Public Health Classics

This section looks back to some ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. Jon Harkness, Susan Lederer and Daniel Wikler review the 1966 paper by Henry K. Beecher on ethics and clinical research. The original article is reproduced from *The New England Journal of Medicine* by permission of the Massachusetts Medical Society.

Laying ethical foundations for clinical research

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Progress in international health will require further research involving human subjects, and this may often take place in developing countries. In recent years, human experimentation has been dogged by controversy. Scientists from industrialized countries, where strict ethical standards protect participants in research and help to win public trust, have been accused of using double standards in carrying out research in poorer countries that they would not be permitted to perform at home.

Even as these debates continue in scientific journals and in the popular press, it is worth while to recall that participants in research in the wealthiest countries have not always been afforded such protection. In his essay "Ethics and clinical research" in 1966 (*1*), Henry K. Beecher identified ethical lapses in research carried out by physician–scientists in renowned universities and published in the world's leading journals. In this paper, which has rightly been deemed the most influential single paper ever written about experimentation involving human subjects (*2*), Beecher demonstrated that poor treatment of human subjects was not confined to the barbaric practices of Nazi doctors that had been documented by the Nuremberg war crimes tribunal after the Second World War. Beecher's paper prompted a reconsideration of research practices that laid the groundwork for today's ethical codes and review committees.

In 1936 at the age of 32, four years after graduating from Harvard Medical School, Beecher became anaesthetist-in-chief at Massachusetts General Hospital and joined the medical faculty; in 1941 Harvard installed him in the world's first endowed professorship in anaesthesiology. During his career, he trained over 300 anaesthesiologists, 50 of whom became professors at other medical schools around the world. When Beecher published this paper he had been the world's foremost figure in anaesthesiology for almost three decades. Beecher made many original scientific contributions in his chosen field, but his research also had broader implications for medical science: he developed a number of techniques for the quantitative measurement of clinical responses that researchers had previously viewed as largely subjective, including pain, thirst, nausea, and even mood. He was also a pioneer in recognizing the placebo effect in medical practice, and was among the most influential early advocates of the need for double-blind controlled studies to account for this phenomenon in clinical research.

It was towards the end of the 1950s that Beecher became increasingly concerned with the ethical aspects of human experimentation. Historian David Rothman has emphasized that Beecher's specialty played a role in this orientation, as well as his commitment to high quality research and the fear that unethical research would bring discredit to the scientific enterprise (*3*). Beecher's deep Christian faith (he is said to have read a chapter of the Bible every day) may also have encouraged his excursion into research ethics (*4*). It also seems possible that he harboured some guilt over experiments that had taken place under his supervision; in a 1965 public lecture, he found himself "obliged to say that, in years gone by, work in my laboratory could have been criticized" on ethical grounds (*5*).

Beecher's first major publication on research ethics appeared in the *Journal of the American Medical Association* in 1959 (*6*), but this extensive scholarly consideration of research ethics did not create much of a professional or public stir. Beecher's agitation over the widespread moral laxity he perceived among his peers grew to a point where he was no longer satisfied with academic discourse, and he exercised his capacity for drama in the spring of 1965, when he chose to explore the problems and complexities of clinical research before a group of journalists convened by the Upjohn Pharmaceutical Company at the Brook Lodge Conference Center in rural

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Ref. No. **01-1218**

Michigan (*5*). His speech must have rocked his conservative corporate conference sponsors. "What seem to be breaches of ethical conduct in experimentation", he informed his audience, "are by no means rare, but are almost, one fears, universal." The body of his presentation centred on a review of eighteen examples of clinical research that he deemed unethical. Beecher claimed that these ethical problems were not restricted to remote corners but were found in the nation's leading medical schools, health centres, military hospitals, and industry.

Several of the nation's most prominent newspapers soon carried stories written by reporters who had attended the conference; the *Boston Globe* published a front-page article that was headlined "Are humans used as guinea pigs not told?" Beecher faced harsh and immediate criticism from some of his colleagues who believed that he had violated professional etiquette by airing his concerns in public and that he had incorrectly characterized ethically dubious clinical research as common rather than exceptional. He submitted a revised version of his presentation, with 32 additional examples of "unethical research", to the *Journal of the American Medical Association,* which rejected it (*5*). Undaunted, Beecher redirected the manuscript to *The New England Journal of Medicine*, where, after a few rounds of revision, the paper appeared in 1966 with 22 examples, as reprinted here.

In his exposé of clinical experimentation practices, Beecher deliberately did not furnish the names of investigators nor did he provide journal citations to their research. He explained to English physician Maurice Pappworth that he had adopted this policy in order to forestall criminal proceedings against the investigators. Four years earlier, in 1962, Pappworth had sounded his own warning in the British press about clinical experimentation. In 1967 his book *Human guinea pigs* (*7, 8*), which harshly criticized clinical research practices in both Britain and the United States, identified researchers by name and provided their institutional affiliations. The less aggressive strategy used by Beecher who, unlike Pappworth, was perceived as a member of the academic and social elite in spite of his humble origins (the son of Henry Unangst, a night watchman and carpenter in Kansas City, Beecher adopted the illustrious surname of a distant relative when he moved to Boston (*4*)), proved to have greater immediate influence on the conduct of research (*9*).

Both Beecher's and Pappworth's efforts at reforming clinical research reflect the turbulent status of human experimentation in the decades after the development of the Nuremberg Code. In 1964, after years of deliberation and committee discussion, the World Medical Association, an international body representing physicians and researchers from countries around the world, adopted the Declaration of Helsinki which established new rules for human experimentation. This Declaration, in the words of Henry Beecher, offered "a more broadly useful instrument" than the "rigid set of legalistic demands" set out in the Nuremberg Code. The Declaration of Helsinki has been amended five times since its adoption. For the most recent version, ratified in October 2000 in Edinburgh, Scotland, consult http://www.wma.net/e/policy/17-c_e.html.

Beecher's 1966 article played a significant role in the implementation of federal rules governing the conduct of human experimentation in the USA, including a clear call for fully informed consent from research subjects. This development ironically did not sit well with Henry Beecher. Although he believed that obtaining consent from research subjects was a worthy and necessary ideal, he expressed scepticism that "consent in any fully informed sense" was obtainable. Rather than formal rules for human experimentation, Beecher argued that the presence of an intelligent, informed, conscientious, compassionate, and responsible investigator offered the best protection for human research subjects. For the same reason, Beecher was not an advocate of the mechanism of the ethical review committee, now a fixture in health research.

The publications of Beecher and Pappworth did not resolve all controversies in research ethics, as the periodic revisions of the Declaration of Helsinki and national regulations demonstrate. But they did prompt the public and the health professions to recognize that questionable research practices could be carried out, and even rewarded, in advanced, democratic states, and that careful attention to ethics should be part of every scientist's approach to research. ■

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