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HUMAN EXPERIMENTATION

It has been said that human experimentation is a "social necessity." This is so, as long as the desired ends cannot be obtained by use of animals. Indeed, the first phases of development of most discoveries do not require a human subject. However, all drugs and all procedures for the benefit of mankind must be ultimately tested on man. The first time a new drug, a new surgical technique or a new medical procedure is used on a man it is a human experiment. Such a step is usually the culmination of the scientific method. This method was first outlined in 1872 by Claude Bernard, the father of physiology. The nature of the method consists of a series of continuous steps and the process is a triad of observation, reasoning and experiment. It consists of accurate observation, of careful study, of imaginative interpretation of facts into a concept, of detailed animal experiments and finally of rational, cautious application in a human.

It is curious as Beecher has noted that there is often intense and emotional objection to experimentation on animals and little objection has been evident until recently to experiments on man.

It is our plan to consider the following aspects of human experimentation. The nature of experimentation, the moral principles of totality and of man's use of his body and the dangers of experimentation.

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NATURE OF EXPERIMENTATION

All knowledge may be divided into two types, the empirical knowledge derived by observation and experience of natural phenomenon (intuitive) and secondly, conceptual knowledge derived by reasoning. In either instance, the particular segment of knowledge may be tested and subject to observed proof. This represents the essence of experimentation. A theory may be derived by either approach and a scientific theory may be defined as a capability to predict events in the natural order with a degree of certainty.

More specifically, under experimentation we understand that activity whereby the investigator deliberately changes the environment or the functioning of an organism under study to observe the results of his interference (Prof. Groen). The first significant animal experiment was performed by W. Harvey, who demonstrated and reproduced physiological facts or phenomenon in his experiments and ended the authoritative hold of Galen over medical thought. Perhaps the first true human experiment and first therapeutic experiment was that of James Lind in 1747, when he observed the curative effects of lemons and limes in scurvy.

Thus, an experiment involves a question put to nature from whom

we expect an answer. The questions are challenges derived from a theory or an idea and the results are observed. If many similar experiments give a common result, then proof of the idea is evident.

TWO TYPES OF EXPERIMENTS CAN BE IDENTIFIED DEPENDING ON THE OBJECTIVE

In each instance, observed facts are integrated to form a theory. Investigators, being natural skeptics, devise tests to find the weakness of a theory, and attempt to disprove its validity. In the first instance, an attempt is made to verify a theory or an assumption (experimental biology). There is no aim to cure a patient, but the ultimate goal would perhaps sacrifice the individual for the benefit of the community. If purely in the interest of science, it must be excluded if not condemned. Witness the Roman testing of poisons on slaves and the cruelty of Nazi Germany. On the other hand, it was known that curare of Amazon Indian arrow fame would cause paralysis in both animals and man. Whether it would be reversible in man could only be decided by actual test in man. So with all precautions and safety, it was injected by Bennett in psychiatric therapy and by Griffith in surgical anesthesia. The theory was proved and the drug has been a boon.

The second human experimental situation is that of therapeutic testing. A disease state must exist. What must be decided is whether the possibility of a cure or of relief for the individual or for a large group with potential advancement of science is worth the risks of a poor outcome or more importantly actual harm to the patient.

THE ETHICS OF HUMAN EXPERIMENTS

In the experimental situation of therapeutic testing, physicians recognize inherently (the ethics of our actions) moral guides to their actions; traditionally these have been stated in various ethical codes of the profession.

Medicine has always honored the precept as contained in the Hippocratic Oath, namely, "the doctor works in the 'interest' of the patient." In the A.M.A. *Principles of Medical Ethics,* it is stated: "A single rule governs the entire medical profession: the *interest* of the patient"; while in the Declaration of Geneva in 1948, it is stated: "the health of my patient will be my first consideration."

Pope Pius XII in 1952, stated in an allocution to the Histopathologists: "that man in his personal being must not be subordinated to the community (including science), but the community exists for the man." Man is not absolute owner of his body, but is held accountable for the use of his body to the community and to God. For example, it is a crime against the community to attempt suicide. Neither can one person sacrifice another individual to community interest. But the interest of the community or of science and interest of the individual may coincide and often do.

Several ethical codes have been established, all being in essence founded on the Christian-Judaic spiritual teachings that man is made in the image of God and possesses human personal dignity that must not be lightly violated.

1. International Code of the WMA.
2. The Nuremberg 10 points.
3. U.S. Public Health Service.
4. A.M.A. Judicial Comm.
5. Wiggers Statements of 1950.

THE MORAL PRINCIPLE

The principle of totality is applicable. This is understood to mean that man has a restricted domain over his body.

In an address in September 1952, on the subject "The Moral Limits of Medical Research and Treatment," Pius XII examined the principle of totality and spoke as follows:

> "The patient then has no right to violate his physical or psychic integrity in medical experiments or research, when they entail serious destruction, mutilation, wounds or perils."

Related to this principle are two aspects, the element of consent and the element of danger. Consent cannot, of course, be valid unless complete knowledge is available and the degree of anticipated danger is known.

No person has the right to consent to a procedure which carries with it the danger of serious mutilation. Neither has an investigator the right (with or without consent) to inflict a serious mutilation or extensively and permanently suppress an organic function.

It is evident that once an act ceases to be one of wise administration of the person's body and becomes one of absolute ownership in which the whole is unjustifiably jeopardized, then the moral object of the act becomes evil and cannot be permitted. The dividing line is the amount of danger involved. That any new venture has inherent danger is self-evident. The degree of seriousness of a given experimental act determines the acceptability morally, ethically, and medically of any procedure. Rev. O'Donnell has stated that this danger should not exceed the meaning of moderate.

THE ELEMENT OF DANGER

An analysis of moderate danger involves a contrast—a consideration of the actual dangers on the one hand and the goals of the experiment on the other. The actual danger is to be stated in terms of the type of danger and its seriousness together with the chance of probability that it will occur. Thus, under one set of circumstances with great hope and great expectance a more dangerous act may be permissible; while if the good to be derived is limited, a dangerous act may be unjustified. The contrast is in the good to be derived versus the harm or evil inflicted. The good derived has been noted under the nature of experiments in the two types of experiments as defined by their objectives namely, 1) the common good, including the verification of a theory or the accumulation of knowledge and 2) the individual good. The common or public good may be considered the determination of a pure concept of an empirical nature with no practical immediate benefit to an individual man. Medical science may be advanced and knowledge increased. But, this good is generally of lesser value than the individual good. Though a contribution to general good and knowledge is important it must not be obtained through harm to the individual. Society and the commonwealth exist for the individual. In the event of common disaster, however, the public good (that of many individuals) justifiably prevails over any single individual good. This feature is noted for completeness and clarification. Generally, in current research it is not pertinent. However, one can conceive of a medical disaster of epidemic proportions where an all out research effort to obtain a cure and involving some human volunteers would benefit the community at large.

THE VARIABLES OF DANGER

In review of the several variables related to danger, it becomes evident that they can be identified as either of a quantitative nature or a qualitative type. These may be considered as coefficients and set down in quasi-mathematical terms. What type of danger exists is qualitative and for each hazard different levels of seriousness may be recognized. In considering the qualitative coefficient we may use the abbreviation *QUAL* or the letter T to signify the type of hazard with a subscript to identify the specific type as a, b, or c. Each specific hazard may be further determined as being insignificant, mild, moderate, severe or lethal and assigned numerical values 1, 2, 3, 4, or 5. Thus, a cardiac hazard or a dangerous effect on the heart can be designated as (Tc). If the degree of danger were moderate it would be [(Tc).3].

Consider now the quantitative coefficient. The significant determinant is the incidence of occurrence. If a particular hazard is rare but serious or even lethal, it might be acceptable if the goal is good or a great gain is to be derived. If the hazard were infrequent and serious it still might be acceptable but if the hazard were frequent and either of moderate or severe degree, it might be unacceptable. If a complication always occurred, even if mild, the procedure might be disapproved. In the event the incidence of a hazard in man is unknown one must resort to probability equations and from animal experiments or other information to estimate a factor of probability.

Thus, the quantitative coefficient must be derived from at least a probability of occurrence. The coefficient can be symbolized as P with a subscript for the actual quantitative feature. This can be best presently designated in descriptive terms as a continuum from never, rare, occasional, frequent and always. In per cent, this spectrum may be assigned the values of zero, 0.1 per cent, 1 per cent, 10 per cent and 100 per cent.

We are now in a position to state a basic equation.

$$\text{Danger} = \frac{\text{Qualitative Factors}}{\text{Type and Degree of Danger}} \times \frac{\text{Quantitative Factors}}{\text{Frequency of Danger}}$$

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Having reviewed the actual determinants of danger which may be considered the numerator of our equation, it is now necessary to consider the denominator or the goals of our research.

Analysis of the goals of experimentation may be summed in terms of the common good (CG) or individual good (IG). We may assign some values to goal directed experimentation. First, it is clear from previous discussion that IG>CG. A project, experiment or act which maintains this relation is likely to be good, moral, and acceptable if the calculated danger is not too high. An experimental act which endangers the individual inordinately but which carries the possibility of great community good is not acceptable under ordinary and peacetime conditions. In times of disaster the endangering of some individuals for the purpose of maintaining the community at large may be permitted. Thus, one recalls the experimental production of malaria and certain other diseases in volunteer prisoners so that new drugs (anti-malaria) could be tested for effectiveness and eventual use in large military populations. The goal

was a worthy one and the good of the community (the military forces) was the objective. Here, the relationship became IG<CG.

In general terms the good derived from a human experimental action has a spectrum ranging from maximal individual good (IG max) through median individual good (IG m) to minimal individual good (IG min); the spectrum of worth shades into moderate community good (CG mod) to minimal community good (CG min). Maximal community good (CG max) is noted last for it is obvious that this represents the good of most individuals and hence, (IG max) and (CG max) must coincide. In fact, the goals of experimentation may be expressed as a ratio of the individual good over the community good: IG/CG. Since each may change with respect to the other the possibility of a differential equation is evident.

Another reasonable question now arises—when does the individual good and the community good coincide? When does IG=CG or when does the ratio IG/CG=1 (one)? This relation may be illustrated by the experiments for the testing of chemicals for treatment of cancer. These drugs are potent and unusually toxic. Their efficiency can only be determined in human beings with cancer. Individuals with cancer may be justified in submitting themselves to these toxic drugs since they have a chance, even remote, to be cured. This is most desirable even though the risk of morbid complications or a lethal outcome is great. The experimenter may be justified in administering the potent and toxic drug because the worthy goal of gaining fundamental knowledge of the therapy of cancer which is basically a community good, coincides with the worthy goal of benefitting the individual. Our final equation may be stated as follows:

> Moderate danger is equal to the Qualitative Coefficient (Factors of type and degree of danger) multiplied by the Quantitative Coefficient (Factors of frequency of occurence) divided by the goals to be attained, and may be written:

$$\text{Moderate Danger} = \frac{\text{Qualitative Coefficient (Type of Danger-Degree of Danger)} \times \text{Quantitative Coefficient (incidence)}}{\text{Goals (IG/dCG)}}$$

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At this point, we let our thesis rest. The purpose of presentation is to stimulate thinking and encourage the mathematical minded to work out tables of relative values. Perhaps the essential factors can be programmed and introduced into a computer. One might find that a determined value of 1.0 is acceptable as the median of moderate danger; values less than 1 would mean a progressively widening margin of safety and relatively little individual harm. Values greater than 1 would indicate that the good to be derived either public or individual is limited and the overall danger progressively great. This presentation is not intended to be mathematically accurate. It is intended to be conceptual.