Acquiring New Information While Retaining Old Ethics

Victor Herbert

Scientific medical ethics are founded on the moral principles and standards of reason that are a part of ethics generally, and on the cumulative wisdom and experience of scientific knowledge and practice (*1*). Scientists of every persuasion, ethicists, philosophers, lawyers, sociologists, economists, and representatives from all walks of life play a role in the shaping of these ethics (*1*). Ethics is that branch of philosophy relating to human conduct, to the rightness and wrongness of certain actions, and to the good and bad of the motives and ends of such actions.

Silverman, in his article on retrolental fibroplasia (*2*) points out that this epidemic of blindness in infants has a moral, not only for medical experimentation on human beings [see (*3, 4*)], but also for self-experimentation by the public such as that with laetrile (amygdalin), and with megavitamin therapy, with increased reports of toxicity (*5, 6*). As Silverman points out (*2*), it is an irony of medicine that the retrolental fibroplasia stemmed from the efforts of physicians to increase the premature baby's chances of survival in good health. After about 12 years of intensive investigation of this epidemic of blindness, the cause was found, and the disease was virtually eradicated. The entire episode sharply presents the painful questions that surround experimentation with human beings, and particularly with newborn infants. When this epidemic appeared, adrenocorticotropic hormone (ACTH) was tried because of its effect on fibrous tissue formation, since the formation of such tissue behind the lens of the eye appeared to be the proximate cause of the blindness in these infants. It seemed curative in three-quarters of the infants on whom it was tried, and was hailed as a therapy for this epidemic. We now know that this disease relates to the oxygen-rich environment that was then standard treatment for premature infants, and that approximately three-fourths of the infants with early eye changes will return spontaneously to normal, with no treatment. The ACTH therapy was irrelevant to the cures achieved, since the 75 percent cure rate would have been achieved without it. Before we knew that, more than 50 separate causes of the disease were proposed. About half of them were formally examined, and four were tested in prospective clinical trials. The question was whether the causative factor was an excess or a lack of oxygen in the retina of the eye. Campbell, in Australia, and Cross, in England, published anecdotal evidence incriminating an excess of oxygen in 142 infants (*2*). But, in Paris, anecdotal observations of 479 infants led to the opposite (and wrong) conclusion, indicating the low worth of anecdotal accounts as a basis for drawing scientific conclusions.

Meanwhile, Ashton, in a very small series of one mother cat and three kittens, observed that exposure to high oxygen, which resulted in withering of the germinating blood vessels, led to subsequent wild regrowth of blood vessels in the retina, with hemorrhage (*2*). This hemorrhage led in infants to fibrous tissue formation, and the fibrous tissue then billowed out from the retina against the back of the lens. This basic and crucial observation was relatively ignored for some time. The use of excess oxygen in the first place in the treatment of premature infants was related to the general acceptance of the hypothesis put forth in the early 1940's that the high toll of brain damage in premature infants was caused by a lack of oxygen. Subsequent evaluation revealed that curtailing oxygen therapy to reduce retrolental fibroplasia is associated with an increased death rate from hyaline membrane disease in certain infants, and also increased brain damage, as the hypothesis had proposed (*2*). It was some time before the narrow, not yet ideal, balance was struck whereby premature infants who need extra oxygen to survive without brain damage get it, but in concentrations that do not seem to give rise to blindness. In his article (*2*), Silverman quoted Brody of Michigan State, who said that "scientists and clinicians are prone to error when they confuse scientific problems with value problems and try to solve the latter with the tools of the former." Proposed treatments must be fully tested before they are presented to the community for consideration and approval (*2, 7*). Silverman concluded with a plea for the controlled clinical trial rather than trial and error empirical studies.

To put in legal terminology what Tukey indicates (*8*), the only source of reliable evidence rising to the level of proof about the usefulness of any new therapy is that obtained from well-planned and carefully conducted randomized and, where possible, coded (double-blind) clinical trials (*8*). Applying that legal terminology to Mosteller's argument (*9*), uncontrolled studies may point a direction but cannot be evidence, as lawyers use the term evidence to mean something probative, which in the law of evidence means having the effect of proof, tending to prove or actually proving (*10*).

Sources of Ethical Difficulties

Problems in the borderline of science, statistics, and public policy have been discussed by Cornfield (*11*) in the context "Carcinogenic risk assessment." As he indicates, the uncertainties involved are not always fully amenable to statistical evaluation. Insofar as this is the case, they are not fully amenable to ethical conclusions and they are subject to difficult ethical controversy.

A dominant theme in Western civilization is that we are each autonomous beings with inherent dignity and value, and that we each control our lives and actions by our own choices to the greatest extent compatible with the rights of others (*1*). Acquiring new information while retaining old ethics need not involve a clash between respect for the individual and desire of the scientist for knowledge, whether his desire for knowledge is for its own sake, for his sake, or for the sake of others.

As Robinson has pointed out (*12*), ethical difficulties with organ transplants, brain death, sterilization, abortion, human experimentation of all types, cloning, genetic screening, psychosurgery, behavior modification, and euthanasia derive from respect for persons. Threats

Dr. Herbert is professor of medicine at the State University of New York, Downstate Medical Center, Brooklyn, and chief of the Hematology and Nutrition Laboratory, Veterans Administration Hospital, Bronx, New York 10468. He is chairman of the Life Sciences Committee, Section of Science and Technology, American Bar Association.

to this respect may take many forms, including inequality, such as when scarce medical resources are allocated on the basis of social worth, as has been done in the past in the selection of a patient for an artificial kidney or for hemodialysis. There is a threat when incompetents rather than consenting adults are used in experimentation. The threat may be manipulation seemingly inconsistent with human dignity, such as behavior modification.

The traditional device for adjusting our knowledge to our ethics in human experimentation has been the concept of consent [see (*4*)], because respect for persons means respect for their free, knowing, intelligent, and therefore informed, consent. Informed consent becomes a problem when persons are not capable of giving such consent because they are too young, or incompetent, or unconscious, or the like. Robinson (*12*) explores the legal concept of the substituted judgment doctrine, which is a reasoned approach to this ethical problem. In the substituted judgment doctrine, the court puts itself in the shoes of the incompetent, and acts on the same motives and considerations that it believes the incompetent would have acted on to make an informed judgment had he been competent. The court seeks to do for the incompetent what he would do himself, if he were capable of formulating and communicating his own choices. This is not only consistent with respect for his person and his dignity, but also recognizes that his welfare, in appropriate instances, may depend on helping others, such as in a transplant of an organ from an incompetent to a close and loving relative.

Good has indicated the need to reflect on the best ways of gaining the new knowledge that we need so badly, while retaining the highest values of our civilization and culture (*13*). These highest values are our ethics, our system of moral principles, our rules of conduct.

As was pointed out in the forword to *Ethics in Medicine* (*1*), ethics is the oldest intellectual discipline in the Judeo-Christian tradition. The fact that ethics may be formalized into law does not mean that those ethics will be adhered to or that the formalization is appropriately handled. Indeed, much of our ethical code, even when formalized in law, has not been reduced to justice. Our morality is our conformity to the rules of right conduct, regardless of whether those rules have or have not been cemented into law. Medical ethics, from the Hippocratic Corpus to the 1975 Tokyo update of the Declaration of Helsinki, are grounded in reflection on what is medically right or wrong, and are a defining characteristic of medicine as a profession (*1*).

Risks

Our problems arise because every physician dreams of treating untreatable diseases, or curing incurable ills. Each new treatment involves a risk. Until a treatment is tested in a human, physicians have no certainty as to how much good or harm that treatment may bring to humans. We take calculated risks.

Many medical researchers are unwilling to try anything on a patient that they have not tried on themselves first. For many studies, however, the subject for evaluation must be sick with the disease under study. For this, if the physician doing the study does not himself have the disease, it is necessary to work with those who do. Altman has collected many instances of self-experimentation by medical researchers (*14*).

It is clear that, in a number of experiments, it is an advantage if the subject is a physician. For example, a physician was evaluating the possibility of folate deficiency occurrence in a normal human without intestinal disease (*15*). Studies at Johns Hopkins and elsewhere had suggested that this vitamin deficiency could only occur in people with intestinal malabsorption because intestinal bacteria made the vitamin and presumably it was then absorbed. He had evidence from animal studies that folate was absorbed largely in the upper third of the small bowel, rather than low in the large bowel where the vitamin was made by bacteria, and thus he was inclined to disbelieve that work. He decided to go on a low folate diet and get bone marrow aspirates every 2 weeks to ascertain whether megaloblastic anemia, a characteristic of folate deficiency, developed. About 2 months after the study was begun, he awoke with lower extremity paralysis (it happened to be on Christmas morning). In thinking about the problem, he remembered an article published just a month earlier, about paralysis due to potassium deficiency. Reflecting on that article, he realized that the thrice-boiling of foods that was used to remove all the food folate was probably also removing the potassium. Had the experimental subject, in this first such experiment, not been a physician, the thought would probably not have occurred at that time. Because it did, and because he had on hand a sample of a saturated solution of potassium iodide that had come in the mail, he could drink some, and have enough potassium to get to the laboratory, where the on-duty research fellow was able, using a spectrophotometer and an electrocardiogram (*15*), to confirm that there was, indeed, a severe potassium deficiency, which was then corrected.

Before the physician tries any new treatment on a patient, he must weigh, as best he can, the potential assets and liabilities of alternative courses of action and consider these not only as a scientist, but also as if he were the patient, and also from the point of view of the social order (*16*). At times he must resist the push by zealots transfixed by a "belief" in a magic cure for a dread disease, as is occurring in the laetrile controversy (*13*).

Our ethical, legal, medical, and scientific codes in the United States each demand proof of diagnosis before accepting a claim of cure. We know that not every lump ("tumor" in medical parlance) is cancer and a lump that goes away with "magic cure" therapy will also go away with no therapy. Such tumors are either not cancers in the first place, or they undergo spontaneous remission, which occurs with variable frequency in various cancers. It is pertinent here to recall the magic ACTH cure for retrolental fibroplasia, which turned out to be nothing more than the fact that three-quarters of the patients with that disease in its early form recovered with no therapy. As scientists, we recognize the low worth of anecdotal evidence, just as lawyers recognize the "hearsay rule," which says that evidence that does not derive its value solely from the witness, but rests mainly on the veracity and competency of other persons, is not generally admissible in a courtroom (*10*). Unless a knowledgeable person can cross-examine the person who made the diagnosis, or gave the treatment, the allegation by a patient that he had cancer or any other incurable disease, or that a given treatment had an effect greater than that of a placebo, is without worth.

Despite the negative facts, we are often pushed into a clinical trial of so-called curative agents. Thomas noted that the only ethical way one can do a clinical trial of a questionable drug (laetrile, for example) is to impose it on existing therapy, rather than to give it instead of existing therapy (*17*). To give it instead of existing therapy could be murder. Let me cite a case in point (*18*). For example, in California, there was an 8-year-old girl who had a cancer of the eye which was believed by her doctors to be surgically curable. She had been admit-

ted to hospital, was scheduled for surgery, but in the waiting room her parents met a couple who told them that their son had been cured of a brain tumor by a chiropractor using vitamins and food supplements (laetrile is a food supplement, say its promoters). The parents canceled the surgery, removed their daughter from the hospital, and took her to a chiropractor. He treated her with vitamins and food supplements until the tumor grew to the point where her eye bulged out of its socket and the parents realized that the vitamins and food supplements were not helping. The malignancy had spread to the point where surgery could no longer save her, and she died. Subsequently, the chiropractor was indicted and convicted of second degree murder and sentenced to prison (*18*).

Ethics in New Kinds of Research

On another subject, we are now witnessing the codification into law of perceived ethics concerning research on recombinant DNA. The federal government is in the process of writing legislation to control research on DNA molecules, which control the characteristics of all known cells. The proposed federal DNA bill (*19*) would preempt all state and local laws regarding the production or use of recombinant DNA molecules unless their requirements are at least as strict as the federal one. This is a particularly delicate undertaking because Congress has no experience with regulating scientific research, and because the kind of research under scrutiny has the potential, not only of bringing great good to mankind, but also of threatening it with untold harm (*20*). This emphasizes the recent plea of Zinder of Rockefeller University to the Senate Subcommittee on Health that this legislative control be carried out with extreme care and without haste (*21*).

The committee on Life Sciences and the Law of the American Bar Association is engaged in evaluating questions relating to recombinant DNA legislation. The ethical considerations raised by members of the committee and others are many and varied, and include imponderables, such as what will actually happen if the advance of this particular science is restricted by legislation. There is no instance in the history of man where legislation to restrict any form of scientific inquiry has advanced that form. If the same type of legislative restriction had been applied to atomic fission research in 1939, we might never have discovered fission. The judgment to retard the advancement of science will always find adherents, but the wisdom of such a course of action is difficult to assess.

In the April 1977 *Hastings Center Report* (*22*) which is the journal of the Institute of Society, Ethics, and the Life Sciences, there were three articles on the ethics of recombinant DNA, and more appear everywhere one looks. Cohen (*23*) reflects on the problem and concludes that there is no legitimate basis for slowing or stopping research on recombinant DNA. A few pages later, Goldstein (*24*), in an editorial in the same journal, calls for the slow, thoughtful approach of a temporary slowdown for 5 to 10 years. He feels that the "Go" signal should be the result of careful evaluation by decision-making bodies democratically appointed and representative of the rich diversity of ethical and scientific points of view.

Our old ethics are our ethics today and will continue to be our ethics in the future. They are the distillate of our philosophic thinking. In deciding what we can and cannot do to acquire new information, we must be in possession of as many scientific facts as possible. Our ethical decisions are based upon such knowledge as we have, and our best informed guesses about what we do not know. Cornfield (*11*) touched very briefly on an ethical-legal decision with relation to sugar substitutes; this of course is the saccharin decision based on the Delaney Amendment. Here we see the tensions when one attempts to make an ethical decision in the presence of inadequate evidence. There is evidence that a significant number of the saccharin-fed offspring of rats who were themselves on diets containing 5 percent saccharin developed bladder tumors. The quantity of saccharin, when translated into human terms, is equal to 800 cans of diet soda per person per day. Compare this to the average consumption by humans in the United States of approximately one and a half cans per day.

Cornfield has indicated (*11*) that certain assumptions are necessary in order to apply statistics to such a problem. In the case of the saccharin-treated rats, we must make two assumptions. The first is that what is so in rats is so in humans, and second is that we are dealing with a straight line curve that has no zero toxicity level (that is, the curve goes back to a baseline of zero). Treating those assumptions as facts, we can project, in the U.S. population of 220 million, a urinary bladder cancer rate of 1200 cases a year. We do not have to consider whether these two assumptions are correct because, as Cornfield noted, we have the Delaney Amendment which eliminates our need to think about the subject, since it states that if any substance in any animal is associated with the development of any cancer, it may not be added to human food; that is, it states that the law is that our two unproven assumptions are proven facts.

Still central to ethical controversies is the concept of informed consent, about which a great deal has been written, and that I reviewed 2 years ago in the context of the use of drugs that have possible undesirable side effects (*16*). A major ethical and legal question is, "Is there any such thing as informed consent?" The reason for this question is twofold: (i) if a subtle form of coercion is involved, as, for example, in the consent of a prisoner, or the consent of a less knowledgeable person to one he perceives as more knowledgeable, is that consent? and (ii) if the patient is told everything appropriate for him to be told, is he then informed?

Regarding this second point, a recent study at Montefiore Hospital in the Bronx (*25*) demonstrated that a majority of surgical patients denied after surgery that they had been told about all the possible undesirable outcomes prior to the surgery, even though discussion of possible undesirable outcomes ran for an hour and a half prior to the surgery and was tape recorded. If the brain does not record, store, or recall the information supplied to it, or suppresses that information, has there been informed consent? Is the concept of informed consent really a legalistic rather than an ethical one, with the legalisms being used instead of ethics rather than in support of ethics? Surely, informed consent should mean that the right thing is being done, as the patient would have wanted it to be done had he truly understood, rather than that the wrong thing has been done and has been justified to the patient.

At the 1977 annual meeting of the American Bar Association, the section on science and technology had a program covering the subjects, regulation of experimentation on human subjects, the federal role in regulation of scientific research, and regulation of experiments in recombinant DNA. One of the major legal considerations in that symposium was, what disclosure standards should exist, that is, what should the patient be told in coded experiments, which are considered by some critics as inherently deceptive because the participants do not know whether or not they are in the control group. Similarly, according to Milgrim, "a majority of the experiments

carried out in social psychology use some degree of misinformation" (*26*, p. 19), and thus "subvert the possibility of informed consent" (*26*, p. 21). "Prior general consent" or "presumptive consent" (*26*, p. 21) have been proposed to deal with this ethical problem.

Recombinant DNA research makes it at least theoretically possible to combine the genetic characteristics of plant and mammal, to produce a "plammal" or a "mant." We need to find a balance between possibly inadvertently producing the means to cause catastrophe to mankind, and potentially high beneficial developments. The genetic splicing of recombinant DNA technology has already been used to transfer the rat gene for insulin production to bacteria (*27*). This development has the potentially high beneficial consequence of making possible massive commercial production of human (instead of other species) insulin for diabetics. It also has, in the eyes of some, the possibility of catastrophe should insulin-producing bacteria get out of the laboratory into the body of a human, to multiply and throw the person into insulin shock.

One argument is that knowledge is power, and if we do not acquire the knowledge, other countries will. Remember that in World War II the other side was also working on an A-bomb. If we acquire the knowledge, we can also acquire the means to control the knowledge. If we do not, the controls may be in other hands. These, too, are ethical considerations.

As Jonas notes (*28*), generally there is something experimental because tentative about every individual treatment, beginning with the diagnosis itself. He would be a poor doctor who would not learn from every case for the benefit of future patients, and a poor member of the profession who would not make any new insights gained from his treatments available to the profession at large.

In summary, we recognize that acquiring new information while retaining old ethics demands adherence to the fundamental rule that a person should not be subjected to avoidable risk of death or physical harm unless he freely and intelligently consents. The problem is to balance rights against benefits with respect for human dignity in the quest for the cure of human diseases.

References and Notes

1. S. J. Reiser, A. J. Dyck, W. J. Curran, Eds., *Ethics in Medicine* (MIT Press, Cambridge, Mass., 1977).
2. W. A. Silverman, *Sci. Am.* **236** (No. 6), 100 (1977).
3. B. Barber *et al.*, *Research on Human Subjects* (Russell Sage Foundation, New York, 1973).
4. G. J. Annas, *The Rights of Hospital Patients*, American Civil Liberties Union Handbook (Avon, New York, 1975).
5. V. Herbert, in *Proceedings, Western Hemisphere Nutrition Congress IV*, P. L. White and N. Selvey, Eds. (Publishing Sciences, Acton, Mass., 1975), pp. 84–91.
6. E. E. Conn, in *Toxicants Naturally Occurring in Foods* (National Academy of Sciences, Washington, D.C., 1973), pp. 299–308; J. P. Lewis, *West. J. Med.* **127**, 55 (1977); *Fed. Regist.* **42**, 39768 (1977).
7. H. K. Beecher, *J. Am. Med. Assoc.* **159**, 1602 (1955); *Research and the Individual: Human Studies* (Little, Brown, Boston, 1970).
8. J. W. Tukey, *Science* **198**, 679 (1977).
9. J. P. Gilbert, B. McPeck, F. Mosteller, *ibid.*, p. 684.
10. H. C. Black, *Black's Law Dictionary, Revised* (St. Paul, Minnesota, ed. 4, 1968). In "United States of America *v.* Articles of Food and Drug Consisting of . . . apricot kernels . . . amygdalin . . .," Civil No. 77-C-285 (U.S. District Court, Eastern District of Wisconsin, 29 July 1977), Judge Reynolds closed a laetrile factory after holding as a Finding of Fact that, "Anecdotal and testimonial evidence as to cures or effects of treatments on cancer victims as described by lay persons, or persons possessing either an M.D. or Ph.D., but who are not qualified by scientific training and experience as experts in the field of cancer therapy, is not probative or substantial evidence of the safety and efficacy of cancer treatments." Judge Reynolds held as a Conclusion of Law, "The testimony of lay witnesses as to the existence of cancer and the safety and efficacy of an alleged cancer treatment based on their personal experience with the treatment is entitled to no weight and is therefore inadmissible as irrelevant and non-probative evidence." As precedents for this Conclusion of Law, Judge Reynolds cited United States *v.* Hoxsey Cancer Clinic, 198 Fed. Rep., 2nd ser. 273 (5th Cir. Ct., 1952); United States *v.* Wier, 281 Fed. Rep., 2nd ser. 850 (5th Cir. Ct., 1960), and Federal Rules of Evidence 401, 402, 403, and 701.
11. J. Cornfield, *Science* **198**, 693 (1977).
12. J. A. Robinson, *Columbia Law Rev.* **76**, 48 (1976).
13. V. Miké and R. A. Good, *Science* **198**, 677 (1977).
14. L. A. Altman, *N. Engl. J. Med.* **286**, 346 (1972).
15. V. Herbert, *Trans. Assoc. Am. Physicians* **75**, 307 (1962).
16. ———, *Am. J. Clin. Nutr.* **28**, 555 (1975).
17. L. Thomas, *Science* **198**, 675 (1977).
18. S. Barrett and G. Knight, Eds., *The Health Robbers: How to Protect Your Money and Your Life* (Stickley, Philadelphia, 1976), J. W. Miner, *J. Forensic Sci.* **9**, 1 (1964); California *v.* Phillips, 75 Calif. Rep. 720 (1969), certiorari denied, 396 U.S. 1021 (1970).
19. S. 1217. A bill to regulate activities involving recombinant deoxyribonucleic acid, 19 May 1977 (introduced by Senator Edward Kennedy, D-Mass.); Newsletter, *Fed. Am. Soc. Exp. Biol.*, **10** (No. 8), 2 (1977).
20. B. D. Davis, E. Chargaff, S. Krimsky, *Chem. Eng. News*, 30 May 1977, pp. 26–42. The latest evidence is that fears regarding recombinant DNA research may be greatly exaggerated [P. H. Abelson, *Science* **197**, 721 (1977); W. Gaylin, *N. Engl. J. Med.* **297**, 665 (1977)].
21. N. Zinder, hearings before the Subcommittee on Health, U.S. Senate, on S. 1217 (1977).
22. T. M. Powledge, *Hastings Cent. Rep.* **7** (No. 2), 18 (1977); D. Callahan, *ibid.*, p. 20; K. Dismukes, *ibid.*, p. 25.
23. C. Cohen, *N. Engl. J. Med.* **296**, 1203 (1977).
24. R. Goldstein, *ibid.*, p. 1226.
25. G. Robinson and A. Merav, *Ann. Thorac. Surg.* **22**, 209 (1977).
26. S. Milgrim, *Hastings Cent. Rep.* **7** (No. 2), 19 (1977).
27. A. Ullrich *et al.*, *Science* **196** 1313 (1977); N. Wade, *ibid.* **197**, 1342 (1977).
28. H. Jonas, in *Ethics in Medicine*, S. J. Reiser, A. J. Dyck, W. J. Curran, Eds. (MIT Press, Cambridge, Mass., 1977).

Carcinogenic Risk Assessment

Jerome Cornfield

Man is exposed to a variety of natural and synthetic substances that are known to be harmful to experimental animals in high doses and consequently are under suspicion of being harmful to humans in low ones. Exposure to many of these substances, particularly those involving involuntary exposure through food, water, air, or the workplace is subject to regulation by governmental agencies. In some instances the benefits conferred by a suspected substance can be achieved by other safe substances in equally satisfactory ways, in which case the most appropriate regulatory action is an outright ban, no regard being given to the strength of the suspicion. But in many cases important benefits are lost if the agent is banned, and the magnitude of the risk must then be balanced against the benefit conferred. The risk may be of such magnitude that banning is appropriate even in the face of the benefits, or it may be so low at the levels to which humans are exposed that a ban is not considered appropriate. Risk assessment is therefore an essential component of regulatory decisions. It is also a particularly appropriate topic for consideration because of the mixture of statistical, scientific, and public policy considerations that it presents. The problem of risk assessment is the same formally, no matter what the route of exposure, but since much of the exposure is by way of food, I will confine my discussion to that topic.

The author is professor of statistics at George Washington University, Washington, D.C. 20052.