "The voluntary consent of the human subject is absolutely essential." To make sure that the intent, conditions, and content of that requirement was clearly understood the Code goes on to explain what it means:

> This means that the person involved should have the 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 (George J. Annas and Michael A. Grodin, (ed.), *The Nazi Doctors and the Nuremberg Code*, New York : Oxford University Press, 1992).

The obligation to see that this provision is properly fulfilled falls on the investigator and those who collaborate 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 (*ibid.*).

Thus, no one can later rightly claim that "I was just following orders." Each person involved has the obligation to ascertain that proper, free, informed consent has been obtained from the human subjects of clinical research. In practice, however, it is not clear that all the participants have taken the time and trouble to verify that free, informed consent was indeed obtained.

The other provisions of the Nuremberg Code include, in summary form:

> *Rule 2.* The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
>
> *Rule 3.* The results 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.
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> *Rule 4.* The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
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> *Rule 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.
>
> *Rule 6.* The degree of risk of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved.
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> *Rule 7.* Proper preparations should be made and adequate facilities provided to protect the experimental subjects against even remote possibilities of injury, disability, or death.
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> *Rule 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.
>
> *Rule 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.
>
> *Rule 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 his good faith, superior skill and careful judgment that a continuation for he experiment is likely to result in injury, disability, or death to the experimental subject. (Taken from Henry K. Beecher, "Experimentation in Man", *Journal of the American Medical Association*, January 31,1959, p.474).

Twenty years after the Nuremberg Trials, Henry Beecher, professor of Anesthesiology at Harvard Medical School, published a watershed article, "Ethics and Clinical Research," in the *New England Journal of Medicine* (June 6, 1966, pp. 1354-1360) which cites some "twenty-two examples of investigators who risked 'the health or the life of their subjects' without informing them of the dangers or obtaining their permission"(*Reich*, p. 2253). Due to a mounting awareness of the ethical problems associated with medical research, two federal agencies, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) developed more specific policies in this regard. Each emphasized different aspects of the issue. The NIH regulations focused more on the review process —without ignoring totally the issue of consent. The FDA developed more fully the aspect of free and voluntary consent (see *Reich.*, pp. 2254-55). Both sets of regulations are directed to protecting the rights of the human subjects while at the same time giving the medical investigator the space needed for creative research.

These regulations also set up local Institutional Review Boards (IRB) by which an investigator's proposal (protocol) is subjected to critical review by a committee of peers (although the IRB is also to include a member of the "public"). In turn the IRBs function by virtue of U.S. Federal Regulations, Title 45 (Public Welfare) of the *Code of Federal Regulations*, part 46 —*Protection of Human Subjects* (revised June 18,1991. The supervision of these regulations is given to the Office for Protection from Research Risks which is contained in National Institutes of Health of the Department of Health and Human Services.

Catholic Teaching

From a Catholic perspective, human experimentation is not ruled out but there are principles which are to be observed when carrying out research or experiments on human subjects. The address of Pope Pius XII to the First International Congress of Histopathology (September 13,1952; Eng.trans., *The Human Body*, St.Paul Editions, #353-360, *passim*) well expresses the possibilities and the moral limitations of research with human subjects:

> For the moral justification of new processes, new experiments, and methods of research, three principles are invoked:

(1) the interests of medical science;

(2) the individual interests of the patient under treatment;

(3) the common interests of the community, the "bonum commune."

Scientific knowledge as its own value in the domain of medical science...a value which should by no means be minimized, and is imposed quite independently of the usefulness and of the use made of the acquired knowledge. This does not mean, however, that every method, even a method well established by scientific research and technique... becomes lawful by the fact that it increases and deepens our knowledge. Sometimes it happens that one method cannot be put into operation without infringing on the rights of another, or violating some absolute moral value....this method is not morally admissible. Why is this? Because science is not the highest value to which all other orders of values —or in a single scale of values, all the particular values— should be subjected. Science itself, then, along with its researches and attainments, must be inserted in the order of values

The basic consideration can be formulated in the following manner: "The medical treatment of the patient demands this particular measure. By that very fact itself its moral legitimacy is established"

Surely one can see here how the true and the false are mingled.

First of all, one must suppose that the doctor, as a private person, cannot take any measure or try any intervention without the consent of the patient. The doctor has only that power over the patient which the latter gives to him, be it explicitly, or implicitly and tacitly. The patient for his part cannot confer rights which he does not possess. The decisive point, in this problem, is the moral legitimacy of the right which the patient has at his own disposal.

As far as the patient is concerned, he is not the absolute master of himself, of his body, or of his own soul. He cannot, therefore, freely dispose of himself as he pleases. Even the motive for which he acts is not by itself either sufficient or determining. The patient is bound by the immanent purpose fixed by nature. He possesses the right to use, limited by natural finality, the faculties and powers of his human nature. Because he is the beneficiary, and not the proprietor, he does not possess unlimited power to allow acts of destruction or of mutilation of anatomic or functional character. But, in virtue of the prin-

> ciple of totality of his right to employ the services of the organism as a whole, he can give individual parts to destruction or mutilation when and to the extent that it is necessary for the good of his being as a whole, to assure its existence or to avoid, and naturally to repair, grave and lasting damage which could otherwise be neither avoided or repaired.
>
> The patient has not the right to involve his physical and psychic integrity in medical experiments or researches when these interventions entail, either immediately or subsequently, acts of destruction, or of mutilation and wounds, or grave dangers.

A more recent Catholic statement based on the forgoing and other relevant Magisterial teaching, the *Ethical and Religious Directives for Catholic Health Care Services* (ERD) of the U.S. National Conference of Catholic Bishops, (1994), specifically notes that

> the inherent dignity of the human person must be respected and protected regardless of the nature of the person's health problem or social status. The respect for human dignity extends to all person who are served by Catholic healthcare. (Dir #23)

A fortiori the protection of human dignity extends to subjects of human experimentation, that is, in particular for research which may not be therapeutic for the individual who is the subject of the research. Indeed, there is a special directive in the ERDs directed to human research:

> No one should be the subject of medical or genetic experimentation even if it is therapeutic, unless the person or surrogate first has given free and informed consent. In instances of nontherapeutic experimentation, the surrogate can give this consent only if the experiment entails no significant risk to the person's well-being. Moreover, the greater the person's incompetency and vulnerability, the greater the reasons must be to perform any medical experimentation, especially nontherapeutic. (#31)

The federal government, specifically, the National Institutes of Health and the Food and Drug Administration, each of these Federal agencies have developed specific guidelines applicable to research in institutions which receive monetary support from the Federal Government. This covers a major part of medical research in this country.

The expression, "Free and informed consent," includes several important considerations:

(1) "Informed" means that the subject must be given accurate information, of sufficient amount, and in a language the individual can understand so that any decision made by the subject will be made on the basis of adequate information regarding the experimental treatment: What pain, discomfort or inconvenience may be involved; what may be some of the more likely side effects; what is the expected desirable effect, and what is the consequence of not trying the new treatment.

(2) "Free" does not mean that it cost nothing; rather it signifies that the experimental treatment cannot be used except with the non-coerced permission of a properly informed subject. Sometimes the request for permission can hide a subtle coercive factor. An individual subject, for example, may be part of what has been called "consent prone subject"; for example, a non-paying person in a public hospital, a graduate student in a university or medical school, one who has been the recipient of medical favors, such a free medical care or advice from the physician or staff. Such individuals are more apt to give consent when asked to participate in an experimental protocol. Sometimes a monetary inducement for participation may be considered as coercive for a particular individual.

Special consideration must be given to the involvement of prisoners as experimental subjects. Some ethicists hold that a prisoner by the very reason of his incarceration is prone to give consent to inclusion is an experimental protocol. Perhaps the factor could be that the participation is perceived as a way to break the boredom of prison routine. Or, perhaps the prisoner hopes to gain a favorable standing with the prison authorities or his sentence might be shortened. Some prisoners, when asked why are they volunteering, will respond that they see participation as a way of paying a debt to society for the crimes they had committed. Whatever be the reason for a prisoner to volunteer, great care should be taken by the medical researcher that the prisoner's consent be truly a "free" consent.

Another area of particular concern is that involving infants and children, as well as others who are not sufficiently competent because of age (see, for example, *Ethics & Medics*, Sept.-Oct., 1977, p.3) or, due to their particular medical condition, are not able to give true informed and free consent. The *Directive* cited (#31) makes it clear that in such

cases (of nontherapeutic experimentation) a surrogate can give consent only (emphasis added) "*if the experiment entails no significant risk to the person's well-being.*" Occasionally, the expression will be that only if there is "no or minimal risk" involved. Clearly, there is room for variation: what constitutes *minimal* risk; or, what is a *significant* risk? Some have attempted to define "minimal" as that level of risk which is found in the ordinary course of daily life. But whose daily life? One could accept as minimal risk such activities as weighing the child, measuring its length, calculating the amount of food a child is consuming, or measuring the unit output, etc. But would drawing a blood sample be an ordinary, daily life risk? It could be painful for a child to be stuck with a needle for a blood sample especially if the puncture would have to be repeated. Also, an infection can occur or a hematoma can result from the process. Are these minimal risks? In these situations, it is clear that much depends on the competency and integrity of the medical experimenter.

Experiments involving children as subjects are required because oftentimes that is the only way to get medical information that is important for that age group of patients. Often, one cannot simply transfer adult information to the child simply by treating the child as if it were a small version of an adult. The dosage of a medication, for example, does not always bear a direct proportion to body weight. Furthermore, there are diseases or conditions which are primarily or exclusively children's disorders. And while getting data about a new medication or procedure from children who actually here and now have that disorder can be realized, there are situations when this is not possible, especially when healthy control subjects are needed to establish the safety and efficacy of the new treatment.

More recently there has been a concern about the under representation of women and minority groups as subjects of medical research. As a consequence of this exclusion, it was felt by many that women and minority groups were being deprived of research that would lead to an improvement of medical care for those groups. Accordingly the *NIH Revitalization Act* of 1993 (PI 103-143) was signed by President Clinton on June 10, 1993. It enshrined the new NIH policy that

> It is the policy of NIH that women and members of minority groups and their sub-population must be included in all NIH-supported biomedical and behavioral research projects involv-

> ing human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research... (Belinda Seto, Ph.D., "The Inclusion of Women and Minorities as Subjects in Clinical Research," an abstract prepared for *Contemporary Issues in Human Research Subject Protection in Vulnerable and Minority Populations: Sharing the Benefits and Burdens of Research*, a Workshop sponsored by NIH, St.Louis, MO, May 4-5, 1995).

The federal guidelines implementing the policy are included in the *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*; Notice, Federal Register, Vol. 59, 1994. These took effect on March 9, 1994, but the notice invited comments in order to determine whether any modifications were warranted.

The Food and Drug Administration also reacted to the public concern about the under representation of women as subjects in clinical research. One step it took to alleviate that situation was to publish a notice of its "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" Federal Register Vol. 58, No.139, July 22,1993. One concern which no doubt was a factor in the reluctance to involve women, especially those in the pregnancy potential age (15-49?), was and is the potential for harm to the developing fetus were wome who were unknowingly pregnant. Of course, the research protocol has to include a provision to prevent such harm which is usually achieved by requiring that the female participants use an approved contraceptive. In a letter (September 16, 1994) to the Institutional Review Boards, Linda A. Suydam, Interim Deputy Commissioner for Operations, FDA, states that

> the guidelines does not, however, specify the type of contraception to be used because the FDA believes that decisions of this nature are best left to the woman in consultation with her health care provider in light of specific features of the product under study, the protocol, and the population under study.

This clarification of the provision for Catholic women and researchers opens the way for participation in clinical research in good conscience since they are free to use Natural Family Planning (NFP) methods. Of course, it is presumed that participants are properly

informed with regard to current NFP procedures which have been shown to be highly effective (see, for example, REJ Ryder, "Natural Family Planning: an Effective Birth Control supported by the Catholic Church," *British Medical Journal*, 18 September.1993, pp. 723-726.

Increasingly studies show that rates equivalent to those with other contraceptive methods are readily achieved in the developed and developing worlds. Indeed a study of 19,843 poor women in India had a pregnancy rate approaching zero. Natural family planning is a cheap, effective, without side effects, and may be particularly acceptable to and efficacious among people in areas of poverty.

Conclusion

The Nazi medical war crimes were indeed atrocities. They helped the world realize that science, medical science, can be abused and that great care must be taken for the well-being of human subjects in medical research. As valuable as the knowledge may be in a particular situation, there is never any ethical warrant for the violation of the rights of any human subject, regardless of their age, medical condition, or their socio-economic status.

What is at stake is the dignity of every human being, from conception (that is, when the process of fertilization has been completed with the formation of the zygote) onward to natural death. Medical experimentation with human subjects is indeed necessary and is good but it must be carried out with a deep respect for the dignity and indeed the sacredness of every human being.❑

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