

## MEDICINE AND SOCIETY

## “Ethics and Clinical Research” — The 50th Anniversary of Beecher’s Bombshell

David S. Jones, M.D., Ph.D., Christine Grady, M.S.N., Ph.D., and Susan E. Lederer, Ph.D.

Human-subjects research receives intense scrutiny today. Researchers, institutions, funders, and journals pay serious attention to ethical conduct. Yet controversies continue, whether about experimenting with oxygen levels in neonatal intensive care or with the duty hours of surgical residents.<sup>1,2</sup> Some commentators have even argued that anxiety over the ethics of Ebola research created delays that resulted in lost opportunities.<sup>3</sup>

Many researchers and bioethicists believe that serious discussions of research ethics began after World War II.<sup>4-6</sup> The actual history is longer and more complex. Nonetheless, Henry Beecher’s “Ethics and Clinical Research,” published 50 years ago, played an important role. Beecher warned researchers and the public about serious problems with research in the United States and exhorted researchers to reform.<sup>7</sup> Research regulations proliferated in the ensuing decades. However, as Beecher surely anticipated, new policies and procedures have not resolved every dilemma. Now, as in 1966, reasonable people disagree about research ethics.

### RESEARCH ETHICS BEFORE 1966: REGULATE OR RELY ON VIRTUE

Humans have experimented on humans for millennia, and they have long been aware of ethical risks.<sup>8</sup> Human research expanded in the late 19th century, as physicians tested new theories and technologies.<sup>9</sup> Ethical concerns remained paramount. Claude Bernard set a high bar in 1865: “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.”<sup>10</sup> William Osler insisted that researchers experiment on patients only if “direct benefit is likely” and only with

“full consent.” Otherwise “the sacred cord which binds physician and patient snaps instantly.”<sup>11</sup>

Some researchers heeded these tenets. Walter Reed solicited volunteers from American soldiers and recent Spanish immigrants in Cuba, offered them payment, and had them sign contracts certifying their awareness of the risks before exposing them to yellow fever. Other researchers triggered scandals by infecting patients, orphans, or asylum inmates with pathogens without their knowledge.<sup>8,9</sup> In 1916, Walter Cannon pushed the American Medical Association (AMA) to mandate informed consent for research.<sup>12</sup> The organization refused, arguing that misconduct was a problem of rogue researchers, not research itself. The AMA believed that trust, not regulation, would foster better research and clinical care.<sup>9</sup>

World War II prompted extensive human experimentation. American researchers were often scrupulous in their use of informed, consenting volunteers but sometimes pressured soldiers to volunteer without full knowledge of the risks and sometimes used institutionalized populations.<sup>8,13-15</sup> German and Japanese researchers went further, committing atrocities in the name of scientific research.<sup>16,17</sup> When allied authorities prosecuted Nazi physicians at the War Crimes Tribunal (Fig. 1), they issued the Nuremberg Code, specifying that researchers should always recruit competent research subjects who understood the nature of the research and voluntarily consented to participate.<sup>18,19</sup>

The Code, however, had no binding legal authority, and American researchers responded in complex ways. Some government agencies issued new guidelines — in 1953, for instance, the secretary of defense mandated written consent in military research on atomic, biologic, and chemical weapons (though this policy was kept



**Figure 1.** The Defendants Dock during the Medical Case (Doctors') Trial at the Military Tribunal at Nuremberg, 1946 to 1947.

U.S. Holocaust Memorial Museum; courtesy of Hedwig Wachenheimer Epstein.



**Figure 2.** Henry Beecher.

Courtesy of Massachusetts General Hospital, Archives and Special Collections.

“top secret”).<sup>20</sup> The same year, the National Institutes of Health (NIH) Clinical Center implemented peer review and informed consent for research on healthy volunteers. In other venues, however, much was left to researchers' discretion.<sup>8,21</sup>

Many U.S. scientists believed that the Code, a response to the work of experiments by Nazi researchers, did not apply to them.<sup>22</sup> Others understood the need for guidelines but sought to moderate the Code's strict language. For instance, as the World Medical Association drafted its 1964 Declaration of Helsinki, U.S. representatives, with funding from the pharmaceutical industry, blocked the requirement for informed consent in all cases, believing it would threaten placebo-controlled drug trials. They also blocked a ban on research on institutionalized children and prison inmates, who were widely used to test vaccines and drugs.<sup>23</sup> Similarly, when the Senate debated a 1962 amendment that would have mandated informed consent for research with experimental drugs, dozens of leading researchers protested. One described informed consent as “a snare and delusion”: “it is for the most part impossible to achieve and is certain to do more harm than good.” Henry Beecher wor-

ried that the provision would cripple the country's lead in drug research, in part by preventing research on children and the mentally ill.<sup>24,25</sup>

Scandals, however, raised questions about whether to trust U.S. researchers. In 1964, news broke that 22 patients at the Jewish Chronic Disease Hospital in Brooklyn had been injected with cancer cells without their knowledge. The media firestorm, hearings, and lawsuits raised fundamental questions about medical research. However, the researchers from Memorial Sloan Kettering who conducted the study received no serious sanction.<sup>26</sup>

#### “ETHICS AND CLINICAL RESEARCH”

By 1950, Henry Beecher (Fig. 2), an anesthesiologist at Massachusetts General Hospital, had emerged as a respected researcher, having examined battlefield trauma, the safety of anesthesia, subjective experiences (e.g., pain, thirst, and nau-

sea), and placebo responses.<sup>4,8,22,27,28</sup> He advocated careful research methods, including the use of placebo controls. He had also consulted for the military about the use of mescaline and LSD as “truth serums,” research that involved discussions with Central Intelligence Agency interrogators and former Gestapo officials.<sup>29</sup> This work got Beecher interested in “certain problems of human experimentation”<sup>30</sup> (for the specific Beecher papers cited here, see the Supplementary Appendix, available with the full text of this article at NEJM.org). In 1952, he asked Pentagon officials for their new policy on human research. In 1955, he wrote to an English colleague to learn about the Medical Research Council instructions for investigators and editors.<sup>30</sup>

In 1959 and 1963, Beecher published articles in *JAMA* about the role conflict faced by physician-investigators.<sup>31,32</sup> Neither generated much response. He then collected examples of troubling behavior by U.S., Canadian, and European researchers. For instance, he examined 100 consecutive articles in the *Journal of Clinical Investigation (JCI)* and concluded that 12 were “unethical or questionably ethical.” He compiled a set of 50 articles on studies funded by government agencies, conducted at leading institutions, and published in leading journals. He took care to ensure that his critiques were fair. For instance, he queried *New England Journal of Medicine* editor Joseph Garland about the *Journal’s* decision to publish a study of thymectomy in children; Garland admitted that the ethical review had been inadequate.<sup>30</sup> Beecher also recognized his own mistakes. He regretted a 1948 study in which researchers in his laboratory, without adequate consent, prolonged anesthesia “beyond that necessary” to study the effects on kidney function.<sup>30,33</sup>

Beecher then accepted an invitation to speak at a conference in March 1965. He delivered a “bombshell.” After reviewing the Jewish Chronic Disease Hospital controversy, he proceeded, without naming names, to describe 17 additional cases in which researchers had failed to obtain consent or had harmed their research subjects: “what seem to be breaches of ethical conduct in experimentation are by no means rare, but are almost, one fears, universal.”<sup>30</sup> Reaction from his colleagues was immediate. Thomas Chalmers and David Rutstein called a press conference

to accuse Beecher of “gross and irresponsible exaggeration.”<sup>34</sup> Beecher condemned their kangaroo court and accused them of defamation of character.<sup>30</sup> The exchange received extensive media coverage.

After an inquiry to *Science*, Beecher submitted his manuscript to *JAMA* in August. The editor rejected it, citing its excessive length (it described 50 research studies) and poor organization. Beecher submitted a revised manuscript to the *Journal* in November. Garland sent it “to some picked reviewers,” expecting no serious problems. Six of the seven recommended against publication: there were too many cases; Beecher did not allow the investigators to tell their side of the story; many readers would recognize the “anonymous” cases; and his critiques had already received extensive media coverage. One reviewer supported publication, but only if the *Journal* obtained a legal opinion “regarding any possible problems.”<sup>30</sup>

The editorial board voted to reject the submission, but Garland overruled them.<sup>35</sup> Blurring the line between editor and coauthor, he helped Beecher revise the manuscript. Beecher reduced the examples to 25 and provided Garland with their citations. Garland convened a “brain cabinet” (two colleagues) to assess Beecher’s accusations; they settled on a final list of 22 cases. Garland also moderated Beecher’s language: “I have tried to omit anything accusatory or especially critical, since what we want is not an indictment but a sober and undramatic presentation of what has been done and is being done in violation of basic ethics.”<sup>30</sup> The *Journal* published the article in June with an editorial by Garland.<sup>7,36</sup>

The cases made for shocking reading. Beecher focused on human experiments in which patients were used not for their benefit, “but for that, at least in theory, of patients in general.”<sup>7</sup> Researchers sometimes withheld known treatments. In the case Beecher considered most egregious, penicillin was withheld from 109 soldiers with streptococcal infections; acute rheumatic fever developed in 2 and acute nephritis in 1. In some cases, patients experienced harm or risk of harm without benefit. In others, researchers had not obtained consent. The examples were not from a lunatic fringe.<sup>4</sup> Four came from Harvard Medical School, three from the NIH Clinical Center, and the rest from other prominent institutions. The

cases had passed peer and editorial review at the *Journal* (five articles), *JCI* (five), *JAMA* (two), and *Circulation* (two).

Beecher insisted that the researchers not be named: “I have no wish to point a finger at individuals. I was pointing to an all-too-general practice.”<sup>30,37</sup> Garland accepted Beecher’s request and asked readers to trust the *Journal*’s assessment of the veracity of Beecher’s accusations. Beecher was besieged by requests to identify his sources but steadfastly refused. As he explained to Arnold Relman, then editor of *JCI*, “I am assured by a professor in the Harvard Law School that the individuals involved could be subjected to criminal prosecution, and I have no wish to invite such action.”<sup>30</sup> Beecher had divided loyalties. Even as he drew attention to misconduct, he did not want researchers to suffer legal consequences.<sup>4</sup> Since he expected that many cases would be recognized by the research community, he might have hoped that the researchers would be shamed among their peers, if not publicly. Remarkably, when the researchers were unmasked in 1991, they received little attention.<sup>8,38,39</sup>

Reactions in 1966 varied widely. Medical researchers were often angry and defensive, clinicians were outraged by researchers’ conduct, and the public piled on with their own accounts of physician misconduct.<sup>28</sup> The researchers responsible for one of Beecher’s cases published a letter to the Editor: “Dr. Beecher quotes out of context, oversimplifies and otherwise distorts the purpose and findings of our investigation.”<sup>40</sup> Beecher dismissed them: “I do not believe this is so, and obviously neither did the 3 editors who checked my cases.”<sup>37</sup> Eugene Braunwald, involved in three of Beecher’s cases at the NIH Clinical Center, prepared a point-by-point critique, arguing that Beecher misunderstood the role of patients and healthy volunteers and the role of consent at the Clinical Center. But recognizing the value of some of Beecher’s critiques, Braunwald decided not to respond.<sup>41</sup>

It was clear that thoughtful researchers could disagree. Beecher’s list included studies at the Willowbrook State School, in which researchers had infected disabled children with hepatitis.<sup>7,42</sup> As he explained to one critic, “The thought that some would have agreed that deliberate infection was all right since the subjects were mental defectives gives me the Nazi shudders.”<sup>30</sup> The study’s defenders, however, appealed to other

justifications. Geoffrey Edsall, from the Massachusetts Department of Public Health, told Beecher that “If I had a child in Willowbrook, and if I had had it clearly explained to me — as Krugman et al. did with the parents of his children — that my child was bound to come down with hepatitis sooner or later, as all the children do in Willowbrook; if I was then asked to permit my child to be part of an experiment which hopefully would be of benefit to man, I would be delighted to have that opportunity to allow the child to contribute.” If ethical barriers were set too high, Edsall argued, they would disrupt “the trend of progress that all human beings want, and that the vast majority are willing to contribute to.”<sup>30</sup>

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#### THE AFTERMATH

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Despite Beecher’s fervor, his goals were modest. He qualified his “troubling charges” with the affirmation that “American medicine is sound, and most progress in it is soundly attained.”<sup>7</sup> He hoped that simply revealing problems would be sufficient to address them. As he told Garland, “most of the ethics errors are owing to thoughtlessness or carelessness, not a vicious disregard for the patients’ rights. I am utterly convinced that calling attention to the ethical problems involved will lead to elimination of the vast majority of mistakes.”<sup>30</sup> He did not recommend new regulations or formal oversight, instead emphasizing the importance of informed consent and “the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator.”<sup>7</sup>

Beecher’s exposé had immediate impact. Members of Congress wrote to the NIH inquiring about possible corrective actions.<sup>8</sup> Beecher’s article provided support for a 1965 proposal by NIH director James Shannon to require peer review of research, protect the rights and welfare of participants, and ensure appropriate informed consent.<sup>43</sup> Historian David Rothman highlights 1966 as the start of a broad transformation of bioethics and the patient–doctor relationship, as patients, lawyers, and ethicists shaped medicine’s moral code. Beecher, according to Rothman, had joined the ranks of Harriet Beecher Stowe, Upton Sinclair, and Rachel Carson.<sup>8</sup>

These changes, however, were not a response to a single article. Beecher had published repeatedly about research ethics. Maurice Pappworth

worked in parallel in England to expose unethical research.<sup>22</sup> In February 1966, between Beecher's conference presentation and publication of the article, the U.S. Surgeon General requested that hospitals and universities establish review boards.<sup>21</sup> Many scholars joined the discussion after Beecher.<sup>44</sup> And scandals continued to emerge. The Tuskegee syphilis study, which seized public attention in 1972, was the most famous.<sup>45</sup> In response, Senator Edward Kennedy (D-MA) held hearings on human experimentation that led to the National Research Act in 1974 and the National Commission for the Protection of Human Subjects. The Commission's 1979 Belmont Report guided the systems that continue to regulate human research in the United States.<sup>8,9</sup>

Would Beecher be satisfied with current arrangements? He put his trust in two safeguards: informed consent and virtuous researchers. Informed consent is almost always obtained today, though it remains imperfect.<sup>46</sup> Investigator virtue is highly valued, yet ironically, the compliance culture of modern human-subjects protection assumes that investigators cannot be relied on.<sup>47</sup> Discussions of ethics have become ubiquitous in the research community, something Beecher would have applauded. However, researchers complain that institutional review boards have lost sight of their original purpose of protecting human subjects, focusing instead on bureaucratic minutiae.<sup>48</sup> And researchers still worry that excessive attention to ethics can hinder the research enterprise.

Are we — 50 years after Beecher — better than our predecessors at recognizing and preventing unethical research? All Beecher's examples had been published in prominent journals, yet few had inspired an outcry. We assume that we are now more sensitive to ethical concerns than past researchers, and we may well be. We have well-established guidelines that did not previously exist.<sup>49</sup> But sensitivity to research ethics did exist, even if past researchers resisted formal regulation: many understood how they ought to behave toward research subjects and worried about their failures to do so. Nevertheless, ethical failures occurred throughout the 20th century and continue in the 21st.

Three lessons are clear. First, ethical values change over time, and it is important to understand how and why. Second, there is not always consensus on what counts as ethical research,

or who can be appropriate research subjects: thoughtful people often disagree. Articles like Beecher's play a crucial role in fostering debate that can lead to consensus about ethical values. Third, many interests — medical, personal, political, military, and commercial — have led researchers to conduct studies they knew to be transgressive. It would be hubris to think that such lapses could not happen again.

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From the Department of Global Health and Social Medicine, Harvard Medical School, Boston (D.S.J.); the Department of the History of Science, Harvard University, Cambridge, MA (D.S.J.); the Department of Bioethics, National Institutes of Health Clinical Center, Bethesda, MD (C.G.); and the Department of Medical History and Bioethics, University of Wisconsin Madison School of Medicine and Public Health, Madison (S.E.L.).

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