The History and Ethics of the Use of Human Subjects in Medical Experiments

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ETHICS MEANS THINKING SINCERELY about rules for human conduct. Experimentation is a highly intellectual form of human activity. Hence, it is appropriate for experimenters to consider the ethics of their activities.

It should be recalled that all science or knowledge has two aspects, the descriptive and the experimental. Knowledge is obtained by describing and systematizing things and processes which are observed to occur in Nature and by designing and executing experiments to reveal the nature of the things and processes observed. Observation without experiment is quite sterile, as is witnessed by the type of culture of ancient civilizations. Observation and experimentation must be effectively combined to produce the culture characteristic of modern civilization. It has been through the experimental method of controlled or conditioned observation, and *only* through this method, that scientists have discovered and will continue to discover the most intimate secrets of Nature.

In the medical sciences, the only method which can clearly reveal and establish the cause, prevention, and treatment of disease is the method of controlled experimentation on animals and volunteer human subjects. Even after the therapy of a disease is discovered, its application to the patient remains in part experimental. Because of the physiological variations in the response of different patients to the same therapy, the therapy of disease is, and will always be, an experimental aspect of medicine.

We frequently forget to recall the fact that a patient is a voluntary experimental subject of the physician. The physician *practices* medicine today, and because the response of different patients to the same therapy will always vary to some extent, the physician will always *practice* medicine on his patient. No physician can honestly guarantee that he will cure a disease or that his treatment will not cause undesirable symptoms or temporary discomfort. In all cases except emergencies, the surgeon obtains the consent of his patient or of a relative of the patient for operative treatment. Similarly, the internist has the consent of his patient or a relative before applying treatment.

The fact that the patient is always to some extent an experimental subject of the physician is the reason that Hippocrates formulated his famous Oath for Physicians. He realized that the scientific and technical philosophy of medicine could not survive without a sound moral philosophy. A society with a profession of medicine that has no moral philosophy is inconceivable.

The Rise, Fall, and Rise of Experimentation in Medicine

Historically, Hippocrates (460–370 B.C.) is credited with the initiation of the descriptive science of medicine. Galen, who lived some 500 years later (131–201 A.D.), is similarly credited with the initiation of the experimental science of medicine, including the use of animals. Of course, there are indications of the performance of experiments on animals and man in the oldest literatures, but these will not be referred to here.

After Galen's death, the experimental method in medicine was not used throughout the Dark and most of the Middle Ages, or for 1,200 years. Then, Vesalius (1514–64 A.D.), by dissection of the human cadaver, which had previously been forbidden, and by animal experimentation, demonstrated certain inaccuracies in Galen's conception of the circulation of blood. This evidence of the renaissance from the barbarism and paganism of the Dark Ages was climaxed in 1628 by Harvey's "discovery of the circulation," which involved controlled observations on animals and man. Harvey used one of his subjects, a patient with an accidental exposure of the heart to the outside, in a demonstration before King Charles I, showing among other things, that the heart could be touched without causing pain. The great importance of controlled experiments was again demonstrated in 1798, when Jenner published his remarkable observations on vaccination against smallpox.

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Random Experiments on Man

Regardless of Harvey's demonstration of the great usefulness of controlled experiments on animals and man, the true significance of the philosophy and application of the method was not generally realized until the latter half of the 19th Century.

In the meantime, numerous physicians had seized the idea of experimentation but not the complete concept of controlled experimentation. So, throughout the 18th and 19th Centuries, numerous physicians performed more or less random experiments on themselves and their friends. Some examples will be cited. John Hunter in 1767 (*3*) confused medical knowledge by supposedly inoculating himself with gonorrhea from a patient. The inoculum produced both gonorrhea and syphilis, which convinced Hunter that the diseases were the same. Purkinje (*7*) in 1790 gave himself a large overdose of digitalis in order to study the changes in vision produced by the drug in his patients. The dose, which by modern standards would have killed 9 cats, produced in Purkinje cardiac pain and irregularity and caused him to vomit for a week. Early in the 19th Century, E. Hale (*10*), of Boston, enthusiastic about the intravenous administration of drugs, had himself injected intravenously with 0.5 ounce of castor oil and fortunately lived to describe his marked reaction. Tonery in 1830 demonstrated the capacity of charcoal to absorb alkaloids by taking an otherwise lethal dose of strychnine before the French Academy. Simpson introduced chloroform and Long, ether anesthesia, after testing them on themselves and friends. Morton (*8*), working more cautiously, tested ether on the family pets before trying it on himself.

After 1850, many instances are to be found in the medical literature in which potentially toxic chemicals and agents were first tried on man. In 1855 Christison chewed one-forth of a Calabar bean (eserine), which resulted in symptoms so marked that his colleagues had to be called to treat him (*11*). Carbon tetrachloride was tried as an anesthetic in 1867 (*9*) in man when a few experiments on animals would have shown it to be unsuitable. Acetanilid was discovered in 1884 to have antipyretic properties when given to one of Prof. Kussmanka's assistants, whose body temperature fell alarmingly before he recovered (*6*). C. Oliver approached Prof. Schafer in 1894 (*2*) and reported that he had made extracts of all of the endocrine glands of the body and had injected them into his own son. Prof. Schafer changed the design of the experiment and was the first to demonstrate the pressor effect of epinephrine in dogs and cats. About 1900, Pierre Curie (*4*), when told that radium would produce skin burns, bandaged some radium bromide onto his forearm, and allowed it to remain for several hours.

While these experiments may be a tribute to the enthusiasm and the bravery of these early medical scientists, they clearly show the limitations and dangers of uncontrolled self-experimentation.

Antivivisection

Men such as Harvey, Jenner, Claude Bernard (1813–78), and Pasteur (1822–95) demonstrated clearly that controlled animal experimentation should be the basic method of research in the zoological sciences.

Despite the contributions of these and other benefactors of mankind, it is a strange fact that their animal experiments were attacked by a group of persons who called themselves Antivivisectionists. But it must be recalled that in the 18th and 19th Centuries chemists and physicists were attacked and maligned because they practiced the "black art" or constructed "devices of the devil." The attack on the latter subsided, however, during the last half of the 19th Century, whereas the attack of the Antivivisectionists grew in vehemence and burst into dramatic expression in Nazi Germany.

One of the first official acts of Hitler after he assumed power was to issue an edict rendering animal experimentation illegal. As a commentary on this action, the world now knows that the Nazis during the recent war used human beings without their consent as experimental subjects and without giving them the consideration which animals are given in scientific laboratories and veterinary hospitals. As another commentary on Hitler's edict, an entry in Goebbel's diary on October 15, 1925, reads: "I have learned to despise the human being from the bottom of my soul"; and another entry on August 17, 1926, reads: "The more I get to know the human species, the more I care for my dog."

Here in the words of Goebbels—the man whose false propaganda and racial views resulted in the most wanton torture and destruction of human beings in the history of the human race—we have the crux of the ethical questions regarding the use of animals and man as subjects in medical experiments. The questions are: Should one love animals more than human beings? Should one love disease more than health? Should one love ignorance more than knowledge of the living body?

Ethics of Animal Experimentation

Modern intelligent or literate people cannot seriously accept the view that animals, disease, and ignorance are preferable to human life, health, and

knowledge. In many ways, the existence of man stands in conflict with that of living plants and animals. The necessity of destroying and injuring living things is imposed on man, for it is by destroying plants and animals that man gets his food and clothing. In order to preserve his own existence, man must defend himself against any existence which would injure him.

How, then, can ethics be maintained in view of the necessities which confront man? Kant presumed that ethics are concerned only with the duty of man to man. A more universal and perhaps defensible view may be stated as follows: when one injures or takes the life of living things, one should be certain that it is necessary.

James Rowland Angell, formerly president of Yale University, in discussing the ethics of animal experimentation, has said in effect: If experimentation on living animals is justified by its results, the basic ethical issue is closed, provided the minimum of pain is caused, and the indirect effects are not such as to augment the spirit of cruelty.

John Dewey, professor of philosophy emeritus at Columbia University, on analyzing the ethics of animal experimentation, concluded: (a) "Scientific men are under definite obligation to experiment upon animals so far as that is the alternative to random and possibly harmful experimentation upon human beings, in so far as such experimentation is a means of saving human life and of increasing human vigor and efficiency. (b) The community at large is under definite obligations to see to it that physicians and scientific men are not needlessly hampered in carrying on the inquiries necessary for an adequate performance of their important social office of sustaining human life and vigor." Prof. Dewey remarks that "these things are so obvious that it almost seems necessary to apologize for mentioning them." *Yet, the acts of legislative assemblies in parts of the United States are such that dogs and cats are wantonly destroyed by so-called humane societies. If scientists did not oppose anti-vivisection legislation, all animal experimentation and even the production of vaccines for man and animals would be abolished within two years.*

This strange attitude on the part of antimedical groups, which is expressed in legislation restricting the procurement of animals, persists in the face of the fact that the vast majority of the American people contribute tens of millions of dollars yearly to research on cancer, heart disease, and infantile paralysis—research which, as we know, would be impossible without experimental animals; it persists regardless of the rules for animal experimentation adopted by the American Medical Association and all zoological groups of scientists.

Obviously, experiments may, and must, be performed on lower animals if medical knowledge is to be advanced, and random, harmful, and unnecessary experimentation on man is to be avoided. The final test, however, must be made on human subjects. No one knows better than the biologist that caution must be exercised in applying to man the results of animal experiments; yet, every biologically literate person knows that the results of animal experiments have directed us to the greater amount of the most valuable part of our practical medical knowledge. There are also some medical experiments which can be performed only on man, because certain diseases are contracted only by man.

The Use of Medical and Lay Subjects

It is a matter of common understanding that an individual may consent to undergo medical or surgical treatment, or other experimentation, for the good of his own body. A part of the body may be sacrificed to preserve the whole body. And, in desperate cases, more liberty is taken to apply remedies which have only a small possibility of accomplishing any good. It is also a matter of common understanding that an individual may justifiably permit a physical evil on himself for the good of another or for the good of humanity, with limitations which need not be mentioned here.

As it is well known, medical scientists, medical students, soldiers, sailors, and other volunteers have on many occasions served as subjects in medical experiments designed to advance human welfare. These have been conducted according to certain ethical principles in all countries of the world which have contributed to the prevention, cure, and control of disease and suffering. These principles, which have been in force by common understanding and practice, may be summarized as follows:

(I) Consent of the human subject has been obtained. All subjects have been volunteers in the absence of coercion in any form. Before volunteering, the subjects have been informed of the hazards, if any.

(II) The experiment to be performed has been based on the results of animal experimentation and on the knowledge of the natural history of the disease under study and has been so designed that the anticipated results will justify the performance of the experiment. It is the obligation of any investigator to study exhaustively a process or a substance in animals before undertaking hazardous experiments of a similar nature on human subjects. In addition, the experiment has been such as to yield results which are unprocurable by other methods of study and are necessary for the good of society.

(III) The experiment must be conducted (a) only

by scientifically qualified persons, (b) so as to avoid all unnecessary physical and mental suffering and injury, and (c) only after the results of adequate animal experimentation have eliminated any *a priori* reason to suspect that accidental death or disabling injury may occur. In such experiments as those of Walter Reed, in which it was demonstrated that the mosquito transmits yellow fever, medical scientists should serve, or should have served, as volunteers along with nonscientific personnel as evidence of the necessity of the experiment and their willingness to experience discomfort along with others for the sake of the solution of the problem.

These rules have been adopted in essence by the House of Delegates of the American Medical Association (*14*) and were introduced into the record of the Nuremberg Trials as representing generally accepted practice among medical scientists.

The Use of Prisoner Volunteers as Subjects

From time to time, prisoner volunteers have been used as subjects in medical experiments in the United States and abroad (*15*). A few examples under which they have been used in this country will be cited.

Col. R. P. Strong, later professor of tropical medicine at Harvard University, was apparently the first in the United States to use prisoners for medical experiments. With the permission of the Governor General of the Philippines, Col. Strong in 1904 used prisoners condemned to death who had volunteered to serve as subjects in experiments on the plague (*12*). Later he and B. C. Crowell (*13*) used prisoners, under similar conditions in the Philippines, as subjects in experiments on beriberi. The only reward given the prisoners during the course of the experiments consisted of gifts of tobacco. In 1914, Drs. Goldberger and Wheeler (*5*), of the U. S. Public Health Service, conducted experiments on pellagra on white male convicts in the State of Mississippi who volunteered for the experiments. The prisoners signed contracts promising to serve faithfully and were accordingly rewarded.

During the recent war, prisoners in both Federal and State Prisons, as is well known, were used in several different types of medical experiments, such as those involving malaria and the testing of drugs and blood plasma substitutes. More prisoners than were required volunteered in most prisons. Referring to prisoners who volunteered for medical research in a prison in New Jersey, Mr. Bixby, Deputy Commissioner of the Department of Institutions and Agencies of New Jersey said:

> All prisoners who had participated in medical experiments were given certificates of merit, copies of which were put into their records and called to the special attention of the Court of Pardons or the Board of Managers when parole was under consideration. Apparently no definite policy was ever formulated, and the participation in a medical experiment was considered only as one favorable factor in the whole case.

T. P. Sullivan, director of the Department of Public Safety of the State of Illinois, reports that essentially the same policy has been followed in the case of prisoners at Stateville who served in malaria experiments. When their cases came up for review, some reduction of sentence was allowed. In a letter to Mr. Sullivan, Mr. Ragen, warden at Stateville, stated: "Each will have to be treated as an individual case and consideration given accordingly."

In experiments conducted by the U. S. Public Health Service on prisoners in the Federal Correctional Institution at Seageville, Texas, the Under Secretary of War has ruled that volunteers (for medical experiments) will receive the same honorarium ($100) and certificates of merit as the Atlanta participants but, in addition, will receive under the parole system some reduction of sentence for their participation.

In the consideration of the ethics involved in the case of prisoner volunteers, the generally accepted purposes of imprisonment should be reviewed. There are 5 such purposes (*1*): (1) *the punitive or retaliative,* historically the oldest purpose of imprisonment, which holds that revenge is the purpose of punishment; (2) *the expiative,* which holds that some sacrifice or atonement of penance by the wrongdoer is necessary and is best fulfilled by punishment; (3) *the exemplary or deterrent,* which attempts to prevent crime by the example of punishing persons who commit crime; (4) *the socio-protective,* or the wish to protect society from dangerous and vicious persons; and (5) *the reformative* which indicates that the purpose of imprisonment is to reform the prisoner.

The purpose of the parole system is also involved in the use of prisoner volunteers and should be reviewed. A reduction of sentence in prison is now recognized under the parole system "for the purpose of encouraging and rewarding good conduct and industry" and for "exceptional bravery or fidelity" in a good cause. The parole law is based on the presumption that the reward of good behavior in prison and the supervision of the paroles after release from prison is reformative. The prisoner who does not cause trouble and manifests industry expiates some of his offense against society and has given some assurance that he can live lawfully. It is also presumed, at least in part, that good conduct in prison is an evidence of true reformation and not of a desire to be released from prison.

Prisoners render meritorious services in prison, such as working in the barber shop, the kitchen, the

shoe shop, or the furniture shop, and this service is rewarded. The rendering of such service is encouraged by the warden and his administrators, and service as a subject in a medical experiment may be similarly encouraged and rewarded.

Since one of the purposes of the parole system is reformative, the reformative value of serving as a subject in a medical experiment should be considered. Serving as a subject in a medical experiment is obviously an act of good conduct, is frequently unpleasant and occasionally hazardous, and demonstrates a type of social consciousness of high order when performed primarily as a service to society. The extent to which the service of a prisoner in an experiment is motivated by good social consciousness on the one hand and by the desire for a reduction of sentence in prison on the other is a matter for consideration in the case of each prisoner.

Regardless of a prisoner's motives for volunteering for an experiment, an habitual criminal or a prisoner who has committed a notorious or heinous crime should not be considered an acceptable volunteer for a medical experiment.

As mentioned above, the most important requirement for the ethical use of human beings as subjects in medical experiments is that they be *volunteers*. Volunteering exists when a prison is able to say "yes" or "no" without fear of being punished or of being deprived of privileges due him in the ordinary course of events.

A reduction of sentence in prison, if excessive or drastic, can amount to undue influence. If the sole motive of the prisoner is to contribute to human welfare, any reduction in sentence would be a reward. If the sole motive of the prisoner is to obtain a reduction in sentence, an excessive reduction of sentence which would exercise undue influence in obtaining the consent of prisoners to serve as subjects would be inconsistent with the principle of voluntary participation (*15*).

Mental Incompetents as Subjects

Mentally incompetent persons have on occasion been used as subjects in medical experiments designed to elucidate the cause and the treatment of mental disorders. They have also occasionally been used as subjects in nutritional experiments and the study of the action of drugs which only indirectly might be related to the cause of mental disorders. In fact, the results of animal experimentation have perhaps less direct application to the study of the treatment of mental disorders in man than the results of animal experimentation in the treatment of other diseases. This means that in the treatment of mental disease, greater chances must be taken, as for example, when the convulsion, hyperthermia, and malaria treatments were first used for certain mental diseases. Even then, the hazards should be as carefully studied as possible in animals before the treatment to be tried is applied to the insane patient. As in amputating a limb, the extent of possible harm must be weighed against the extent of possible good for the patient treated.

The ethical principles involved in the use of the mentally incompetent are the same as for mentally competent persons. The only difference involves the matter of consent. Since mental cases are likened to children in an ethical and legal sense, the consent of the guardian is required.

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