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THE EXPERIMENTAL USE OF DRUGS IN HUMANS

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Consideration of the ethical and moral aspects of the experimental use of drugs in humans is not an easy task. A discussion of it is impossible without expressing some personal opinions of the various aspects. This is not surprising when one considers the criticism leveled at the various "codes" introduced through the years.

There are many reasons for the controversy about the experimental use of drugs but perhaps the basic reason is the great number of really new medications introduced within recent years. Chlorpromazine was not just another barbituate, for when introduced it represented a structure never before used in therapeutics. Virtually all the antibiotics have structures heretofore unknown. Even a remote guess as to the toxicities of these compounds was impossible.

Of course experiments are carried out in various species of animals before human use but finally the drug must be administered to humans. The well known species differences associates the first administration to man with a degree of danger. This paper deals with the circumstances under which we are justified to administer experimental drugs to humans.

We will dismiss the purely legal aspects of the subject by referring the reader to a recent comprehensive anthology with an extensive bibliography.[1]

Considering then the ethical and moral aspects, it seems that we must at the onset pose three critical questions, 1) When is the administration of a drug experimental and when is it therapeutic?, 2) What is the basis for any ethical and moral consideration?, and assuming there is a valid basis, 3) What are the guiding principles for the use of new drugs in humans?

WHEN EXPERIMENTAL AND WHEN THERAPEUTIC

Drugs have often been defined simply as selective poisons. This is true only if the drug produces the desired therapeutic effect without any side effects but as all physicians know this is true of very few if any drugs. Virtually all have unwanted effects accompanying the desired one and therefore the simplest definition of a drug must be a *not too* selective poison.

Obviously drugs differ widely in their toxicities. On the one hand, there are the innocuous ones which have been in use for many years, and on the other, potent agents newly introduced for human use.

Legally the definition of an experimental drug for human use is simply a drug released by the Food

and Drug Administration for investigational use in humans. However, the agent may actually be just a new salt of a well-known drug whose administration is obviously quite safe. In contrast the administration of many drugs in general use is accompanied by a degree of risk. Chloramphenicol, for example, will produce agranulocytosis in a small percentage of people. Is not then the administration of any drug an experiment? The answer depends on the motive behind its administration. If chloramphenicol is given to healthy volunteers to determine the incidence of agranulocytosis its administration is without a doubt an experiment. If given to patients with typhoid fever and the incidence of toxicity noted it may still be an experiment but its reason for administration is therapeutic.

We therefore deal with a spectrum of motives between administration of drugs in general use for their proven therapeutic effect to the administration of new drugs to healthy human volunteers. These are the two extremes between which determining the ground for drug administration may not always be obvious. For example the administration of an old drug for a new indication may be as experimental as the use of new drugs in volunteers.

In actual practice however one does have some guidelines to ascertain the risk in the use of a drug. The use of an agent should be considered experimental when 1) it is legally defined as such, 2) a mixture is used the safety of which has not been established, 3) an established drug is used for a new indication, and 4) any study of drugs is carried out in healthy persons.

BASIS FOR ETHICAL OR MORAL CONSIDERATION

Many people claim that moral limitations to human experimentation are intuitively obvious and any guiding statements are unnecessary. One need not look too far into the past to realize the fallacy of this concept. Less than two generations ago a civilized government permitted, through its scientists, human experimentation the atrocities of which are still shocking the world.

Human subjects were used with complete disregard for their personal rights or safety. As stated in "The Medical Case" before the Nuremberg Military Tribunal, "Manifestly human experiments under such conditions are contrary to the principles of the law of nations as they result from the usages established among civilized peoples, from the laws of humanity, and from the dictates of public conscience."

Here then is one basis for establishing a moral code, namely, that man through the centuries of his physical and social evolution has come to realize that he *cannot disregard the rights of his fellow-men for any reason* — even in the name of science. The dangers of any governmental concept that maintains the rights of society over the rights of the individual are obvious.

An organized government however, can, through indoctrination and rationalization establish a code of ethics contrary to accepted human standards and this is exactly what happened in the Nazi regime. This is also the danger in the godless concept of humanism.

While the laws of society usually reflect the rights of individuals, there is no guarantee that a group will not spring up to upset these ideals. There is however a moral basis for the rights of every individual which has been unyielding through the ages. It is the Christian concept of man, a creature with a material body and immortal soul, created to the image and likeness of God, united with God through Christ.

It follows that man cannot freely dispose of his body as he chooses. In the words of Pope Pius XII:

> As for the patient, he is not absolute master of himself, of his body or of his soul. He cannot, therefore, freely dispose of himself as he pleases. Even the reason for which he acts is of itself neither sufficient nor determining. The patient is bound to the immanent teleology laid down by nature. He has the right of *use*, limited by natural finality, of the faculties and powers of his human nature. Because he is a user and not a proprietor, he does not have unlimited power to destroy or mutilate his body and its functions.

As for the physician, Pius XII states:

> In the first place it must be assumed that, as a private person, the doctor can take no measure or try no course of action without the consent of the patient. The doctor has no other rights or power over the patient than those which the latter gives him, explicitly or implicitly and tacitly. On his side, the patient cannot confer rights he does not possess.

It is obvious that there are bases for establishing limitations to human actions including experimentation. A governing body representing individuals in a society has not only a right but an obligation to oversee and protect the rights of each individual member.

GUIDING PRINCIPLES FOR THE USE OF NEW DRUGS IN HUMANS

Just as any organization has by-laws, it behooves societies and institutions with an interest in human experimentation to set down a series of principles as a *guide* to its members. It is possible to set down only a guide, the application of which in any particular case being the responsibility of the physician in charge. As stated by Pope Pius XII on addressing the Congress on Histopathology of the Nervous System:

> We would like to set forth briefly the *essential principles* which permit an answer to be given to this question. *The application to specific cases* you will make yourselves in your role of doctor, because only the doctor understands the medical evidence thoroughly both in itself and in its effects and because without exact knowledge of the medical facts it is impossible to determine what moral principle applies to the treatment under discussion.

This is a very important point since all medications to humans must be administered by a qualified physician and it is his responsibility to determine all the factors and dangers involved in administering the drug. He must not serve merely as a technician between the investigator and the patient. He should be willing to take all the responsibility for the legal and moral obligations of the study and must personally inform the patient of the nature and dangers of the study.

Since the Nuremberg Code was

formulated in the late 1940's there have been many formal codifications by various societies. The latest, endorsed by the American Medical Association and many other societies, is the *Declaration of Helsinki (Annals of Internal Medicine* 65, 367, 1966).

Specific points in each of these codes have been criticized as rapidly as they have been released. New codifications will continue to be formulated in coming years, and perhaps a more general agreement among interested parties will arise.

In the interest of brevity we will extract and comment on three generalizations which seem to be the main foundations of the various codes.

1) *Experiments should be conducted by qualified personnel with proper facilities.*

The statement is self-explanatory. As stated above the physician administering the drug to the subject must take full responsibility. The physician involved should always ask himself if he is qualified to carry out the experiment and he has the moral obligation to familiarize himself with all the animal data and previous human studies. He should be aware of all the dangers which are likely to arise and assume responsibility for assuring facilities to cope with any reactions. These duties cannot be relegated to anyone less qualified.

2) *The voluntary consent of the subject (or legal guardian) is mandatory.*

Patient consent in itself does not justify an experimental procedure and the subject is not free to consent to anything he chooses. A subject cannot for example enter into an experiment that would probably result in death. As quoted above, the patient has only the right of use of his body and since he is not the proprietor he cannot consent to destruction or mutilation. Many factors, such as the patient's disease, previous studies with the drug, etc., enter into whether or not a patient is morally justified to consent to take a new medication.

The problem of subject responsibility is well-considered in an article by Father Lynch *(Clinical Pharm. and Therap. 1,* 396, 1960).

The physician has a duty to explain to the subject the purpose, nature and side effects of the experiment. This poses a heavy moral obligation on the physician because few subjects are able to understand the intricacies and possible consequences of the study. The physician however must be convinced he has carried out his duty on this point as well as possible.

It must also be mentioned here that the subject must be informed that he is free to terminate the experiment at any time. The physician must not hesitate to terminate the experiment when a dangerous reaction occurs or at the request of the subject.

3) *The potential results of the experiment must be great enough to justify the dangers involved.*

This is the most difficult concept because it is not easy to judge what value the results of the experiment will have.

Pope Pius XII lists three principles which must be kept in mind to justify medical research: 1) the interests of medical science; 2) the interests of the individual patient and, 3) the interests of the community.

The "interests of science" apply to medicine as any other science however when man is the experimental subject an entirely different set of principles must be followed. If this were not true this paper as well as many thousands of others on the subject need not have been written.

As for the interests of the patient the Helsinki Code makes a distinction between "clinical research combined with professional care" and "non-therapeutic clinical research." We have already considered the differences between therapeutic and experimental administration of drugs and the difficulty at times in determining the motive for administration. We have also considered the rights of individual subjects.

In the case of research combined with therapy, the research is justified only by the potential therapeutic value it may produce for the patient. A consent should still be obtained from the patient or legal guardian if at all possible.

A physician should feel obligated not to withhold an established therapy in favor of an experimental drug unless the drug may offer considerable advantage over the old. In seriously ill patients a new drug is justified only if it is, beyond reasonable doubt, as effective as the established therapy.

Pius XII commented on this point:

> In doubtful cases, when means already known have failed, it may happen that a new method still insufficiently tried offers, together with very dangerous elements, appreciable chances of success. If the patient gives his consent, the use of the procedure is licit. But this way of acting cannot be upheld as a line of conduct in normal cases.

For non-therapeutic clinical research the investigator's obligations are the greatest. All the statements made on the moral obligations of human research apply most fully in this case.

Research carried out in the "interest of the community" is not illicit if the right of the individual subject is not forgotten. Obviously the observation of benefits and side effects of a drug administered to a patient will benefit all subsequent patients.

We have already considered the rights of individuals. Man does not exist for society but society exists for each man. In the words of Pope Pius XII, "The community is the great means intended by nature and God to regulate the exchange of mutual needs and to aid each man to develop his personality fully according to his individual and social abiilties."

No relaxation of the rules applying to individual subjects is justified on grounds of benefit to the community.

In conclusion, we have attempted to examine some of the factors involved in the experimental use of drugs in humans. Accurate definitions are seldom possible. We have listed a basis for moral codes of conduct and commented on the guiding principles which have been proposed.

The purpose of limitations to human research is not to stymie scientific progress but to point out the rights of each individual man. The purpose of guidelines is not to stop human research but to channel it. Again in the words of Pope Pius XII:

> The great moral demands force the impetus flow of human thought and will to flow, like water from the mountains, into certain channels. They contain the flow to increase its efficiency and usefulness. They dam it so that it does not overflow and cause ravages that can never be compensated for by the special good it seeks. In appearance moral demands are a brake. In fact they contribute to the best and most beautiful of what man has produced for science, the individual and the community.

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[1] Ladimer, I. and Newman, R. W.: *Clinical Investigation in Medicine: Legal, Ethical and Moral Aspects*. Boston University, Boston, 1963.

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