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From Laboratory to Bedside: Ethical, Legal, and Social Issues In Translational Research

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This symposium addresses a few of the many controversial ethical issues arising from translation research. A very brief review of early development of research ethics may be useful in setting the stage for the controversies debated and discussed in this collection of essays.

The first broadly accepted guidelines for clinical ethics in this country was the Code of Medical Ethics of the American Medical Association, adopted at its first official meeting in Philadelphia in 1847; it was based on Thomas Percival's 1803 Code of Medical Ethics.¹ Percival mentioned research only in passing, encouraging trials of new medical and surgical treatments when existing therapies have not been successful.² Early statements of ethical guidelines specifically addressing research involving human subjects were published sporadically in the nineteenth century, then systematically in the twentieth century.

William Beaumont, writing about his classic digestive physiology experiments on Alexis St. Martin in 1833, was probably the first to mention the necessity for *voluntary consent* when human beings are the subjects of research.³ The principle of *avoiding harm* to human experimental subjects was emphasized and made explicit by Claude Bernard in 1865.⁴ An official document specifically addressing experimentation involving human beings was a directive issued in Prussia in 1900. It required consent based on an explanation of potential harms resulting from the experiment—that is, *informed consent*.⁵

The first national ethical guidelines for research on human subjects, the 1931 German Reich Health Council Circular, arose from widespread public criticism of clinical and research abuses by physicians. The Circular required that research be based on good methodology and record-keeping, risk-benefit analysis, disclosure of risks to the subject, and consent by the subject.⁶ Unfortunately, the Circular had little long-term salutary effect, for horrific medical experiments were carried out on unconsenting prisoners in Nazi concentration camps, starting in the late 1930s. These abuses continued until the defeat of Germany in

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1945, which ended World War II. After the war, between December 1946 and July 1947, 23 doctors were tried for war crimes and crimes against humanity at Nuremberg. Fifteen doctors were found guilty: 7 were hanged, 5 received life sentences, and 3 received 10–20 years in prison. Of the 31 lesser staff who were tried on the same charges and convicted, 22 were sentenced to hang.⁷

Two Americans, psychiatrist and neurologist Leo Alexander and physiologist Andrew Ivy provided key expert testimony on the ethics of human experimentation. Their testimony later served as the basis for the Nuremberg Code, the first international document dealing with research on human subjects.⁸ Expanding the basic principles enunciated in the Nuremberg Code, the World Medical Association adopted and promulgated The Declaration of Helsinki in 1964. The Declaration has undergone 8 revisions, most recently in 2008, and remains the international standard for the ethical treatment of human subjects of research.⁹

In 1966, Henry Beecher reviewed the human research literature and found that unethical procedures were not uncommon, including the use of institutionalized subjects without consent.¹⁰ Such studies were published in mainstream journals with funding by government agencies and leading pharmaceutical companies, and were sponsored by leading academic institutions.

Within a few years of Beecher's work, research scandals such as the Willowbrook¹¹ and Tuskegee experiments¹² led to the enactment of the National Research Act in 1974, which created the National Commission for the Protection of Human Subjects of Research. The Commission met in the Belmont Center of the Smithsonian Institution and published its conclusions in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research in April 1979.¹³ This report became the basis of the federal “Common Rule”, so called because it is used by 17 federal agencies in the regulation of human subjects research.¹⁴

Despite the many attempts over the last two centuries to guide and regulate human subjects research, many of the issues that motivated their development remain problematic. For example, Beaumont's Code of 1833, states, “The voluntary consent of the subject is necessary.”³ This theme is the focal point of the 1948 Nuremberg Code; the opening sentence of that document states, “The voluntary consent of the human subject is absolutely essential.”⁸ Yet, we still debate exactly what “voluntary” means—for example, some incentives to induce potential subjects to enroll in a clinical trial, such as cash payments, are coercive, according to some scholars. The question of coercive payments is debated in this symposium by Scott Halpern (Financial Incentives for Research Participation: Empirical Questions, Available Answers, and the Burden of Further Proof) (see page XXX) and Janice Wong and Mark Bernstein (Payment of Research Subjects for More Than Minimal Risk Trials is Unethical) (see page XXX).

The potential subject's understanding of the risks and benefits of the proposed study was required by the 1931 Reich Circular: a potential subject's consent to participate in research should be given only “...in the light of relevant information provided in advance.”⁶ The Nuremberg Code emphasized the requirement for understanding: the potential subject “...

should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.”⁸ Despite many subsequent guidelines and regulations, there is still no consensus on how one can ensure that sufficient information has been provided and that the disclosed information has been understood by the potential subject. For example, one of the unresolved problems about the adequacy of current processes for obtaining informed consent is the well-documented phenomenon of therapeutic misconception—the potential subject's mistaken belief that participation in research will be for his own benefit rather than for the benefit of others. This issue is explored in this symposium in the differing viewpoints of Gail Henderson (Is Informed Consent Broken?) (see page XXX) and Charles Lidz (Informed Consent: a Critical Part of Modern Medical Research) (see page XXX).

Some of the early guidance for clinical research emphasized avoidance of harm. Bernard warned against causing harm to a research subject: “The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent...”⁴ The Reich Circular required risk-benefit analysis before any experiment is carried out: “In all cases, the question of whether any adverse effects that may occur are proportionate to the anticipated benefits shall be examined and assessed.”⁶ Methods to evaluate the balance of benefits and harms are still controversial. For example, in a randomized clinical trial, patient-subjects are harmed if they are given a treatment that is known to be inferior to treatment in alternative arms of the study. When the investigator or community of experts in a particular field are uncertain about relative effectiveness of proposed treatments to the point of indifference to which group a patient-subject is placed, clinical equipoise is present and the trial is ethically justified.¹⁵ This seemingly well-established paradigm of clinical research, however, is now undergoing reconsideration and debate, represented in this symposium by the papers of Franklin Miller (Dispensing with Equipoise) (see page XXX) and Benjamin Djulbegovic (Uncertainty and Equipoise: an Interplay Between Epistemology, Decision-Making and Ethics) (see page XXX).

Ethical concerns are generated not only by human subject research, but also by investigations using animal as subjects. Animal experimentation by late eighteenth and early nineteenth century scientists, such as Francois Magendie and Charles Bell, as well as Bernard later in the nineteenth century, were widely criticized because of their apparent cruelty to the experimental subjects. The first organization to crusade against animal experimentation was created in England in 1875, the National Anti-Vivisection Society, which is still active today. In the U.S., the animal rights movement beginning in the late 1960s spawned several organizations, such as the Animal Legal Defense Fund (ALDF) and People for the Ethical Treatment of Animals (PETA). The latter organization used and continues to use highly visible tactics to call attention to their message, including violence and threats against scientists. One biomedical researcher who was the victim of such violence and threats, Dario Ringach,¹⁶ argues in this symposium for responsible use of animals in research and civil discourse between scientists and those who oppose animal experimentation (On the Use of Nonhuman Animals in Biomedical Research) (see page XXX). Presenting the view of animal rights scholars is philosopher Nathan Nobis (The Harmful, Non-Therapeutic Use of Animals in Research is Morally Wrong) (see page XXX).

The topics covered in this symposium touch upon only a few of the more controversial issues in research ethics. Problems and disagreements about how research should be done, particularly the ethics of human research, are broad and deep, yet clinical investigation and translational research continue on a firm, though not rock solid, foundation of the long-established and empirically successful methodology of science. Continual ethical debate in support of the integrity of medical science helps to ensure future achievement of the scientific knowledge needed for progressive improvement of the human condition.

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