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SPECIAL ARTICLE

ETHICS AND HUMAN EXPERIMENTATION

Henry Beecher Revisited

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TWENTY-ONE years ago, in June 1966, Henry Beecher, Dorr Professor of Research in Anesthesia at Harvard Medical School, published in these pages an analysis of "Ethics and Clinical Research" and thereby accelerated the movement that brought human experimentation under rigorous federal and institutional control.[1] Although Beecher was not the first to direct attention to abuses in human experimentation, and the National Institutes of Health was already formulating stricter rules, his presentation of 22 examples of investigators who endangered "the health or the life of their subjects" without informing them of the risks or obtaining their permission was a critical element in reshaping the ideas and practices governing human experimentation.[2,3]

Beecher's most important and controversial conclusion was that "unethical or questionably ethical procedures are not uncommon" among researchers — that his 22 cases represented the mainstream of science. To explain why researchers adopted invasive or risky procedures without informing their subjects or seeking consent, Beecher cited the pressures that advancement and promotion exerted "on ambitious young physicians." In their drive to win tenure in medical schools "increasingly dominated by investigators," they were led to commit "ethical errors." How valid were these arguments? Were Beecher's 22 examples the work of marginal researchers? Was the mountain of regulations that followed an exaggerated response to a few aberrant incidents? And what explains the investigators' behavior?

One answer has been to deny that the 22 cases fell within the mainstream of science. Beecher did not name the researchers or footnote the article — the *Journal* editors reviewed an annotated copy and vouched for the accuracy of his references — but his brief accounts suggested that the research he cited was not marginal. Experiments on servicemen (example 2) indicated the cooperation of the U.S. Army; research in cardiac catheterization (example 17) required the facilities of a major university or government hospital. An analysis of the original journal articles from which

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Beecher drew his cases (the first since its publication) reveals that all the articles were recent (13 published between 1950 and 1959 and 8 between 1960 and 1965) and had appeared in such prestigious journals as the *New England Journal of Medicine* (examples 1, 4 through 6, 14, and 16), the *Journal of Clinical Investigation* (examples 8, 10, 13, 15, and 20), the *Journal of the American Medical Association* (examples 2 and 9), and *Circulation* (examples 19 and 20). (Beecher concluded that citing the specific articles would distract attention from the larger points he was trying to make, and I have here followed his example. The sources for the analysis are the original articles on which Beecher based his 22 examples; these articles are filed with his personal papers.) The funders included the Surgeon General's office and the Armed Forces Epidemiology Board (five studies); the National Institutes of Health (five studies); drug companies, including Parke–Davis and Merck (three studies); and the Public Health Service and Atomic Energy Commission (three studies).

Even more indicative of the mainstream character of the science were the sponsoring organizations: 14 of the 22 protocols were carried out in university medical school clinics and laboratories: Western Reserve University (examples 1 and 2); the University of California Center for Health Sciences, Los Angeles (example 5); Harvard Medical School or two of its affiliated hospitals, Peter Bent Brigham and Children's Hospital (examples 6, 9, 13, and 14); the University of Pennsylvania (example 7); Georgetown and George Washington universities (example 8); Ohio State University (example 12); New York University (example 16); Northwestern University (example 18); and Emory and Duke universities (example 21). Three of the studies were conducted at the Clinical Center of the National Institutes of Health (examples 10, 11, and 20).

A second response is the insistence that the researchers involved were working in an ethical vacuum, because the basic principles of informed consent were as yet unformulated. Such a response, however, claims both too much and too little for the state of clinical ethics in the 1950s. The field was not as underdeveloped as this argument suggests. But researchers were working in a framework that insulated them from such considerations.

Human experimentation has a lengthy history, and so does the effort to define appropriate codes of conduct.[4] In the modern period, experimenters were expected to have the agreement of subjects, however casual the request or general the approval. Research ethics, however, was discussed infrequently, not only because medical ethics was not an active field (codes mostly addressed medical etiquette), but because human experimentation was a cottage industry, conducted by a handful of physicians whose subjects were, typically, themselves or family members or neighbors and whose aims were directly therapeutic for the subjects. Edward Jenner, for example, first tested his smallpox vaccines on his firstborn son and on neighbors' children.[5] The physician Johann Jorg, 1779–1856, swallowed various doses of 17 drugs to analyze their effects; James Simpson, searching for an anesthetic superior to ether, inhaled chloroform and awoke flat on the floor.[6] Even as Louis Pasteur conducted successful research in the laboratory and on animals in his search for an antidote to rabies, he worried about testing the preparation on humans.[7] When Joseph Meister was brought to him for treatment, Pasteur agonized over the decision, consulted with two medical colleagues, and intervened only after everyone was convinced that "the death of the child appeared inevitable."[8]

In the 1890s, germ theory spurred research trials that were far more likely to use hospital patients. Nevertheless, clinical investigation remained a relatively intimate and directly therapeutic enterprise. German physicians tested a serum against diphtheria on 30 hospitalized patients,[9] and Banting and Best tested their insulin therapy on diabetic patients in coma or on the verge of it.[10] To be sure, in 1901 the Russian physician V.V. Smidovich cited more than a dozen experiments, mostly in Germany, in which patients were unknowingly inoculated with microorganisms of syphilis and gonorrhea.[11] In the United States in the 1910s, Hideyop Noguchi, at the Rockefeller Institute for Medical Research, sought to establish the diagnostic value of luetin, an extract from the causative agent of syphilis, by first testing the substance on himself and then, with the assistance of 15 New York physicians, on some 400 subjects, many of them inmates of mental hospitals and orphan asylums.[12] But before the 1940s, such incidents were highly exceptional, and research ethics was not a subject of widespread concern.

As long as clinical research continued to be conducted on a relatively small scale and with directly therapeutic intent, research ethics did not have to be a subject of extensive investigation, debate, or concern. Although one can cite earlier statements on research ethics from Avicenna, Roger Bacon,[9] or Claude Bernard, such statements reflect the moral acuity of individual commentators more than a shared sense of crisis. Bernard, for example, was far better known among contemporaries for his research on glycogen than for his ethical formulations. His 1865 statement,

> The principle of medical and surgical morality consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., the health of others,[13]

has been repeated more frequently in the past 20 years than in the previous 100.

The turning point in human experimentation in the United States was World War II, and practices established during these years profoundly influenced researchers' behavior in the postwar era. For the first time, clinical investigations became well-coordinated, extensive, and centrally funded team efforts; experiments were now frequently designed to benefit not the

research subjects but others — namely, soldiers vulnerable to the disease in question. And this transformation occurred just when wartime conditions were undercutting a sensitivity to the need to obtain the consent of subjects or to respect their rights.

In the summer of 1941, President Franklin Roosevelt created the Office of Scientific Research and Development to oversee the work of two parallel committees — one devoted to weapons research, and the other, the Committee on Medical Research (CMR), to medical research. The CMR, as Chester Keefer, one of its key figures, later explained, represented "a novel experiment in American medicine, for planned and coordinated medical research had never been essayed on such a scale."[14] Over the war years, the CMR expended some $25 million in research contracts with 135 universities, hospitals, institutes, and companies.[15] Its chief concerns were to create antidotes to dysentery, influenza, venereal diseases, and malaria, which would require extensive trials with human subjects.

The first difficulty confronting investigators seeking to identify preventives or antidotes to dysentery was to locate suitable research sites. Research on the battlefield was out of the question, not only because potential vaccines might prove toxic, but because controlled trials and statistical evaluation were impossible. Instead, asylum wards where dysentery was endemic were substituted as the setting of research,[16] and no one objected to experiments on impaired inmates.[15] In fact, researchers with links to custodial institutions had an edge in securing grants.[17]

Accordingly, CMR contract 293 funded investigators to conduct five experiments that attempted to immunize children at the Ohio Soldiers and Sailors Orphanage with "killed suspensions of various types of shigella group of bacteria." The experiments, all of which were unsuccessful, did produce serious side effects. The team injected some suspensions subcutaneously, others intravenously; particularly severe was the reaction to the intravenous injections of

> ten million [dysentery] bacteria. . . . The skin was pale and ashy grey in color . . . the temperature sky-rocketed to 105°F and up in spite of measures to counteract the rise. Severe pounding headache and a constricting type of backache were almost universal complaints. . . . Rapidly, nausea, vomiting and watery diarrhea ensued. Fever persisted for 24 hours and when it subsided the subjects were exhausted.[18]

Trials were also carried out on the retarded residents of a Dixon, Illinois, institution and at the New Jersey State Colony for the Feeble-Minded.[19-21]

The most pressing problem confronting the CMR in 1941 was malaria,[15] because the disease was debilitating and deadly and the Japanese controlled the quinine supply. Unlike dysentery, malaria was rarely found in the United States, so researchers infected subjects and then measured the effectiveness of their antidotes. To this end, a team from the University of Chicago, under CMR grant 450, established a 60-bed clinical unit at the Manteno Illinois State Hospital. The subjects, psychotic backward patients, were infected with malaria through blood transfusions and then given antimalarial therapies.[22] The Chicago group, and other investigators as well, relied even more heavily on prisoners in state penitentiaries; one floor of the prison hospital at the Statesville, Illinois, penitentiary was turned over to the University of Chicago for research on malaria, with some 500 inmates volunteering. Some of them were infected by mosquito bites and given pentaquine; researchers then correlated the severity of the malaria challenge (moderate, severe, or extraordinarily severe) with the drug regimen, the relapse rate, and the side effects, which included nausea, vomiting, electrocardiographic changes (depression of T waves), severe weakness, anoxia, and blackouts.[23-25] The public response was not to ask whether prisoners were able to give voluntary consent, but to congratulate "these one-time enemies to society" for demonstrating "to the fullest extent just how completely this is everybody's war."[26]

The CMR also sought to create a vaccine against influenza, "the cause of the greatest amount of disability" among soldiers, and given the World War I epidemics, a much-feared disease. One team from the University of Pennsylvania Medical School and Philadelphia's Children's Hospital tested vaccines against influenza A and B by administering the vaccine to several hundred residents at the nearby state facility for the retarded (Pennhurst) and at a correctional center for young offenders and then, three or six months later, challenging them with influenza. The team also injected control groups with the virus but not the vaccine in order to compare the different rates of infection. As was expected, those who contracted the disease had fevers (temperatures up to 40°C) as well as aches and pains.[27-29] Although the vaccines often provided some protection, the recipients did not always escape side effects. A group of women residents of Pennhurst who received a vaccine in a mineral-oil base had nodules at the injection site for 6 to 18 months, and two had very severe abscesses (one requiring corrective surgery).[30]

Only one set of experiments conducted under the auspices of the CMR prompted a remarkably complete discussion of ethics, and that was research into the prevention and cure of gonorrhea. Investigators were so apprehensive about the legal, political, and ethical implications that they asked, and received, formal permission from the CMR to conduct human experiments with prisoners.[31] The CMR insisted here (but nowhere else) that

> When any risks are involved, volunteers only should be utilized as subjects, and these only after the risks have been fully explained and after signed statements have been obtained. . . . An accurate record should be kept of the terms in which the risks involved were described.[32]

The CMR even convened a special committee to review protocol decisions about the prisoners ineligible to volunteer (those who had had negative reactions to sulfonamides and so on), the infective agent to be

transmitted (a strain not resistant to sulfonamides, with a low thermal death point), and a two-page, single-spaced "Statement of Explanation of the Experiment and Its Risks to Tentative Volunteers" — in effect, a consent form.[33] Although an institutional review board today might object that the document exaggerates the potential benefit of the research to the subjects and is too aggressive in its recruitment, the form is notably accurate about the risks posed by the research.

The exception that was represented by the gonorrhea studies indicates that if principles of informed consent and risk–benefit calculations were occasionally recognized, wartime demands usually obscured them. When research promised to buttress the war effort (as did research on influenza, malaria, and dysentery), considerations of consent and voluntariness disappeared. When the research did not have unambiguous social approval (as with gonorrhea), formal review and procedures for obtaining consent became necessary.

A wartime environment also undercut the protection of human subjects, because of the power of the example of the draft. Every day thousands of men were compelled to risk death, however limited their understanding of the aims of the war or the immediate campaign might be. By extension, researchers doing laboratory work were also engaged in a military activity, and they did not need to seek the permission of their subjects any more than the selective service or field commanders did of draftees.

Using mentally incompetent inmates as research subjects also accorded closely with popular ideas about the sacrifices appropriate to the home front. All citizens should be doing their part, even at great personal cost — a sentiment that helped to legitimize experiments on the mentally ill and retarded. The disabled, too, had a stake in an allied victory, and therefore, the presumption went, if they had been capable of a momentary flash of competence, they would have agreed to participate in research that furthered the war effort. Hence, using them as research subjects did not violate their interests.

In a society mobilized for war, these arguments carried great weight. Some people were ordered to face bullets and storm a hill; others were told to take an injection and test a vaccine. In philosophical terms, wartime inevitably promoted utilitarian over absolutist positions. The greatest good for the greatest number is a precept that justifies sending some men to be killed so that others may live, and a utilitarian ethic has little difficulty justifying the use of the institutionalized retarded or mentally ill for experimentation. Of course, the investigations had to be scientifically sound and built on appropriate tests in animals, and they could not place the subjects at risk of grievous injury or death; the CMR projects consistently satisfied these criteria. In sum, the ethics of American research during World War II were frankly and unashamedly utilitarian.

A perspective on human experimentation born in the war against totalitarianism carried over into the war against disease, which helps to explain the behavior of the researchers in Beecher's 22 examples. The CMR gave the National Institutes of Health not only its organizational framework but its ethos as well.[34] The case for continuing federal support for research after World War II cited the CMR's record of accomplishments in anticipation of even greater achievements.[35,36] And the prospect of winning the war against contagious and degenerative illness gave researchers in the 1950s and the 1960s a sense of both mission and urgency that kept the spirit of the wartime laboratories alive.

Most of the researchers in Beecher's protocols were the products of medical and scientific training in the immediate postwar period. They had not been part of the war effort or held CMR contracts or grants. Of the 32 American investigators, only 8 had been born before 1920 (of whom 4 saw military service); 17 were born between 1921 and 1929, and 7 between 1931 and 1934. But a utilitarian ethic continued to govern human experimentation — partly because of the war precedent, partly because the benefits seemed so much greater than the costs, and partly, too, because there were no groups or individuals prominently opposing such an ethic. To be sure, numerous international codes defined ethical standards for human experimentation, most notably the Nuremberg Code, but the issue did not command much attention. The Nuremberg trial of the Nazi doctors, for example, received very little press coverage, and before the 1970s, the code itself was infrequently cited or discussed in medical journals. American researchers and physicians apparently found Nuremberg irrelevant to their own work. They believed (incorrectly, as it turned out) that the bizarre and cruel experiments had been conducted not by scientists and doctors but by sadistic Nazi officers, and therefore that dedicated investigators had nothing to learn from the experience.

This approach at once reflected and encouraged a particular selection of subjects for human experimentation. In almost all the 22 protocols, the subjects were institutionalized or in some other situation that compromised their ability to give free consent: soldiers in the armed forces (examples 1 and 2), charity patients in a hospital (example 3), institutionalized mentally retarded children (examples 4 and 16) or newborns (examples 6 and 22), the very elderly (examples 9 and 17), the terminally ill (example 12), chronic alcoholics with advanced cirrhosis (examples 13 through 15), and subjects at the National Institutes of Health Clinical Center, which at the time did not require full disclosure to its patients.

That investigators continued to pursue a utilitarian ethic is not as surprising as the public revolt against it in the late 1960s. The revolt was fueled not only by the publication of Beecher's article, but by a new wariness about the fruits of scientific research (nuclear developments, pesticides) and a general hostility toward authority. One result was the rise of rights-oriented movements on behalf of prisoners, mental patients,

women, and of course, human subjects. Moreover, because of human experimentation, lawyers, philosophers, social scientists, and elected officials entered the world of medicine. Articles on human experimentation proliferated,[2] and so did calls for formal review procedures.

In short order, federal regulations mandated the creation of institutional review boards to review all protocols submitted for federal funding to make certain that subjects had given informed consent and that the risks did not outweigh the benefits. For the first time, decisions that were traditionally left to the consciences of individual physicians came under collective surveillance. Controversies marked not only the origins but the continued operation of the institutional review boards. Some critics argue that the committees are poorly administered, time consuming, and uneven in performance, and that most patients are unable to give informed consent, making it preferable to trust to the integrity of the researcher. But in policy terms, this remains the minority view. The memory of the postwar record precludes a return to a hands-off policy, and institutional review boards are now regarded as symbolically and actually valuable. At the least, researchers today would not consider submitting protocols like those in Beecher's list of 22. At the most, more subjects are giving truly informed consent.

No matter how favorable to deregulation the political climate may be, it is likely that researchers will continue to operate under close supervision and in the glare of committee lights.

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