# EXPERIMENTATION IN MAN

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*By*

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# EXPERIMENTATION IN MAN

## PRESENT AIMS

EXPERIMENTATION in man for scientific purposes is as old as recorded history. The need for constant examination of the procedure is equally ancient. This is required by progress in science and by the advance of ethical and moral concepts.

In the two decades just passed, two reasons have emerged which especially point up the need for a new review of the subject: First, there were the outrages of Hitler's Germany. The puzzle is, how such things could have occurred in modern society. While the philosophical problems raised by those gross actions are beyond the area surveyed in this report, they too indicate the need for a long, straight look at our current practices. Second, there is the rather newly recognized fact that some types of basic scientific advance can be made only in the presence of disease. Nature presents us with bolder experiments than we would ever dare to perform ourselves. We profit from a study of them, *basic* science profits. (This will be discussed a little later on.) Having seen what fundamental ends can be achieved, the experimentalist is led to carry on where Nature leaves off. The purposes of human experimentation thus become deeper and more complex than ever before and so also do the problems surrounding it, reasons enough for this study.

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The problems of human experimentation do not lend themselves in most cases to a series of rigid rules. While one purpose of the present study is to set down views, concepts, even "rules" that have been accepted by one group or another, this is done so that the investigator troubled by a given problem can find references to past thinking on this subject, so that he can have a framework against which he can measure his problems in terms of the experiences and conclusions of others in similar situations.

The breaches of ethical conduct which have come to the personal attention of the reviewer were owing to ignorance or thoughtlessness. They were not willful or unscrupulous in origin. It is hoped that the material included here will help those who would do so to protect themselves from the errors of inexperience.

Finally, it can be said that while human experimentation has accompanied the practice of medicine from times of antiquity, the current concept of medical research has not really been presented as such to the courts. As the courts have understood it, it has not been, nor is it now, *legally* recognized as a legitimate part of the physician's activities. "So far, planned and directed medical research on human beings has not been tested" (29). The universal and longstanding recognition that research is essential to the advancement of medical science and the newer recognition that some aspects of basic science cannot advance without it, have led to a correct, although still extra-legal, expansion of human experimentation. Curiously, such work when well conceived and soundly conducted is everywhere

recognized as being properly within the ethical and moral concepts of our time, yet it remains outside legally. Legal inclusion will depend on an understanding of all facets of the problem.

## BRIEF HISTORY

THE oldest world literatures contain references to experimental work with both animals and man (24). It was the practice in ancient Persia for the king to hand over condemned criminals for experimental purposes in science. Later the Ptolemies did the same in Egypt (3). See also Paré (18). About 1800 years ago Galen, the founder of experimental physiology (13) somewhat formalized medical experimentation, but this fell under a cloud for the 1400 years of the Dark and Middle Ages, until Vesalius in the Sixteenth Century overrode the tradition against dissection of the human body and demonstrated certain errors in Galen's concept of the circulation of the blood. Three generations later Harvey, after carrying out controlled experiments in animals and in man (24), demonstrated the circulation of the blood, in particular that it all had to pass through the heart, if his calculations of volume and velocity were correct, and thus the first idea of measurement in biological investigation bore fruit (1616, 1628) (13). More than a hundred years later, Lind, in 1747, carried out a wonderfully well controlled study and demonstrated that oranges and lemons could cure the scurvy. A half-century after this, in 1798, Jenner, after controlled experiments in man, published his proof of the value of vaccination against smallpox. The world was ready for two of its greatest experimentalists, Claude Bernard and Louis Pasteur.

All was not smooth sailing for the eager investigator: Experimentation on other men requires a *willingness* to experiment upon oneself as evidence of good faith, although in a given case self-experimentation may be wholly impractical. When it is carried out, it must be done with the same safeguards that are applied to other subjects. Ivy (24) cites a number of examples to indicate that willingness without the discipline of proper controls can be misleading or devastating, or both, to the participant: There was the case of John Hunter who inoculated himself, in 1767, with gonorrheal pus to prove the disease transmissible in this way. He succeeded. But from the same inoculum he also acquired syphilis and concluded that gonorrhea and syphilis were merely manifestations of the same disease! Purkinjé in 1790, gave himself enough digitalis to kill nine cats in order to study the visual changes in himself. He had cardiac pain and irregularity and vomited for a week. Hales, enthusiastic about the marvels of intravenous injection, received a half ounce of castor oil by this route and lived to describe its remarkable effects. Tonery in 1830, in order to convince the French Academy of the extraordinary powers of charcoal to absorb alkaloids, took with this safeguard a dose of strychnine which without it would have been lethal. In 1857 carbon tetrachloride was tried out as an anesthetic in man; a few animal experiments would have shown it to be unsuitable. In 1894 Oliver told Professor Schafer that he had made extracts of all of the endocrine glands and injected them into his own son. Schafer altered the experiment and was first to demonstrate the pressor effect of epinephrine

in dogs and cats. Ivy concludes that "these experiments may be a tribute to the enthusiasm and bravery of these early medical scientists, but they clearly show the limitations and dangers of uncontrolled self-experimentation."

Clearing a hundred years at one leap we can come down to the present and find able men still in difficulties. When one shifts from a study of objective manifestation of disease to subjective effects, specifically, for example, to a quantitative study of the effect of drugs on symptoms, it becomes apparent that added controls are mandatory. Chief among these is the use of the "double unknowns" approach to eliminate bias, not possible when the experimenters are also the subjects, who, as drug experience and sophistication grows, cannot remain in ignorance of the "aura" produced by opiates, for example. The scores of studies that have been lost because of a failure once again to recognize and employ adequate controls have been reviewed elsewhere (5).

Paradoxically enough, in the last century at least, those who experiment in man have been freer of attack than those who carry out animal experimentation. The ethics of human experimentation will be discussed in a section to follow.

## SCOPE

THERE are many good reasons for a careful consideration of this subject: Protection of the subjects, the investigators and their research, their institutions, and the sound development of medicine. These all require a level-headed approach to experimentation in man.

Comparatively recent developments in medicine and changes in emphasis give added weight to an examination of human experimentation at this time. While prior experimentation in animals is absolutely necessary when possible, the crucial study of new techniques and agents must be carried out in man. The extraordinary skill of the organic chemist and the biologist working together in identifying active agents in natural products and the chemist's progress in creating new and promising compounds which ultimately must be tried out in man, all throw an exceptionally heavy load on the experimentalist. Man as the essential final test site has come into adequate prominence only in recent decades. The current development of human biochemistry, human physiology and human pharmacology has made it plain that man is the "animal of necessity" here. In addition to all this there is a new interest on the part of the truly basic scientist in human experimentation. This will be described in terms of the scientists' goals.

The investigator has many goals and it can be seen that these in ultimate aim are in many of their aspects like those of the practitioner: The investigator is concerned with health and its preservation and the betterment of life as well as with the causes and consequences of disease, the mechanism and relief of its symptoms, correction of its signs, prevention of lasting effects, the very eradication of disease. Activities directed toward these ends involve, very often, alteration of function of the body or the mind, in health or in disease, ". . . directly or indirectly, in individuals or in groups, primarily for the advancement of human welfare. Although use of a new procedure or its withholding may directly benefit the person involved (28) . . ." The investigator's basic purpose as distinct from the practitioner's, is to elucidate and to generalize. When possible, investigation begins in animals but finally must be applied to man.

The goals mentioned are ancient ones. There is a new one, or, more accurately, a newly recognized one: In the last decade or so it has become increasingly clear, as referred to in the introduction, that study of disease in man can have a deeper meaning than once was believed to be the case. The view was widely held—and still is in some quarters—that study of disease at the bedside level represents nothing more than applied science at best. A more thoughtful approach could long ago have led to a broader grasp of the situation: some parts of *basic* scientific advance (and I use the term in its classical sense) are utterly dependent on disease. An abundance of examples comes to mind: Pauling's interest in "molec-

ular disease" arose in part from work with abnormal forms of hemoglobin. While neurophysiologists have long been interested in the biochemistry of the potassium ion, recent basic advances in knowledge of this ion have come from studies of dehydration. Knowledge of the physiology of the endocrine glands is largely indebted to the fundamental leads found in disease. The anatomy of the central nervous system has in significant part been learned by study of cerebrovascular accidents. Such diverse matters as the discovery and understanding of vitamins, the development of microbiology, even the advance of genetics in study of hereditary factors in disease, all of these leave no room for doubt that truly basic science can be advanced by a study of disease processes. This awareness leads to a further extension of human experimentation. With these developments it is time once again to examine the many-faceted problem of experimentation in man.

"Properly conducted experimentation [in man] by qualified scientists must therefore be considered an integral branch of biologic and medical science, but it does not thereby become customary medical practice. Nor does its essentiality and acceptance establish clearly its character or place the methods employed beyond scrutiny. The responsible professions have a duty to delineate for their own members and for a critically vigilant public the nature of medical research and the limits within which it may be properly undertaken" (Ladimer, 1957).

These introductory remarks can be concluded with the comment that prevention of experimentation can also be an experiment, even a very dangerous one,

as for example withholding treatment of a control group. If experimentation is to be withheld, ". . . it should be demonstrated that the proposed experiment is more dangerous or more painful than the known [or probable] results of inaction" (Shimkin, 1953). This is the expression of an ideal rather than a practical possibility in most cases.

Throughout this article the aim has been to present sound background data, common sense views and principles of procedure rather than "rules." The intricate considerations which must be brought to bear on this general subject leave room for only a very few absolute statements. These are discussed in the section on CODES, to follow.

## SOCIAL NECESSITY

It is clearly evident in the foregoing remarks that human experimentation is essential for the welfare of the race, for in medical research lies "a common benefit not obtainable by other means" (28). The development of medicine, the safeguarding of health and some types of basic scientific advance all require human experimentation. But with the recent Hitlerian acts freshly in mind, it is not surprising that such phrases as "for the good of society" rightly meet a wary caution on the part of responsible investigators. In any case the scientist or physician has no right "to choose martyrs for society" as Kety (1957) has put it.

"It should be apparent that no stigma is attached to the performance of human experiments *per se;* disgrace and infamy can arise only through its misuse. The moral obligation of performing all human experiments, with due regard to the sensibility, welfare, and safety of the subject, must not be violated. As phrased by Claude Bernard in 1856, 'Christian morals forbid only one thing, doing ill to one's neighbor. So, among experiments that may be tried on man, those that can only do harm are forbidden, those that are harmless are permissible, and those that may do good are obligatory'." (Quoted from Wiggers, 1950) Unfortunately decision is usually not so simple as this sounds: choice very often lies among various shades of grey, not between black and white.