Research Ethics I: Responsible Conduct of Research (RCR)—Historical and Contemporary Issues Pertaining to Human and Animal Experimentation

SUPPLEMENT

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Purpose: In this series of articles—*Research Ethics I, Research Ethics II,* and *Research Ethics III*—the authors provide a comprehensive review of the 9 core domains for the responsible conduct of research (RCR) as articulated by the Office of Research Integrity. In *Research Ethics I,* they present a historical overview of the evolution of RCR in the United States then examine the evolution of human and animal experimentation from the birth of scientific medicine through World War II to the present day.
Method: They relied on authoritative documents, both historical and contemporary, insightful commentary, and empirical research in order to identify current issues and controversies of potential interest to both faculty and students.
Conclusions: The authors have written this article from a historical perspective because they think all readers interested in RCR should appreciate how the history of science and all the good—and harm—it has produced can inform how researchers practice responsible research in the 21st century and beyond.

KEY WORDS: responsible conduct of research, scientific integrity, historical review, human research, animal research

In *Research Ethics I,* we provide the historical context for the responsible conduct of research (RCR). Our review of the historical underpinnings of the RCR movement in the United States (1970s forward) is intended to provide readers a context for later discussions about the nine RCR domains identified by the Office of Research Integrity (ORI, n.d., 1992, 2000e, 2001). The Office of Research Integrity's RCR domains are as follows:

- Research involving animals
- Research involving humans
- Mentor and trainee responsibilities
- Collaborative science
- Peer review
- Data acquisition, management, sharing, and ownership
- Publication practices and authorship
- Conflicts of interest
- Research misconduct

In all sections of this three-part tutorial, our purpose is to heighten readers' appreciation for past controversies and present challenges by

citing the work of scientists, physicians, ethicists, policymakers, and legal scholars.

After providing an overview of the evolution of RCR in the United States, we go back in history in an attempt to explain how the ethics of human and animal experimentation evolved in the United States before 1900 through World War II to the present day. Coincident with the growth of scientific medicine, antivivisectionists strived to protect both humans and animals from harmful experimentation. During this time, notable scientists, physicians, and ethicists explained that potential harms should be balanced with the value of knowledge to be gained and that participation by humans should be consensual. Nevertheless, these ethical principles were not formally adopted in the United States until well after the Doctors Trials at Nuremberg (1947; U.S. Government Printing Office, 1949–1953) and after human experimentation abuses in the United States were revealed in the 1970s.

Definitions

During the past three decades, scientists have progressively focused on the importance of RCR, a phrase that encompasses overlapping concepts related to the discovery and dissemination of new knowledge: research, responsible science, scientific integrity, and responsible researchers.

Research

Research "means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge" (Protection of Human Subjects, 45 C.F.R. pt. 46 §4.102(d), 1991, most recently revised June 23, 2005). "The object of research is to extend human knowledge of the physical, biological, or social world beyond what is already known. But an individual's knowledge properly enters the domain of science only after it is presented to others in such a fashion that they can independently judge its validity" (Committee on Science, Engineering, and Public Policy [COSEPUP], National Academy of Sciences, National Academy of Engineering, & Institute of Medicine, 1995, p. 3; COSEPUP, National Academy of Sciences, National Academy of Engineering, & Institute of Medicine, 2009).

Responsible Science

Responsible science, responsible scientific policies and practices, involves "adherence by scientists and their institutions to honest and verifiable methods in proposing, performing, evaluating, and reporting research activities" (Panel on Scientific Responsibility and the Conduct of Research, COSEPUP, National Academy of Sciences, National Academy of Engineering, & Institute of Medicine, 1992, p. 17).

Scientific Integrity

Scientific integrity refers not only to a body of knowledge scientists produce—"composed of current knowledge, theories, and observations"—but also to the research process—"a social enterprise that involves individuals and institutions engaged in developing, certifying, and communicating research results" (Panel on Scientific Responsibility and the Conduct of Research, COSEPUP, National Academy of Sciences, National Academy of Engineering, & Institute of Medicine, 1992, p. 25).

Responsible Researcher

The responsible researcher not only eschews intentional research misconduct (falsification, fabrication, and plagiarism; see Horner & Minifie, 2011b) but also practices and teaches responsible scientific methods and practices, protects the rights and welfare of human participants (Beecher, 1966, 1970; Fuchs & Macrina, 2005a; Williams, 2006), and respects the welfare of animal subjects (Janssen, 2003).

In summary, RCR refers to the commitment and integrity of researchers—and all who participate in the research enterprise—to the norms of science, who—by engaging in systematic, responsible practices while proposing, performing, evaluating, and reporting research—contribute to an accurate, worthwhile, and enduring scientific record. It is "the quest for scientific authenticity," a concept emphasized by Marco and Larkin (2000, p. 693), that ties together the forgoing values of science and the aspirations of RCR.

History of the RCR Movement in the United States

In the early 1970s, two important events occurred in the United States: Congress passed the National Research Act (Public Law 93-348, 1974), and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was formed. In 1979, the commission published *The Belmont Report* (1979). Concurrently, professional societies throughout the United States were producing white papers and guidelines to articulate the principles of RCR. The American Association for the Advancement of Science (AAAS & Edsall, 1975), in *Scientific Freedom and Responsibility,* wrote, "One of the basic responsibilities of scientists is to maintain the quality *and integrity* of the work of the scientific community" (p. 8). In 1982, the Association of

American Medical Colleges outlined procedures for dealing with alleged research fraud in *The Maintenance of High Ethical Standards in the Conduct of Research*. In 1985, Congress passed the Health Research Extension Act (Pub. L. No. 99-158). Although primarily addressing animal research, Section 493 of this act "required research institutions to review reports of 'scientific fraud' and required the director of the National Institutes of Health (NIH) to establish an administrative process to respond to such information and to recommend sanctions where appropriate" (Price, 1994, p. 486; see also Benos et al., 2005).

The Association of American Universities (1983, 1989), respectively, contributed to this RCR discussion in its *Report of the Association of American Universities Committee on the Integrity of Research* and *Framework for Institutional Policies and Procedures to Deal with Fraud in Research*. Also in 1989, the Institute of Medicine and National Research Council examined *The Responsible Conduct of Research in the Health Sciences*. At that time, the "absence of definitive data documenting the integrity of existing research practices and the level of misconduct in health sciences research" led the Institute of Medicine and National Research Council (1989) to rely upon expert opinion (p. 2). The Institute of Medicine and National Research Council attributed research misconduct to three factors: (a) "an excessively permissive research environment that tolerates careless practices," (b) "funding pressures and an overemphasis on publication," and (c) "individual deviance" (p. 3; see also Douglas, 1993; Petersdorf, 1986; Racker, 1997). Major documents pertaining to the evolution of RCR are summarized in Table 1.

Concerns about research misconduct led to Congressional hearings in 1981 and 1989 about scientific fraud (U.S. House of Representatives, 1981, 1989a, 1989b, 1989c; see also Dingell, 1993; Goldner, 1998; Institute of Medicine & National Research Council, 2002). In 1995, the Commission on Research Integrity (known as the "Ryan Commission" after its chair Kenneth J. Ryan, MD) produced *Integrity and Misconduct in Research* (Ryan & Commission of Research Integrity, 1995). The report addressed several principal issues: (a) the definition of research misconduct, (b) the process owed the accused scientist, (c) the character of federal oversight, (d) the protection of whistleblowers, and (e) the role of the federal government in prevention of research misconduct. The work of the Ryan Commission opened a constructive dialogue among scientists, academic institutions, and the federal government. Its recommendations set the stage for the federal regulatory process known today. Furthermore, the Ryan Commission addressed education about RCR and recommended that the Public Health Service require institutions receiving its funds "to provide assurances regarding their efforts to promote research integrity" (Ryan & Commission on Research Integrity, 1995, p. 21). In 1998, the *American Journal of Law & Medicine* of Boston University School of Law published a special issue entitled *Law, Medicine, and Socially Responsible Research*. The symposium editor (Horner, 1998) invited noted legal scholars to address the following topics: (a) introduction to socially responsible research (Holmes-Farley & Grodin, 1998); (b) use of investigational drugs and vaccines in combat (Annas, 1998); (c) medical and legal issues surrounding complementary medicine (Boozang, 1998); (d) permissibility of waiving informed consent for emergency research (Fost, 1998), (e) research with children (Glantz, 1998); (f) legal controls over scientific misconduct (Goldner, 1998); and (g) policy issues for research after life (Nelkin & Andrews, 1998). More recently, because of the expanding use of electronic medical records and electronic medical billing, Congress passed the Health Insurance Portability and Accountability Act (HIPAA) of 1996 (Public Law 104-191). By 2003, the Privacy Rule of HIPAA was fully enacted, and its application to research was widely promulgated. In 2005, Horner and Wheeler (2005b) published an article in *The ASHA Leader* explaining the HIPAA Privacy Rule to Communication Sciences and Disorders researchers. (See also National Institutes of Health, 2003, *Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule*.)

Values in Science

The aforementioned documents, both professional and legal, were grounded in a growing awareness of the moral and ethical foundations of science. For example, the off-cited Belmont Report (1979) identified three ethics principles relevant to research involving human participants: respect for persons, beneficence, and justice. When applied, these principles yield ethical practices such as informed consent, research protocols that balance risks with potential benefits, and fairness in subject selection (as well as distributing the benefits of knowledge learned to participants). Additional values recognized as fundamental to the scientific enterprise as a whole are as follows: truthfulness, trust, and best interests. Related values identified by Resnik (1998) are as follows: carefulness, openness, freedom, credit, education, social responsibility, legality, opportunity, and mutual respect.

Truthfulness. In 1992, the Panel on Scientific Responsibility and the Conduct of Research, Committee on Science, Engineering, and Public Policy wrote, "Truthfulness [is] both . . . a moral imperative and . . . a fundamental operational principle in the scientific research process" (p. 17).

Trust. In his Shattuck Lecture, Congressman John Dingell (1993) said, "The foundation of public support for science, or for any public endeavor, is trust—in this case,

Table 1. Chronological list of major documents relevant to the responsible Conduct of Research (RCR) in the United States.

Year	Document	Source
1975	Scientific Freedom and Responsibility	American Association for the Advancement of Science
1974	National Research Act (Public Law 93-348)	U.S. Congress
1979	The Belmont Report	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
1982	The Maintenance of High Ethical Standards in the Conduct of Research	Association of American Medical Colleges
1983	Report of the Association of American Universities Committee on the Integrity of Research	Association of American Universities
1989	Framework for Institutional Policies and Procedures to Deal with Fraud in Research	Association of American Universities
1989	The Responsible Conduct of Research in the Health Sciences	Institute of Medicine & National Research Council
1992	Responsible Science, Vol. I: Ensuring the Integrity of the Research Process	Panel on Scientific Responsibility and the Conduct of Research, Committee on Science, Engineering, and Public Policy, National Academy of Sciences, National Academy of Engineering, & Institute of Medicine
1993	Responsible Science, Vol. II: Background Papers and Resource Documents	Panel on Scientific Responsibility and the Conduct of Research, Committee on Science, Engineering, and Public Policy, National Academy of Sciences, National Academy of Engineering, & Institute of Medicine
1993	Shattuck Lecture	U.S. Congressman John Dingell
1995	On Being a Scientist: Responsible Conduct in Research (2nd ed.)	Committee on Science, Engineering, and Public Policy, National Academy of Sciences, National Academy of Engineering, & Institute of Medicine
1996	Health Insurance Portability and Accountability Act (HIPAA)	U.S. Congress
1997	Adviser, Teacher, Role Model, Friend: On Being a Mentor to Students in Science and Engineering	National Academy of Sciences, National Academy of Engineering, & Institute of Medicine
1995	Integrity and Misconduct in Research	Ryan, & Commission on Research Integrity
1997	Developing a Code of Ethics in Research: A Guide for Scientific Societies	Association of American Medical Colleges
1998	Law, Medicine, and Socially Responsible Research (Symposium issue)	*American Journal of Law & Medicine*
2001	Preserving Public Trust: Accreditation and Human Research Participant Protection Programs	Institute of Medicine, Committee on Assessing the System for Protecting Human Research Subjects, & Board on Health Sciences Policy
2002	Integrity in Scientific Research: Creating an Environment that Promotes Responsible Conduct	Institute of Medicine & National Research Council
2002	Investigating Research Integrity: Proceedings of the First ORI Research Conference on Research Integrity	Steneck and Scheetz (Eds.)
2003	Responsible Research: A Systems Approach to Protecting Research Participants	Institute of Medicine, Committee on Assessing the System for Protecting Human Research, Federman, Hanna, & Rodriguez
2003a	Protecting Subjects, Preserving Trust, Promoting Progress I: Policy Guidelines for the Oversight of Individual Financial Interest in Human Subjects Research	Association of American Medical Colleges
2003b	Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research	Association of American Medical Colleges
2008	Uniform Requirements for Manuscripts Submitted to Biomedical Journals	International Committee of Medical Journal Editors
2009	Best Practices in Graduate Education for the Responsible Conduct of Research	Council of Graduate Schools
2009	On Being a Scientist: A Guide to Responsible Conduct in Research (3rd ed.)	Committee on Science, Engineering, and Public Policy, National Academy of Sciences, National Academy of Engineering, & Institute of Medicine
2009	Ethics Education and Scientific and Engineering Research: What's Been Learned? What Should Be Done?	Hollander & Arenberg, & Center for Engineering, Ethics, and Society

trust that scientists and research institutions are engaged in the dispassionate search for the truth" (p. 1610). In *Integrity in Scientific Research: Creating an Environment that Promotes Responsible Conduct,* the Institute of Medicine and National Research Council (2002) wrote, "The public will support science only if it can trust the scientists and institutions that conduct research" (p. 1). Mastroianni and Kahn (2002) emphasized that scientists need to create and foster a "culture of ethical research"—not merely regulatory compliance—if they are to preserve the public's trust (p. 1076; see also Faden, Klag, Kass, & Krag, 2002; Kahn & Mastroianni, 2001; Steneck & Bulger, 2007; Whitbeck, 2004; Yarborough & Sharp, 2002).

Best interests. The Ryan Commission approached its analysis with the threshold question, "What is in the best interest of the public and science?" (Ryan & Commission on Research Integrity, 1995, p. 3). Best interests is a broad and inclusive principle that relates to animals, humans, investigators, faculty, students, institutions, the cultural environment, the economic milieu, and society at large—both present and future.

These themes of truthfulness, trust, and best interests recur in subsequent reports, monographs and texts (American Speech-Language-Hearing Association [ASHA] & Public Health Service, 2001; Broad & Wade, 1982; J. J. Cohen, 2001; Elliott & Stern, 1997; Emanuel, Crouch, Arras, Moreno, & Grady, 2003; Fuchs & Macrina, 2005a; Institute of Medicine, Federman, Hanna, & Rodriguez, 2003; Institute of Medicine & National Research Council, 2002; Judson, 2004; Panel on Scientific Responsibility & COSEPUP, 1992, 1993; Penslar, 1995; Resnik, 1998; Shamoo & Resnik, 2003), in articles about research practices (Bulger & Heitman, 2007; Heitman, 2000; Kahn & Mastroianni, 2001; Kelch, 2002; Whitbeck, 2004), and in articles about the public's perception of research in the United States (for a review, see Woolley & Propst, 2005).

Education and Professional Codes

Many scientific and professional organizations have demonstrated interest in the topic of RCR (e.g., Association of American Medical Colleges, 1982, 2003a, 2003b; Bernstein & American Pediatric Society, 1999; Bullock & Panicker, 2003; Hollander, Arenberg, & Center for Engineering, Ethics, and Society, 2009; Iverson, Frankel, & Siang, 2003). For example, the work of ASHA and its members is aligned not only with the regulations, policies, and guidelines of the Office of Research Integrity, but also with National Institutes of Health initiatives to educate scientists, clinicians, and students about their responsibilities (see ASHA, 1994, 2003, 2005, 2007; ASHA & Public Health Service, 2001; Horner, 2003, 2007; Horner & Wheeler, 2005a, 2005b; Ingham, 2003; Ingham & Horner, 2004; Jones, 2000; Jones & Mock, 2007; Metz & Folkins, 1985; Moss, 2011).

Those who educate students and faculty about RCR can find authoritative guidance not only in the Office of Research Integrity's RCR policy (2000e; see also ORI, 2000a, 2000b, 2000c, 2000d, 2001) but also in National Institutes of Health documents (National Institutes of Health, 1992; National Institutes of Health & Alcohol, Drug Abuse, and Mental Health Administration, 1989), authoritative educational articles and monographs (Macrina, 2005, 2007; Pimple, 2002; Steneck, 1994, 2002, 2006), and research misconduct policies (National Science Foundation, 2002; Public Health Service, 2005). See Table 1 for seminal RCR documents; see Table 2 for documents pertaining specifically to protections for human participants.

Despite the impressive advances in RCR that have been achieved in the United States over several decades, the ethical practices of scientists are open to empirical scrutiny, as we illustrate in this article and in companion articles (*Research Ethics II* and *Research Ethics III*; Horner & Minifie, 2011a, 2011b, respectively). We used Office of Research Integrity's core RCR instructional areas to organize our review and analysis of the literature (ORI, n.d., 2000e). We begin by discussing research involving human participants.

Research Involving Human Participants

The protection of human participants, volunteers, in research investigations is a high priority for the Office of Research Integrity, the National Institutes of Health, the Office for Human Research Protections, and the broader scientific community. According to the Office of Research Integrity (2000e), this broad topic pertains to:

> Issues important in conducting research involving human subjects. Includes topics such as the definition of human subjects research, ethical principles for conducting human subjects research, informed consent, confidentiality and privacy of data and patient records, risks and benefits, preparation of a research protocol, institutional review boards, adherence to study protocol, proper conduct of the study, and special protections for targeted populations, e.g., children, minorities, and the elderly. (p. VIII.B.6)

History of Human Experimentation

Human experimentation in Europe and the United States in the late 1800s grew in parallel with advances in science and the institutionalization of medicine. Between 1873 and 1909, the number of hospital beds in the United States increased from 50,000 (178 institutions) to 421,065 (4,359 institutions; Lederer, 1995). Johns Hopkins University School of Medicine opened in 1893, and the

Table 2. Chronological list of major sources relevant to the protection of human research participants.

Year	Document	Source
1803	Thomas Percival's Code of Medical Ethics (English)	As cited in Grodin (1994)
1833	William Beaumont's Code of Ethics (United States)	As cited in Grodin (1994)
1865	Claude Bernard's Introduction to the Study of Experimental Medicine (French)	Copley (Trans., 1927); as cited in Grodin (1994)
1910	Code for Animal Experimentation, American Medical Association, Principles of Medical Ethics	Lederer (1995)
1947	Code for Human Experimentation, American Medical Association, Principles of Medical Ethics	Lederer (1995)
1947	Nuremberg Code	U.S. Government Printing Office (1949–1953)
1964/2008	Declaration of Helsinki	World Medical Association
1979	The Belmont Report	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
1991/2005	Multiagency Common Rule	Protection of Human Subjects, 45 C.F.R. pt. 46 (1991, amended 2005, June 23)
1992	The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation	Annas and Grodin (Eds.)
1994	Children as Research Subjects: Science, Ethics & Law	Grodin and Glantz (Eds.)
1995	Subjected to Science: Human Experimentation in America Before the Second World War	Lederer
1996	The Human Radiation Experiments	Advisory Committee on Human Radiation Experiments
1996	Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule	Pub. Law 104-191, 45 C.F.R. pts. 160, 164
1996	Scientific Research: Continued Vigilance Critical to Protecting Human Subjects	U.S. Government Accountability Office
1998a	Institutional Review Boards: A System in Jeopardy?	Office of the Inspector General
1998b	Institutional Review Boards: A Time for Reform	Office of the Inspector General
1998	Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity	National Bioethics Advisory Commission
1998b	NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects	National Institutes of Health
1999	Research Involving Individuals with Questionable Capacity to Consent: Points to Consider	National Institutes of Health
2000	Office for Human Research Protections established in U.S. Department of Health and Human Services	Office of Protection from Research Risks renamed
2000a	Recruiting Human Subjects: Sample Guidelines for Practice	Office of the Inspector General
2000b	Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research	Office of the Inspector General
2001	Ethical and Policy Issues in Research Involving Human Participants	National Bioethics Advisory Commission
2001	Preserving Public Trust: Accreditation and Human Research Participant Protection Programs	Institute of Medicine
1985/2008	International Ethical Guidelines for Biomedical Research Involving Human Subjects	Council for International Organizations of Medical Sciences
2003	Ethical and Regulatory Aspects of Clinical Research	Emanuel, Crouch, Arras, Moreno, and Grady (Eds.)
2003	Protecting Participants and Facilitating Social and Behavioral Sciences Research	National Research Council
2003a	Protecting Subjects, Preserving Trust, Promoting Progress I: Policy Guidelines for the Oversight of Individual Financial Interest in Human Subjects Research	Association of American Medical Colleges
2003b	Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research	Association of American Medical Colleges
2003	Responsible Research: A Systems Approach to Protecting Research Participants	Institute of Medicine
2004	Ethical Conduct of Clinical Research Involving Children	Institute of Medicine
2006	Ethical Considerations for Research Involving Prisoners	Institute of Medicine

Rockefeller Institute Hospital, designed exclusively for the purpose of clinical research, opened in 1910 (Lederer, 1995). In 1896, the *Journal of Experimental Medicine* and the *Journal of Medical Research* were established; in 1898, the *American Journal of Physiology* was founded (Lederer, 1995).

During this period, it was not uncommon for scientists to use animals, hospitalized patients, children in orphanages, indigent "feeble-minded" or terminally ill patients, and soldiers without their knowledge or consent. Nonconsensual investigations pertained to the transmission of cancer, gonorrhea, and other diseases; the effects of surgical techniques on stomach and brain function; the usefulness of serial X-rays; and the effects of novel drugs and vaccines (Grodin & Glantz, 1994; Lederer, 1995). These experimental practices were not uniformly condoned; in fact, they created a great deal of media attention and controversy among members of the public and within the medical and scientific communities during the late 1800s and early 1900s (Lederer, 1995; Lederer & Grodin, 1994).

Vivisection (Nontherapeutic Experimentation)

Vivisection refers to "cutting into a live organism, animal or human" (Lederer, 1995, p. xiv). During the last quarter of the 19th century, antivivisectionists campaigned against the vivisection of both domesticated animals and humans (Leffingwell, 1897, 1916, as cited in Lederer, 1995). The American Humane Association was created in 1874 to coordinate activities designed to protect both animals and children (Lederer, 1995). Antivivisectionists' alarm grew as scientific medicine expanded because antivivisectionists equated human vivisection with "nontherapeutic human experimentation" (Keen, 1914, as cited in Lederer, 1995, p. xiv). Antivivisectionists were outraged by the lack of disclosure to, or the lack of voluntary participation by, patients.

A remarkable exception to the norm of nondisclosure to human participants was the use of a written consent procedure in 1900 by U.S. Army physician Walter Reed's Yellow Fever Board during its investigation of the transmission of the fever by mosquitoes in Cuba (Lederer, 1995, pp. 19–21). This exception aside, increasing human experimentation fueled the antivivisectionist movement, documented by Lederer in her scholarly work *Subjected to Science: Human Experimentation in America Before the Second World War,* and Grodin and Glantz's (1994) highly informative text, *Children as Research Subjects: Science, Ethics & Law.*

Other useful references regarding the distant and recent history of human experimentation are as follows: Adams et al. (1996); Advisory Committee on Human Radiation Experiments (1996); Annas and Grodin (1992); Beecher (1966, 1970); C. Cohen (1978); Cruse (1999); Faden, Lederer, and Moreno (1996); Harris (2003); Jones (1993); Katz (1996); Katz, Capron, and Glass (1972); Kopp (1999); Moreno (1998); Oliver, (2001); and Shamoo and Resnik (2003). An anthology made up of both historical and contemporary articles is *Ethical and Regulatory Aspects of Clinical Research* edited by Emanuel et al. (2003).

Evolution of Research Ethics Before and After World War II

In defense of medical research. Partly in reaction to the antivivisectionist movement, the American Medical Association (AMA) created a Council on the Defense of Medical Research in 1909 to promote medical innovation and scientific research, and to lobby against antivivisectionists' numerous legislative proposals (Lederer, 1995). According to Lederer, the AMA successfully defeated a Bill for the Regulation of Scientific Experiments upon Human Beings in the District of Columbia, introduced to the 56th U.S. Congress in March 1900. The bill that was defeated sanctioned "any scientific experiment involving pain, distress, or risk to life and health … for any other object than the amelioration of the patient" (as cited in Lederer, 1995, Appendix, p. 143). In 1910, the AMA revised its Principles of Medical Ethics (first published in 1847) to include a uniform code for animal experimentation (Lederer, 1995). In 1916, the AMA considered a similar code for human experimentation but did not enact it until 1947 (Lederer, 1995).

Do no harm. Despite differing opinions at the turn of the century about the ethics of human experimentation, and despite the failure of antivivisectionists' legislative proposals, physicians and biomedical and behavioral scientists were well aware of the "do no harm" principle (Hippocratic Oath, 470–360 B.C.E.; see Chadwick & Mann, 1950). In his chapter *Historical Origins of the Nuremberg Code,* Grodin (1992) reported that British physician Thomas Percival (1740–1804) discussed the importance of consent for innovative—therapeutic—medical care in his 1803 code of ethics (see also Beecher, 1970; Rothman, 1987). In 1833, an American physician William Beaumont (1785–1853) addressed the ethical requirements for nontherapeutic experimentation. Beaumont's (1833) code was noted by Beecher to be the first American document dealing with the ethics of human experimentation (as cited in Grodin, 1992). Beaumont's code of ethics required (a) the voluntary consent of the subject, (b) the use of humans only "when the information cannot otherwise be obtained," and (c) that the experiments should be "discontinued when [they] cause[-] distress" or "abandoned when the subject becomes dissatisfied" (as cited in Grodin, 1992, p. 125). See Table 3

Table 3. Landmarks in the evolution of protections for human research participants from the Hippocratic Oath to the enactment of the Common Rule.

Year	Principle/Regulation/Experiment
470–360 B.C.E.	Do no harm principle: Hippocratic Oath
1767	Nonconsensual experimental surgery grounds for negligence; *Slater v. Baker and Stapleton*
1803	Code of ethics emphasized consent for innovative (therapeutic) medical care; Thomas Percival (England)
1833	Code of ethics emphasized voluntary consent and right to withdraw from experimentation; William Beaumont (United States)
1865	Nontherapeutic research should personally benefit human participants; Claude Bernard (France)
1874	American Humane Association formed
1900	Emphasizing informed consent; Berlin Code, Prussian Directive
1900	First written informed consent in the United States; Walter Reed's Yellow Fever Experiment
1900	A Bill for the Regulation of Scientific Experiments upon Human Beings defeated by the American Medical Association
1909	Council on the Defense of Medical Research, American Medical Association
1914	"Every human being of adult years and sound mind has a right to determine what shall be done with his own body"; *Schloendorff v. The Society of New York Hospital*
1916	"There is no more primitive and fundamental right which any individual possesses than that of controlling the uses to which his own body is put"; Walter Bradford Cannon's editorial in the *Journal of the American Medical Association*
1931	Regulations on New Therapy and Human Experimentation; Reich Minister of the Interior
1932–1972	Nonconsensual syphilis experiment; Tuskegee Syphilis Study, U.S. Public Health Service
1935	Medical/surgical experiments "must be done with the knowledge and consent of the patient"; *Fortner v. Koch* (Michigan Supreme Court)
1943	Nonconsensual injection of children with bacteria; Ohio Soldiers and Sailors Orphanage
1944–1974	Human radiation environmental and individual experiments in the United States; historical events documented by the Advisory Committee on Human Radiation Experiments, 1996
1947	"The voluntary consent of the human subject is absolutely essential"; Principle 1, Nuremberg Code
1947	Informed consent to human experimentation included in the AMA's Code of Medical Ethics
1950s–1970s	Children with mental retardation injected with strains of hepatitis virus; Willowbrook State School
1963	Liver cancer cells injected in debilitated patients; Jewish Chronic Disease Hospital
1964/2008	"Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights"; Declaration of Helsinki
1966	Nonconsensual and harmful human research in the United States exposed; H. K. Beecher
1974	National Research Act; Pub. L. No. 93-348
1991	Protection of Human Subjects (Common Rule); 45 C.F.R. pt. 46 (revised 2005)

for events illustrating the evolution of ethics and law pertaining to human experimentation.

In *An Introduction to the Study of Experimental Medicine* (1865), a French scientist, Claude Bernard (1813–1878), limited permissible human research to those situations in which

> [I]t can save his life, cure him or gain him some personal benefit .... So, among the experiments that might be tried on man, those that can only *harm* are forbidden. Those that are innocent are permissible, and those that may do good are obligatory. (as cited in Grodin, 1992, pp. 125–126).

Thus, Bernard "appear[ed] to exclude any nontherapeutic research by demanding the personal benefit of the subject" (Grodin, 1992, p. 126).

In defense of patients' rights. During the early part of the 1900s, despite the lack of federal regulations, courts in the United States grew more protective of patients' rights. Judicial opinions articulated a common law of informed consent for nonconsensual interventions—vivisections—following the seminal British case Slater v. Baker and Stapleton (1767) in which a surgeon was liable for negligence when gangrene occurred after the surgeon performed an innovative procedure on Slater's leg. In 1914, in a famous case involving nonconsensual surgery, Justice Cardozo wrote: "Every human being of adult years and sound mind has a right to determine what shall be done with his own body" (Schloendorff v. The Society of New York Hospital, 1914, p. 129). Courts approved of innovative therapy, designed to benefit the individual patient, but only when patients gave their permission. In Fortner v. Koch (1935), the Supreme Court of Michigan recorded a seminal informed consent decision, stating:

> We recognize the fact that if the general practice of medicine and surgery is to progress, there must be a certain amount of experimentation carried on; but

> such experiments must be done with the knowledge and consent of the patient or those responsible for him and must not vary too radically from the accepted method of [sic] procedure. (p. 282; cf. Ambrose & Yairi, 2002; Goldfarb, 2006)

In 1916, an American physician Walter Bradford Cannon (1871–1945)—described by Brown and Fee (2002) as a "pioneer physiologist" and "scientific statesman"—wrote an enlightened editorial in the *Journal of the American Medical Association* well before either the AMA or the U.S. government formally embraced an ethic of human experimentation. Cannon (1916) explained physicians' "duty of learning" (p. 1372) and warned against using the desire to obtain new knowledge as the justification for experimentation without consent, emphasizing: "There is no more primitive and fundamental right which any individual possesses than that of controlling the uses to which his own body is put" (p. 1372).

Human rights in Germany. As explained in the foregoing review, there is an ample historical record that the ethics and morality of both therapeutic and nontherapeutic human experimentation were on the mind of the American public, scientists, physicians, policymakers, and the courts well before World War II. Similarly, there is evidence that German physicians were aware of their obligations to patients well before inhumane experiments were conducted by Nazi physicians on individuals incarcerated in concentration camps. In 1900, the Berlin Code, a Prussian directive by the Prussian Minister of Religious, Educational and Medical Affairs, stated:

> All medical interventions for other than diagnostic, healing, and immunization purposes, regardless of other legal or moral authorization, are excluded under all circumstances, if (a) the human subject is a minor or not competent due to other reasons; (b) the human subject has not given his unambiguous consent; (c) the consent is not preceded by a proper explanation of the possible negative consequences of the intervention. (as cited in Grodin, 1992, p. 127; Sharav, n.d.)

In 1931, the Reich Minister of the Interior promulgated "Regulations on New Therapy and Human Experimentation" that incorporated most of points later found in the Nuremberg Code (as cited in Grodin, 1992, p. 129; Sharav, n.d.).

This historical review illustrates that many individuals in the United States in the latter half of the 19th century and the early half of the 20th century—lay public, antivivisectionists, scientists, physicians, ethicists, and the courts—embraced innovative medical therapy when the intent was to benefit the patient and participation was voluntary, and believed that exposure of vulnerable humans to nontherapeutic or nonconsensual experiments was unethical. Medical historians have explained that investigators were "at no time … free to do whatever they pleased" (Lederer, 1995, p. xv). Both before and after World War II, scientists knew—or, arguably, should have known—that their ethical obligations included (a) balancing potential risks of harm against the knowledge to be gained and (b) assuring that participants had agreed voluntarily to participate. The U.S. Congress was aware of public sentiment about human experimentation but failed to enact any law or regulation until after World War II, leading to a permissive environment for scientists who were intent on human experimentation.

The trial of the Nazi Doctors that incorporated the Nuremberg Code (1947; U.S. Government Printing Office, 1949–1953) laid the groundwork for eventual, and for continuing, changes in policies governing research involving human participants in the United States (Annas & Grodin, 1992; Faden et al., 1996; Grodin, 1992; Katz, 1996; Lenrow, 2006; O'Connor, 2002; Pellegrino, 1997; Shuster, 1997).

The Nuremberg Code (1947) has 10 principles, among them:

- Principle 1: The voluntary consent of the human subject is absolutely essential.
- Principle 2: The experiment should be such as to yield fruitful results for the good of society; the experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury; and
- Principle 6: The degree or risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment. (as cited in Annas & Grodin, 1992, p. 2; U.S. Government Printing Office, 1949–1953)

Progress in the United States. In 1947, the AMA formally incorporated human research standards into the AMA Code of Ethics (Lederer, 1995). In the winter of 1946, AMA's House of Delegates received a report from its Judicial Council written by Andrew Ivy, an American physician who assisted the prosecutors at Nuremberg and contributed to the writing of the Nuremberg Code (with Leo Alexander, also an American physician; Shuster, 1997). The following text is part of the AMA's House of Delegates' minutes, which were dated December 11, 1946:

> [T]he experiments described in Dr. Ivy's report are opposed to the Principles of Medical Ethics of the American Medical Association which have three basic requirements: 1. The voluntary consent of the person on whom the experiment is to be performed must be obtained; 2. The danger of each experiment must be previously investigated by animal experimentation; and 3. The experiment must be performed under proper medical protection and management. Therefore, this House of Delegates condemns any other manner of experimentation on human beings than that mentioned herein. (p. 1090)

In 1964, the World Medical Association wrote the Declaration of Helsinki, most recently revised in 2008.

Although not part of U.S. law, the Declaration of Helsinki is widely recognized and cited worldwide as an authoritative document informing the ethics of human experimentation, and is cited as a guiding document by the International Committee of Medical Journal Editors in its *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (2008). Provisions in the Declaration of Helsinki (World Medical Association, 1964/2008) emphasize the precedence of research subjects' well-being (A.6); the importance of protecting vulnerable populations (A.8); and the duty of investigators to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects (B.11).

For current principles pertaining to the ethics of clinical research, see a comprehensive analysis by Emanuel, Wendler, and Grady (2000) in "What Makes Clinical Research Ethical?" and Emanuel et al.'s (2003) anthology, *Ethical and Regulatory Aspects of Clinical Research: Readings and Commentary*.

Nonconsensual Research in the United States: 1930s–1970s

Despite promulgation of the Nuremberg Code (1947; U.S. Government Printing Office, 1949–1953) and the Declaration of Helsinki (World Medical Association, 1964/2008), as well as widespread public dialogue about the ethics of research involving human participants, U.S. scientists have not always honored individual rights when the promise of scientific gains for the putative benefit of public health and national security hung in the balance. This was particularly true if the individuals were orphans, military personnel, slaves, prisoners, desperately or terminally ill patients, or were otherwise fragile or vulnerable. For example, between 1932 and 1972, the U.S. Public Health Service examined the natural history of syphilis in a large cohort of Black American men, and intentionally withheld penicillin from them when it became available in the early 1950s; this study is known as the "Tuskegee Syphilis Study" (Adams et al., 1996; Brandt, 1978; Jones, 1993).

In 1939, Tudor, a graduate student at the University of Iowa, published her thesis entitled *An Experimental Study of the Effect of Evaluative Labeling on Speech Fluency*. Her advisor and mentor, Wendell Johnson, later came to be known for his "diagnosogenic" theory of stuttering—namely, that adverse responses from parents and others, including the label of *stuttering,* could cause stuttering in otherwise normally developing children. The participants were orphans living at the Soldiers and Sailor's Orphans' Home in Davenport, Iowa. Of 22 participants (ages 5–16 years), 10 were observed at baseline to "stutter"; the other 12 participants spoke normally. Both types of children were divided into two groups and were given feedback from Tudor and the orphanage staff. Children in Group IA were stutters who were labeled *normal speakers*; Group IB were stutterers who were labeled *stutterers*; Group IIA were normal speakers labeled *stutterers*; and Group IIB were normal speakers who were labeled as *good speakers*. According to a careful scientific critique of the study's design, Ambrose and Yairi (2002) rejected the notion that this study caused stuttering, notably in Group IIA, and, "in fact, the Tudor study yielded the earliest evidence against the diagnosogenic theory" (p. 200).

Nevertheless, when the study was revealed in the press, Dyer (2001) reported that several surviving participants had suffered lasting damage—both in their psychological well-being and in their persistently hesitant speech. Reynolds (2003) reported that none of the children or the orphanage staff were told the intent of the study and that even Tudor, in her thesis, had noted hesitant speech and embarrassed reactions by the children. At the Iowa university, students referred to Tudor's thesis as "The Monster Study." Although Schwartz (2006) suggested that an Institutional Review Board today would not have approved the Tudor study, perhaps because the ethics of the time were different, this study remains controversial and is an excellent case study for faculty and students studying communication sciences and disorders (Goldfarb, 2006). Schwartz correctly pointed out its flaws: There was no potential benefit for the participants, the experimental design had limitations, and instructions to the orphanage staff involved deception. Furthermore, "There was no planned debriefing and no provisions were made to ameliorate any of the effects … of the intervention" (Schwartz, p. 92; see also Fisher, 2005, "Deception Research Involving Children: Ethical Practices and Paradoxes").

In 1943, physician–scientists injected children at the Ohio Soldiers and Sailors Orphanage with bacteria in a study of dysentery (Lederer & Grodin, 1994). Between the 1950s and the 1970s, physician–scientists injected children at Willowbrook State School for children with mental retardation with strains of the hepatitis virus (Lederer & Grodin, 1994). In 1963, doctors injected live cancer cells into debilitated patients at the Jewish Chronic Disease Hospital (Katz et al., 1972). In 1966, Beecher exposed numerous examples of nonconsensual and harmful human research published in the American medical literature (Beecher, 1966).

Between 1944 and 1974, the U.S. government and many universities collaborated on nonconsensual human experimentation that included intentional exposure of humans to harmful or potentially harmful radiation via injection, ingestion, or environmental exposures. The Advisory Committee on Human Radiation Experiments

analyzed the factual record with reference to the ethical norms available to scientists and collaborators at the time the radiation studies were conducted. The following is an excerpt from a comprehensive report by the this advisory committee:

> The Advisory Committee finds that government officials and investigators are blameworthy for not having had policies and practices in place to protect the rights and interests of human subjects who were used in research from which the subjects could not possibly derive medical benefits.
>
> Government officials and biomedical professionals should have recognized that when research offers *no prospect* of medical benefit, whether subjects are healthy or sick, research should not proceed without the person's consent. It should have been recognized that despite the significant decision-making authority ceded to the physician within the doctor-patient relationship, this authority did not extend to procedures conducted solely to advance science without a prospect of offsetting benefit to the person. This finding is supported by the moral principle, deeply embedded in the American experience, that individuals may not be used as mere means toward the ends of others. (Advisory Committee on Human Radiation Experiments, 1996, Chapter 17, Finding 11; see also Faden et al., 1996)

Finally, during the 1960s, Stanley Milgram at Yale University conducted several studies aimed at determining the effect of authority on obedience behaviors (Milgram, 1974). The origins of Milgram's interests are explored by Russell (2010); the ethics of his experiments are explored by others (Slater et al., 2006). In summary, college students were instructed to deliver electric shocks to a peer (the "learner") who was attempting to learn word association lists. The main finding was that participants were willing to deliver increasingly large electric shocks to poorly performing learners when encouraged to do so, even when the learner demonstrated distress and cries of pain. The reasons for submission to authority are worthy of scientific study, but the ethics of subjecting human subjects to psychologically harmful studies, particularly when the study protocol is deceptive, is a subject of continuing controversy.

In the Milgram studies, the "shock" was fake (no shocks were delivered); the "learner" was a "confederate" of the investigators and feigned distress and pain; and, regardless of participants' distress at delivering increasing levels of shock, they were encouraged to proceed (Encina, 2004). This now-infamous series of studies by Milgram has received extensive and continuing analysis—particularly regarding the impact of psychological harm of certain types of study protocols, and whether deception should ever be used during human experimentation. The Milgram studies should be required reading for any student interested in RCR (see Miller, Gluck, & Wendler, 2008; Slater et al., 2006).

U.S. Federal Regulations: 1970s and Beyond

After the Tuskegee Syphilis Study was exposed to the public, the U.S. Congress enacted the National Research Act of 1974 (Pub. L. No. 93-348). Subsequently, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research published *The Belmont Report* (1979), explaining how the ethics principles of respect for persons, beneficence, and justice should apply to research involving humans. Guided by precedents in the National Institutes of Health and the Food and Drug Administration—which had oversight and prior peer-review requirements for human research between 1953–1971—federal research regulations were widely promulgated. Regulations for fetuses were finalized in 1975; for prisoners, in 1978; and for children, in 1983 (Glantz, 1998). In 1991, 16 federal agencies and departments harmonized regulatory standards in an updated federal policy known as the *Common Rule* that was codified in the Code of Federal Regulations (Protection of Human Subjects, 2005, 45 C.F.R. pt. 46; see also Shamoo & Resnik, 2003). The Common Rule includes a definition of research; a requirement that participants must consent only after receiving material information; that participants should not be induced, coerced, or be asked to waive any legal right; and that participants may withdraw from an experiment at any time.

The Common Rule requires prior review by Institutional Review Boards at all institutions receiving federal grant funds. In addition, the Common Rule requires investigators to tell potential participants that the work involves research, the nature of known or potential risks or benefits, and whether the participant might receive any benefit from the intervention. The Common Rule has special protections for pregnant women, fetuses, in vitro fertilization, prisoners, and children, but no special protections for seriously or terminally ill patients or those who lack decisional capacity (Protection for Human Subjects, 2005; National Bioethics Advisory Commission, 1999). Finally, privacy protections (e.g., de-linked data and de-identified data sets) under HIPAA's (1996) Privacy Rule are part of each research institution's responsibilities (Horner & Wheeler, 2005a, 2005b; Keith-Spiegel, Koocher, & Tabachnick, 2006; Korenman, Berk, Wenger, & Lew, 1998; Kulynych & Korn, 2003; Neale & Schwartz, 2004; Shamoo & Resnik, 2003; Swerdlow, 2005).

Office for Human Research Protections

In 2000, the Office of Protection from Research Risks (in the U.S. Department of Health and Human Services) was renamed the Office for Human Research Protections, and assumed the task of overseeing regulatory

compliance of federally funded research. The Office for Human Research Protections investigates complaints, provides compliance and interpretive guidance, and periodically publishes reports of compliance infractions. For example, the Office for Human Research Protection's 2009 publication reported numerous areas of noncompliance. The types of compliance problems found by Office for Human Research Protections included research conducted without Institutional Review Board review and/or approval; contingent approval of research with substantive changes and no additional review by the convened Institutional Review Board; and failure of investigators to report unanticipated problems, noncompliance, suspensions, and terminations to Institutional Review Board, institutional officials, and Office for Human Research Protections.

To analyze and correct these types of problems, several analyses have been done by the Office of the Inspector General of the U.S. Department of Health and Human Services, the Institute of Medicine, and other authoritative bodies (see Table 2). These analyses point to concerns about institutional support, adequacy of Institutional Review Board staffing and education, and the availability of educational opportunities for investigators—at all levels—about optimal research designs, protection of human participants, disclosure requirements, balancing harms and benefits, and protocol compliance (Anderlik & Elster, 2001; Clayton, 2004; Emanuel et al., 2000; Miser, 2005; National Institutes of Health, n.d.a, n.d.b, "Frequently Asked Questions"; Powell, 2002; Resnik & Sharp, 2006; Wolf, Croughan, & Lo, 2002). Quoting Greg Koski, director of the Office for Human Research Protections, Steinbrook (2002b) wrote, "Importantly, although compliance with federal regulations is essential, the goal is not to ensure compliance, ... The goal is to prevent harm or injury to individuals who are taking part in research" (p. 1425).

Contemporary Cases and Issues

Contemporary cases remind the scientific community that federal regulation of research is not enough to protect human participants: Scientific questions must have value; research must be designed to maximize benefits and minimize harms to research participants; consent forms must be informative; parents and other surrogates must not consent to high-risk nontherapeutic interventions; institutional ethics boards must oversee protocols carefully; and individual scientists must not only be compliant with regulations but also be competent and ethical.

Nevertheless, instances of noncompliance and ethical lapses have occurred. For example, Hoiyan Wan, a 19-year-old healthy nursing student, tragically died in 1996 at the University of Rochester after receiving lidocaine (Steinbrook, 2002b). Jesse Gelsinger, a young man with a chronic but stable illness, died during a gene therapy study in 1999 at the University of Pennsylvania (Gelsinger v. Trustees of the University of Pennsylvania, 2000). Ellen Roche, a young healthy volunteer, died in 2001 at Johns Hopkins University after ingestion of a respiratory depressant (Steinbrook, 2002a). In a research investigation led by the Kennedy Krieger Institute, healthy children were exposed to environmental lead for the purpose of comparing lead abatement methods (Grimes v. Kennedy Krieger Institute, 2001; Mastroianni & Kahn, 2002; Schwartz, 2002; Spriggs, 2004).

In 1966, Beecher reminded readers that the integrity of each individual investigator is essential for protecting research participants' interests. In the *Grimes v. Kennedy Krieger Institute* case, Judge Cathell also emphasized the responsibilities of investigators. He explained that the tort of negligence in the research context is based on investigators' "special relationships" with research participants, and that such special relationships are formed either from the informed consent agreement or from federal regulations governing research. In both instances, special relationships create obligations for investigators and research institutions. If they breach these obligations, legal duties, they can be held liable to research participants who are harmed by those breaches. Notably, Judge Cathell wrote: "We will not defer to science to be the sole determinant of the ethicality or legality of such experiments" (Grimes v. Kennedy Krieger Institute, 2001, p. 122). See Morreim (2004) for a review of contemporary cases (see also Cassell, 2000; Katz et al., 1972; Morreim, 2003; Mulford, 1967; Shalala, 2000).

Thus, our analysis of the literature showed that lapses in the protection of human research participants, particularly during times of rapid scientific advances, are enduring concerns. A host of ethical questions remain unresolved:

- What is the appropriate balance between potential harm and potential benefits in research investigations (Glantz, 1998; Weijer & Miller, 2004), and does this balance depend on whether the research is characterized as therapeutic or nontherapeutic (Lemaire, 2004; Miller & Joffe, 2006; Moreno, Caplan, Wolpe, & Members of the Project on Informed Consent, 1998)?
- Is the concept of "vulnerability" sufficient to protect the interests of research participants (Henderson et al., 2004; Institute of Medicine et al., 2003; Levine et al., 2004; National Bioethics Advisory Commission, 2001; National Institutes of Health, n.d.a, n.d.b, "Research Involving Vulnerable Populations"; Schaeffer et al., 1996; U.S. Government Accountability Office, 1996) or to protect third parties (Resnik & Sharp, 2006)?
- Is it appropriate to conduct research with deceased individuals (Nelkin & Andrews, 1998; Wicclair, 2008)?

- Are procedures to protect children clear and appropriate (Gercas, 2006; Hartman, 2006; Institute of Medicine, Committee on Clinical Research Involving Children, Field, & Berman, 2004; Kopelman, 2004; National Institutes of Health, 1998; Weil, Nelson, & Ross, 2002; Wendler & Glantz, 2007; Whittle, Shah, Wilfond, Gensler, & Wendler, 2004), especially when children have cancer or other grave illnesses (Joffe et al., 2006)?
- Do the federal regulations adequately consider the unique circumstances of newborns (Franck, 2005), persons with cognitive impairments (Cohen-Mansfield, 2003; Flory & Emanuel, 2004; Karlawish, 2003; National Institutes of Health, 1999; Sundram, 1998), individuals with psychiatric illnesses (Capron, 1999; National Bioethics Advisory Commission, 1999), prisoners (Calleigh, 2000; C. Cohen, 1978; Institute of Medicine, 2006; Lerner, 2007), persons with disabilities (Stineman & Musick, 2001), students (Moreno, 1998), and workers (Rose & Pietri, 2002)?
- What are appropriate limits on consent by parents or other legally authorized representatives (Glantz, 1998; Shalowitz, Garrett-Mayer, & Wendler, 2006; Spriggs, 2004)?
- Do regulations governing data, specimens, and images as well as "secondary uses" or "future uses" adequately protect participants' privacy (Barnes & Heffernan, 2004; Barnes, Hermes, & Brooks, 2006; Clayton, 2004; Illes, de Vries, Cho, & Schraedley-Desmond, 2006; Kapp, 2006; Kulynych, 2002; Kulynych & Korn, 2003; Law, 2005; Wendler, 2006)?
- Is it appropriate to waive consent in intensive care units (Alt-White & Pranulis, 2006; Williams & Haywood, 2003), emergency research settings (Bateman, Meyers, Schumacher, Mangla, & Pile-Spellman, 2003; Ernst & Fish, 2005), or military contexts (Annas, 1998; Brown, 2006)?
- Are coercion and inducements appropriately limited by Institutional Review Boards (Emanuel, 2005; Grady, Dickert, Jawetz, Gensler, & Emanuel, 2005; Grant & Sugarman, 2004)?
- Are members of communities representing minorities fairly included in human research (Corbie-Smith, Durant, & St. George, 2006; Seto, 2001; Wendler et al., 2006; Wynia & Gamble, 2006)?
- To what extent do "deception" (Wendler, 2004) and "therapeutic misconception" influence participant consent (Appelbaum, Roth, Lidz, Benson, & Winslade, 1987; BeLue, Taylor-Richardson, Lin, Rivera, & Grandison, 2006; Kimmelman, 2007; Miller & Joffe, 2006; Miller & Rosenstein, 2003)?
- What are the ethical and legal responsibilities of investigators (Koski, 2003; Lenrow, 2006; Morreim, 2003, 2004; Saver, 2006) and Institutional Review Boards (Anderlik & Elster, 2001)?
- Do all research settings, both public and private, meet federal standards for human participation protections (Gibelman & Gelman, 2001; Hueston et al., 2006; Miser, 2005; Wolf et al., 2002)?
- Are protections for participants in social and behavioral sciences, as distinct from the biomedical sciences, well articulated and understood by Institutional Review Boards and investigators (National Research Council, Citra, Ilgen, & Marrett, 2003)?
- Does random assignment cause harm (Gross, Krumholz, Van Wye, Emanuel, & Wendler, 2006; Palmer & Rosenberger, 1999)? Are placebo control arms ethical (Rothman & Michels, 1994)?
- Should research participants be permitted to access experimental pharmaceutical, devices, or other interventions when studies have not proven the intervention to be safe or efficacious (*Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach,* 2007; *Abney v. Amgen,* 2006)?

Human Dignity and the Ethics of Human Experimentation

A core issue that ties all of these questions together is whether voluntary consent—the Nuremberg Code's first principle—is sufficient to protect research participants' interests. See Table 3 for a chronology of the evolution of protections for human research participants from the Hippocratic Oath, through the Doctors Trials resulting in the Nuremberg Code, through U.S. court cases, to the enactment of the National Research Act of 1974 (Pub. L. No. 93-348) and the Common Rule in 1991 (Protection of Human Subjects, 45 C.F.R. pt. 46). Despite the centrality of informed consent to our ethics of human experimentation, Garnett (1996) argued persuasively that voluntary consent is necessary but not sufficient; rather, preservation of participants' dignity is the most important guiding principle (see also Pellegrino, 1997). If the scientific community is not meeting this fundamental "voluntary consent" standard, it might be time for reform (Brainard, 2000; Brody, McCullough, & Sharp, 2005; Childress, Meslin, & Shapiro, 2005; De Melo-Martin, Palmer, & Fins, 2007; Emanuel et al., 2004; Feussner, Burris, McGlynn, & Lavori, 2002; Kubetin, 2006; Menikoff, 2007; Sung et al., 2003).

In closing, the ethics of human experimentation has a long history, predating World War II. In 1947, the Nuremberg Code was written into international law, but, in the United States, widely applicable legal regulations governing human research were not adopted until the National Research Act of 1974, with numerous subsequent

amendments (see Protection of Human Subjects, 45 C.F.R. pt. 46, 2005). Subsequently, Garnett (1996) and Emanuel et al. (2000) opined that the consent of the subject is necessary but not sufficient to assure that research is ethical. Rather, investigators, and institutions, have obligations to protect participants' dignity as well as to maximize the benefits and minimize the harms associated with every investigation. A compelling historical example of unscrupulous human experimentation is that of Joseph Mengele, a Nazi physician at the Auschwitz–Birkenau concentration camp, who subjected twins to germ and genetics experimentation. Eva Mozes-Kor (1992), a survivor of Mengele's experiments, reminds scientists of their obligations:

> Scientists should continue to do research. But if a human being is ever used in the experiments, the scientists must make a moral commitment never to violate a person's human rights and human dignity. The scientist must respect the wishes of the subjects .... The scientists of the world must remember that the research is being done for the sake of mankind and not for the sake of science; scientists must never detach themselves from the humans they serve. (p. 58)

Research Involving Animals

According to the Office of Research Integrity (2000e), this topic pertains to:

> Issues important to conducting research involving animals. Includes topics such as definition of research involving animals, ethical principles for conducting research on animals. Federal regulations governing animal research, institutional animal care and use committees, and treatment of animals. (p. VIII.B.7)

The Emergence of Humane Treatment of Animals

During the Middle Ages, man believed he had "God-given dominion over the world ... [and] medieval cruelty to animals reflected man's sense of his own place in God's order" (Man's Mirror: History of Animal Rights, 1991). Feudal societies jailed and prosecuted animals (side by side with human perpetrators) for their crimes against property and humans, not only to deter and punish animals, but also in an attempt to maintain social order (Beirne, 1994; Brooman, 2007; Girgen, 2003). The Renaissance (14th–17th century) was marked by cruelty to animals, but Enlightenment philosophers such as Rousseau and Voltaire (18th century) espoused humane treatment of animals, "and Europeans began to pamper their household pets after 1700" (Man's Mirror: History of Animal Rights, 1991). Thus, whereas in the 16th century, Descartes maintained that animals were nonsentient "automata" (machines), in the 19th century, Darwin explained that animals were not only sentient but were also related in an evolutionary chain to higher mammals (Magnotti, 2006, p. 180; Singer, 1975).

The growth of scientific medicine and the increased use of animals in scientific research in the 19th century have been attributed to the philosophy espoused by Claude Bernard (1813–1878), the "patron saint of experimental medicine" (LaFollette & Shanks, 1994, 1995; see also Lederer, 1995). Bernard believed in the "interchangeability of the species"—that all living systems obeyed the same universal physiological laws (LaFollette & Shanks, 1994, p. 201). In response to the increasing prevalence of scientific physiological research, antivivisectionists campaigned vehemently against research using animals as experimental subjects during the 1800s and through World War II and beyond (Lederer, 1995; see also *Animals as Cold Warriors: Missiles, Medicine, and Man's Best Friend,* 2006).

The Royal Society for Prevention of Cruelty to Animals and the American Society for Prevention of Cruelty to Animals were founded 1824 and 1866, respectively (Lederer, 1995). In 1874, concerned citizens formed the American Humane Association to protect the interests of both animals and children (Lederer, 1995). Two contemporary associations are the Humane Society of the United States and the National Association for Biomedical Research. On the one hand, the Humane Society of the United States' *Statement on Animals in Biomedical Research, Testing, and Education* "advocates an end to the use of animals in research and testing that is harmful to the animals [and] strive[s] to decrease and eventually eliminate harm to animals used for these purposes" (Humane Society of the United States, n.d.). On the other hand, the National Association for Biomedical Research (n.d.a, *A Voice in Government*), is "dedicated solely to advocating for sound public policy that recognizes the vital role that animals play in biomedical research. On behalf of the biomedical research community, the National Association for Biomedical Research advocates for sound policy in support of ethical and essential laboratory animal research" (paragraph 1).

Animal Welfare Versus Animal Rights

The contemporary reasons for using animals in research are to advance scientific knowledge and medical care, for both humans and animals, and to confine early studies with unknown risks to nonhumans. Those who advocate animal welfare recognize the value of medical research with animals, and campaign for the humane care and use of animals; those who advocate animal rights seek the abolition of animal experimentation. (See Folkins, Gorga, Luschei, Vetter, & Watson, 1993; Foundation for

Biomedical Research, n.d.; National Association for Biomedical Research, n.d.b).

In contrast, People for the Ethical Treatment of Animals (PETA), a well-known animal rights group, "works through public education, cruelty investigations, research, animal rescue, legislation, special events, celebrity involvement, and protest campaigns" (PETA, n.d.). The Animal Liberation Front's (n.d.) *Philosophy Behind the Animal Liberation Movement* states, "The Animal Liberation movement is a loosely-associated collection of cells of people who intentionally violate the law in order to free animals from captivity and the horrors of exploitation" (see Animal Liberation Front, n.d.). Activist animal rights groups reportedly campaign against experimentation with animals, often using threatening and coercive methods (see commentaries by Kennedy, 2006; Smallwood, 2005).

Literature about these subjects includes inquiries on the following topics:

- "why animals matter" (Donnelley, 1999; Gluck & Bell, 2003; Goodman, 2006);
- studies of animal cognition (Cunningham & Janson, 2007; Watanabe & Huber, 2006);
- studies of pain in man, vertebrate animals (Keefe, Fillingim, & Williams, 1991), and invertebrate animals (Smith, 1991); and
- philosophical analyses of the moral status of animals (Magnotti, 2006; Man's Mirror: History of Animal Rights, 1991; McCarthy, 1999; Pluhar, 2006; Rollin, 2007a, 2007b; Russow, 1999; Sideris, McCarthy, & Smith, 1999).

For excellent reviews, see Fuchs and Macrina's (2005b) chapter entitled "Use of Animals in Biomedical Experimentation" and Kolar's (2006) paper, "Animal Experimentation."

Evolving Regulations and Guidelines for Animal Research

Early and evolving principles for research involving animals. In 1910, the AMA revised its Principles of Medical Ethics—first published in 1847—to include a uniform code for animal experimentation (Lederer, 1995, p. 73). In 1966, the Animal Welfare Act (Pub. L. No. 89-544) was enacted; this was the first U.S. federal law governing animal laboratory research. The Health Research Extension Act of 1985 (Pub. L. No. 99-158) amended the Animal Welfare Act and established Institutional Animal Care and Use Committees (Anderson, 2007). Other major guiding documents are the National Research Council's *Guide for the Care and Use of Laboratory Animals* (1963/1996); the National Research Council's *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* (2003; see also National Research Council, 2004); *U.S. Governmental Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training* (Office of Laboratory Animal Welfare, 1985); and *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (Office of Laboratory Animal Welfare, 2002).

Public Health Service policy is overseen by Office of Laboratory Animal Welfare, and applies to both extramural and intramural research. The U.S. Department of Agriculture's Animal and Plant Health Inspection Service regulates and inspects animal dealers, exhibitors, and research laboratories under the Animal Welfare Act (Animal and Plant Health Inspection Service, n.d., *Animal Welfare,* 2007). In addition, the AMA has a policy governing research involving animals (see AMA CEJA, 1989; Petersen, 1990) as does the American Psychological Association's (n.d.) *Guidelines for Ethical Conduct in the Care and Use of Animals*.

In 1993, the National Institutes of Health Revitalization Act (Pub. L. No. 103-43) established an Interagency Coordinating Committee on the Use of Animals in Research within National Institutes of Health, and charged it with conducting or supporting research into

> (A) methods of biomedical research and experimentation that do not require the use of animals; (B) methods of such research and experimentation that reduce the number of animals used in such research; (C) methods of such research and experimentation that produce less pain and distress in such animals; and (D) methods of such research and experimentation that involve the use of marine life (other than marine mammals). (§404C.(a)(1)(A)-(D))

Public Health Service policy. The "PHS Policy for the Care and Use of Laboratory Animals," promulgated by National Institutes of Health's Office of Laboratory Animal Welfare (2002), stipulates that Public Health Service grants and institutional assurances must include the following:

- identification of the species and approximate number of animals to be used;
- rationale for involving animals, and for the appropriateness of the species and numbers used;
- a complete description of the proposed use of the animals;
- a description of procedures designed to assure that discomfort and injury to animals will be limited to that which is unavoidable in the conduct of scientifically valuable research, and that analgesic, anesthetic, and tranquilizing drugs will be used where indicated and appropriate to minimize discomfort and pain to animals; and

- a description of any euthanasia method to be used. (pp. 15–16)

In addition, research facilities must be either accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (n.d.) or evaluated by an Institutional Animal Care and Use Committee, and must report semiannually to the Office of Laboratory Animal Welfare. Research must be conducted in a manner consistent with the Animal Welfare Act and the Public Health Service guide, as well as all other applicable laws and regulations (Anderson, 2007).

Animal research guidelines. The National Research Council has published several documents to guide researchers who use animals in their research. The National Research Council's (1996) *Guide for Care and Use of Laboratory Animals* is considered to be authoritative. To supplement laws and regulations, the Applied Research Ethics National Association and the Office of Laboratory Animal Welfare (2002) published the *Institutional Animal Care and Use Committee Guidebook*. The evolution of protections for animals as research subjects in the United States is summarized in Table 4.

In essence, these legal regulations and guidelines aim to hold investigators and institutions accountable for the humane care and use of animals used in research. Animal and Plant Health Inspection Service (2007) makes its policy manual available on its Web site, and, each fiscal year, it produces an annual report summarizing the law, the number of animals used in biomedical research, and government's investigative and enforcement activities. (See the Animal and Plant Health Inspection Service, n.d.)

The "Three Rs." Contemporary animal research policy embraces the "Three Rs":

- Reduce the number of animals used in experiments.
- Refine experimental procedures to minimize animal pain and suffering.
- Replace animal subjects with nonanimal alternatives when scientifically feasible (Ibrahim, 2006; Kolar, 2006).

Despite the putative benefits of animal experimentation (Cramer, 2003; Keefe, 1995), knowledgeable commentators have raised concerns about whether pain is adequately measured and controlled (Keefe et al., 1991), whether the Three Rs are succeeding in practice (Ibrahim, 2006), and whether the Animal Welfare Act is effective (Venderau, 2006). According to Venderau (2006), 95% of animals used in research are completely unprotected by the Animal Welfare Act; the Animal Welfare Act defines neither "humane" (p. 726) nor "scientific necessity" (p. 728); and the Animal Welfare Act neither reviews nor regulates the appropriateness of experimental designs or methods (p. 728). Venderau suggested that some experiments "lack necessity and purpose," and that, in some cases, animals may not be the most appropriate test subjects (pp. 734–736).

Current issues. The literature identifies the need for science-based guidelines for laboratory animal care programs (National Research Council, 2004) and the need for "comparative studies to assess the costs and effectiveness of new education and training methods" (Ketelhut & Niemi, 2007, p. 164; see also Conarello & Shepherd, 2007; Foshay & Tinkey, 2007; Medina & Anderson, 2007; Medina, Hrapkiewica, Tear, & Anderson, 2007; National Research Council, 1991).

Table 4. Protections for animals as research subjects.

Year	Document	Source
1966	Animal Welfare Act, as amended	Pub. L. No. 89-544
1985	Health Research Extension Act of 1985	Pub. L. No. 99-158
1985	International Guiding Principles for Biomedical Research Involving Animals	Council for International Organizations of Medical Sciences
1989	Animals in Research	American Medical Association
1991	Education and Training in the Care and Use of Laboratory Animals: A Guide for Developing Institutional Programs	National Research Council
1996	Guide for the Care and Use of Laboratory Animals (7th ed.)	National Research Council
2002	Institutional Animal Care and Use Committee Guidebook	Applied Research Ethics National Association & Office of Laboratory Animal Welfare
2003	Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research	National Research Council
2004	Development of Science-Based Guidelines for Laboratory Animal Care	National Research Council
2006	Animal Enterprise Terrorism Act	Pub. L. No. 109–374
2007	Animal Care Policy Manual	Animal and Plant Inspection Service
n.d.	Laboratory animal online training program	Laboratory Animal Training Association
n.d.	Guidelines for Ethical Conduct in the Care and Use of Animals	American Psychological Association

Recently, Mangan (2007) reported that medical schools are using fewer dogs and pigs in teaching.

> Medical educators say three main factors have prompted the shift: the increasing availability of realistic alternatives, such as interactive computer simulations, cadavers, and lifelike mannequins; students' ethical concerns about using live animals; and the expense of staffing and maintaining animal labs. (p. A12)

In light of the training requirement for laboratory personnel (established by the Health Research Extension Act of 1985; Anderson, 2007), Conarello and Shepherd (2007) asserted that training should be both technique and species specific, and should include instruction regarding:

- methods of restraint,
- use of anesthetics,
- monitoring anesthetic depth,
- blood collection techniques,
- dosing routes (e.g., intravenous, oral/nasogastric, subcutaneous, intramuscular, intraperitoneal, intradermal),
- institutional standards for dosing volumes, and
- accepted euthanasia methodologies. (p. 121)

In closing, animal experimentation, like human experimentation, raises concerns about necessity and purpose, scientific design, and risks and benefits. Just as Institutional Review Boards oversee human experimentation, Institutional Animal Care and Use Committees oversee animal experimentation. Just as the Office for Human Research Protections oversees compliance with human research regulations, the Office of Laboratory Animal Welfare and the U.S. Department of Agriculture oversee animal research and research laboratories. Whereas the guiding principles in human research are informed consent and the proper balance of the knowledge to be gained with risks and benefits, the guiding principles in animal research are encompassed by the Three Rs—reduce, refine, and replace. The extent to which scientists succeed in achieving these goals in research with animals depends on their education and training in the humane care and use of animals, their philosophy about "why animals matter" to our society and ecology, and on their willingness to embrace evolving standards about standards of care governing research involving animals.

According to Klein and Bayne (2007), "A strong research program and a well-developed animal care and use program are predicated on performance standards that are based on a culture of ethical conscience and responsibility, on science, and on a commitment to compliance with applicable standards" (p. 7). Finally, both philosophers and citizens concerned about the moral status of animals, and our moral responsibility to them, cite the words of 18th-century philosopher Jeremy Bentham: "The question is not, can they reason? Nor, can they talk? But can they suffer?" (Man's Mirror: History of Animal Rights, 1991).

Summary

The purpose of *Research Ethics I* was to review the evolution of RCR in the United States (1970s to the present) and to provide readers' access to important documents produced by scientists, physicians, ethicists, policymakers, and legal scholars. In the United States, the dialogue about responsible research practices has evolved significantly over the past two centuries, and particularly in the past four decades. After we reviewed the state of RCR in the United States, we stepped back in time to analyze experimentation using humans and animals, two important RCR domains as defined by the Office of Research Integrity, enterprises linked by history, humane societies, and the public's response to experimental practices. The prosecution of Nazi physicians in Germany after World War II was the watershed of ethics of human experimentation as understood today. Despite the fact that the legal record of the Doctors Trials became part of international law in 1947, professional societies, scientists, and the U.S. government were slow to put the Nuremberg Code principles into practice. It was not until the 1970s and beyond that investigators and institutions in the United States fully appreciated individuals' right to consensual participation in research or the need to balance benefits and harms. In light of the remarkable advances in scientific medicine over this long time period, and in spite of regrettable lapses, progress toward responsible research in all its dimensions, in the United States and internationally, has been remarkable and positive overall. We have written this article from a historical perspective because we think all readers interested in RCR should appreciate how the history of science and all the good, and harm, it has produced can inform how researchers practice responsible research in the 21st century and beyond.

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