Franklin G. Miller and Jonathan D. Moreno, "The State of Research Ethics: A Tribute to John C. Fletcher," *The Journal of Clinical Ethics* 16, no. 4 (Winter 2005): 355-64.

The State of Research Ethics: A Tribute to John C. Fletcher

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The ethics of research involving human subjects was one of the first topics on the agenda of bioethics when it emerged approximately 40 years ago. It remains central to the work of bioethicists today in scholarship, teaching, and institutional service. We dedicate this essay on the state of research ethics to the memory of John C. Fletcher, who died 27 May 2004. From the beginning to the end of his remarkable career, he grappled with ethical issues relating to human experimentation.[1]

As a young theologian interested in ethics, Fletcher undertook fieldwork at the Clinical Center of the National Institutes of Health (NIH) in the mid-1960s, at a time when American theologians, philosophers, and legal scholars began to focus systematic, ethical reflection on medicine and biomedical research. Fletcher wrote what may be the first PhD dissertation in bioethics, devoted to the ethics of clinical research, with particular attention to informed consent. The very first issue (1973) of *Hastings Center Studies,* an early publication of the Hastings Center, contained an article by Fletcher entitled "Realities of Patient Consent to Medical Research."[2] Facing the realities of research involving human subjects from a moral perspective occupied much of Fletcher's professional attention over the next 30 years. From 1977 to 1987 he served as the first chief of bioethics at the NIH Clinical Center, bringing the "soft" but powerful discipline of ethical thinking to bear on hard-core biomedical investigation. Fletcher's last sustained systematic contribution consisted of a commissioned paper for the National Bioethics Advisory Commission (NBAC) on the ethics of embryonic stem cell research, published in 2000.[3]

Over time, religious vocabulary dropped out of Fletcher's ethical reflections, and he ultimately resigned from the ministry. However, he carried the pastoral style of teaching and leadership into his secular vocation of bioethics. Teaching and preaching interpenetrated in Fletcher's work. Accordingly, we have developed this essay on the state of research ethics today as a secular sermon, oriented around five maxims that encompassed Fletcher's scholarship and teaching on the ethics of clinical research. (1) Because moral goals conflict, balancing competing considerations is unavoidable. (2) Bioethicists need to do their homework to understand methodological issues relevant to research design. (3) The history of research ethics is an invaluable source of moral reflection. (4) Institutional resources for promoting the ethics and regulation of clinical research must be developed, and their integrity must be maintained; and (5) Respect for the self-determina-

tion of research subjects remains a basic moral requirement. These maxims, and the issues to which they pertain, remain salient in contemporary research ethics and vital to progress in this domain of bioethics. Neglecting the moral force of these maxims, we shall argue, accounts for some of the prominent weaknesses in current scholarship and practical service in the field of research ethics.

COMPETING MORAL CONSIDERATIONS

Research ethics is often understood as the protection of human subjects of biomedical research. Though obviously central, this is only part of the story. The ethical imperative to protect human subjects operates as a moral constraint on the ethically grounded goal of promoting socially valuable science in the service of public health and improving medical care. Whereas the primary benefits of clinical research accrue to future patients and society, the risks and burdens of research interventions are borne by research subjects. This is not to suggest that there are no benefits to research subjects deriving from their participation in research. In some cases, enrolling in a clinical trial offers the best medical option available to some patients. Yet virtually every research study involving human subjects poses some risks to subjects that are not compensated by the medical benefits to them. Many studies carry risks to some or all subjects without any prospect of direct medical benefit. Accordingly, the central challenge of research ethics is how to promote valuable and valid scientific investigation without exploiting research participants.

The very nature of research involving human subjects, from a moral perspective, calls for a readiness to compromise experimental design to protect human subjects. Anyone with moral sensitivity recognizes that methods of valuable experimentation that pose lethal consequences to laboratory animals such as rats and mice would be "unthinkable" in the case of human subjects. Nevertheless, the dark history of human experimentation in Nazi Germany involved just such unthinkable abuses of human subjects, who were treated essentially as laboratory animals—research that was rationalized by the fact that the human subjects were condemned to die in any case, and that they came from a despised ethnic group believed by the investigators to be subhuman.[4] Lesser but morally outrageous abuses of human subjects occurred in the United States, despite *The Nuremberg Code*.[5]

Santayana famously declared that those who cannot remember the past are condemned to repeat it.[6] But we also are at risk of learning the wrong lessons from history. It would be a mistake to infer from this historical legacy of abuse in experimentation involving human subjects that the only ethical desideratum is to protect the subjects. If we take seriously the moral considerations favoring the pursuit of biomedical research, then we must recognize that, inevitably, tensions and conflicts arise between promoting socially valuable science and protecting human subjects. How do we balance, and make the trade-offs necessary to do justice to, these competing moral considerations?

Situations that call for moral balancing often provoke moral discomfort. In cases of moral complexity, it is natural to search for moral formulas that give us the right guidance without facing the burdens of moral uncertainty and fallible judgment. Thus bioethicists not infrequently appeal to absolute, categorical pronouncements aimed at settling moral conflicts. A notable example is the principle of clinical equipoise, widely believed to be an unassailable axiom governing the ethics of clinical trials. This principle requires, as a condition for ethical clinical trials, the existence of a state of uncertainty in the expert medical community concerning the therapeutic merits of the treatments under investigation, and other clinically available treatments, if any.[7]

Clinical equipoise is often invoked to rule out randomized, placebo-controlled trials whenever a proven, effective treatment exists for the disorder under investigation. Behind this principle lies the seemingly unobjectionable idea that patients who seek treatment in the context of a clinical trial should not have their medical care compromised by being randomized to interventions known to be inferior to the standard of care. Apart from conflating the ethics of clinical research with the ethics of medical care, clinical equipoise pre-empts ethical reflection aimed at balancing considerations of scientific validity in the design of clinical trials with adequate protection of subjects from undue risks of harm.[8] To be sure, in many cases the implica-

tions of clinical equipoise would be endorsed by all morally serious commentators. Virtually no one advocates randomizing patient-volunteers to placebo controls, when withholding clinically available treatment would pose substantial risks of death or irreversible, serious morbidity. But there exists a wide range of cases in which placebo-controlled trials are methodologically indicated, and the risks to subjects from withholding proven effective treatment are relatively minor or not excessive, so long as adequate safeguards are in place.[9] Is it clear that the use of placebo controls is always unethical in such situations? If not, how do we decide what level of risks to subjects is morally acceptable and what criteria must be met for these trials to be ethically justifiable, all things considered?

Clinical equipoise is by no means the only example of this strategy of evading moral conflict by issuing categorical pronouncements. A related case is the debate over invasive placebo controls in randomized trials of surgical interventions. Faced with the complex case of a sham-controlled trial evaluating fetal neural tissue transplantation to treat refractory Parkinson's disease, several bioethical commentators went far beyond the facts of the case at hand to claim that sham surgery is always unethical.[10] They argued that it violates the therapeutic obligation of physician-investigators to promote the medical best interests of patients enrolled in surgical trials and/or that it necessarily violates the ethical requirement to minimize risks. Ethical analysis of sham-controlled surgery trials that pose considerably less risks to subjects than the case of fetal tissue transplantation research demonstrates that the categorical prohibition is erroneous.[11]

The point of invoking these examples is not to contribute to the debate over placebo-controlled trials; rather, it is to suggest that some prominent positions in research ethics short-circuit the challenging task of balancing competing moral considerations. Moreover, we speculate that such positions become entrenched, despite being dubious in theory and practice, because they promote the comforting illusion of moral certainty, which obviates the anxiety provoked by moral conflict and the hard work of seeking morally satisfactory, but uncertain, compromises aimed at doing justice to competing moral considerations. John Fletcher, who late in his career came to embrace American philosophical pragmatism as a guide to bioethics, always eschewed "the quest for certainty." The first chapter of John Dewey's masterpiece, *The Quest for Certainty,* is entitled "Escape from Peril."[12] The search for and appeal to categorical, absolute principles manifests an escape from the peril of uncertainty inherent in the task of facing and balancing conflicting values and norms. In formulating ethical positions, Fletcher didn't always get it right, but he never flinched from the challenge of making fallible but reasoned judgments, knowing that reasonable people might differ.

Once we take to heart the recognition that research ethics inescapably involves balancing the competing moral considerations of promoting valuable science and protecting subjects, it becomes apparent that there are two ways that we can go wrong in the effort to find morally satisfactory resolutions. First, we can err by failing to provide adequate protection for human subjects. The severe abuses of the past have largely been avoided, owing especially to the innovation of prior independent review and approval of research protocols, which we discuss below. Nonetheless, complex issues of trial design continue to raise difficult challenges for the protection of subjects, as exemplified by the recent debate over a prominent critical-care trial comparing two methods of mechanical ventilation.[13] Second, we can err by unduly constraining valuable research. Overprotection of human subjects may prevent or severely hamper the conduct of important studies with significant potential for improving medical care, when such studies might be designed in a way that provides adequate protection of subjects. Vigilance, creative thinking, and honest debate are needed to find acceptable balances of the competing moral considerations at stake in the design and conduct of clinical research.

UNDERSTANDING SCIENTIFIC DESIGN

The most interesting and difficult issues of research ethics derive from the intersection of methodological considerations relating to the design of research and ethical concerns for protecting subjects. It is tempting to see this territory as "science versus ethics," and to adopt the moral posture that ethics trumps. However, this perspective is based on a false dichotomy. The first two requirements of research ethics are that research protocols must have adequate potential social value and that these studies must be designed with

sufficient methodological rigor to produce valid results.[14] Otherwise, the risks to which research participants are exposed cannot be justified. It follows that methodological considerations are integral to research ethics.

When bioethicists operate with a mindset that problems in research ethics are a matter of science versus ethics, they may presume that they possess the moral resources necessary and sufficient to resolve these problems without the need to study carefully the methodological considerations that are relevant to sound study design. This presumption is erroneous. The ability to diagnose pertinent ethical issues and balance competing moral considerations depends on appreciating the scientific reasons that underly the choices of research design that investigators make and defend. When participating in institutional review boards (IRBs), bioethicists are just as responsible for making judgments about the social value of research and the adequacy of research design as members with scientific training, although they certainly may need to seek advice from experts.

Moreover, the obviously ethical requirement of minimizing risks is impossible to apply without bringing methodological considerations to bear. Minimizing risks is not an imperative to eliminate risks, which would prevent nearly all clinical research; nor does it require that research risks are no more than "minimal." Rather, it calls for choosing those research designs that are methodologically adequate for producing valid, generalizable knowledge and that pose the least risks to subjects. For example, in the case of surgical trials aimed at evaluating treatment efficacy in terms of an inherently subjective outcome such as relief of pain, it is arguable that methodologically sound research design requires a sham surgery control.[15] These trials, then, satisfy the requirement of minimizing risks, despite the fact that they pose more than minimal risks to subjects who have been randomized to the sham control without the prospect of compensating medical benefit.

The upshot of these reflections is that bioethicists who are interested in research involving human subjects need to develop a basic understanding of the methodological principles of research design and do their homework in studying research protocols and the relevant scientific literature. Otherwise, they are ill-equipped to engage responsibly in debates over complex issues of research ethics. If the categorical pronouncements criticized above held sway, then bioethicists would be free of this professional obligation. There is no need, for example, to understand the methodological reasons for using placebo controls, despite proven effective treatment, if clinical equipoise is a valid absolute requirement of all clinical trials. It suffices to know that proven effective treatment exists. Such moral simplicity, however, *is* simplistic. There is no professional substitute for bioethicists doing their homework. Long experience in the ethics and regulation of research involving human subjects, and the exemplary performance in this respect of John Fletcher (who always did his homework), indicate that this responsibility is not merely an onerous task, but a source of intellectual stimulation, as well as a vital component of moral reflection.

THE RELEVANCE OF HISTORY

Bioethicists are not required to be historians, but they are obliged to be informed about the origins, development, and historical context of the central concepts of the field. This professional requirement follows from the fact that bioethics is, in part, a humanistic study, and that human values are shaped and tested in the crucible of concrete experience. Nor can we escape our collective past; it lives in our language and subsists in the way we conceptualize the moral life and the ethical problems that confront us.

A bioethics that lacks historical self-consciousness is liable to lapse into smug self-confidence about the soundness of its moral compass, and a naïvete about its intersection with social, political, and economic currents. Take, for example, the standard "origin story" of bioethics, that it emerged practically *de novo* in the late 1960s among a few farsighted physicians, philosophers, and theologians in response to drastically novel issues created by breakthroughs in the life sciences. These few perceptive thinkers, the story goes, suddenly recognized the unacceptable influence of physicians' paternalism; the social implications of genetics, artificial organs, and organ transplantation; and the threats to human dignity represented in thoughtless applications of technology.

This account not only ignores the complex history of medical ethics, it removes the founders of modern bioethics from their personal and professional experience, and suggests a purity of purpose that drains the field of its relevance. For example, the original icon of research ethics, Henry Beecher, had written about problems in human experiments since the late 1950s, a period during which he and many other distinguished scientists were supported by federal agencies that were interested in the national security implications of their work. Beecher himself conducted LSD research under military auspices and regularly updated the Central Intelligence Agency on his talks with his European colleagues.[16]

Beecher died in 1976, just as the first series of scandals about secret government-sponsored experiments were being investigated, so we will never have direct knowledge of his views on the matter. But we do know that Beecher was a profoundly religious man who read the Bible daily. In a 1994 interview, Beecher's former research assistant and Louis Lasagna, also an early commentator on bioethics, reflected "not with pride" on that period.[17] Beecher's subsequent interest in ethics and his preoccupation with the need for virtuous investigators must surely have flowed partly from similar considerations.

Beecher's devotion to the ideal of the virtuous scientist as the best protection for the human subject of research, the position for which he was criticized by Fletcher, also led him to oppose the application of *The Nuremberg Code* by Harvard researchers. Beecher took this position in 1962, when U.S. Army contracts began to incorporate *The Nuremberg Code* by reference. He joined a committee of Harvard faculty that protested this measure until the Pentagon backed down and agreed to let the scientists devise their own ethics code.[18] Our point is not to depreciate the courage required for Beecher to separate himself from many of his colleagues and identify unethical practices in his justly celebrated 1966 essay, but to exemplify the complexities and ambiguities of the origins of modern bioethics in the experience of one of its founders, and the relatedness of bioethics to society well beyond the boundaries of medical science itself.[19]

Similarly, to learn that *The Nuremberg Code* was adopted by the U.S. Department of Defense long before its tenets were recognized as applicable to civilian research, or that at least some research hospitals had IRBs 40 years before they were mandated by federal regulation, or that scandals and debates about the morality of experiments involving human subjects started as early as the 1890s, challenges our prejudices and vastly enriches our appreciation of the depth of the problems confronted today and how much we owe to previous generations. Perhaps even more jarring for Americans is the way that our German colleagues view the history of bioethics, as rooted in the first journal devoted to ethics in medicine (called simply *Ethics*), which started in the early 1930s as a forum for serious debate about values in medicine, and deteriorated into an organ for Nazi eugenics. Our judgment is likely to be far more measured and supple as our sophistication about the forces at work in bioethical issues is informed by a quantity of experience far greater than any one generation can acquire.

John Fletcher enjoyed his role as a continuous student of the history of bioethics because he understood that the past resides in the present. Although the victims of the Tuskegee Syphilis Study received federal compensation in 1978, Fletcher appreciated that money does not in itself provide moral closure. Thus, in 1995 at a public meeting in Charlottesville, Virginia, he proposed a long overdue presidential apology, an idea that made its way to the White House and was realized in a Rose Garden ceremony in 1997, just before the deaths of the study's remaining survivors. Fletcher's concern with this issue joined his early and long-standing commitment to the Civil Rights Movement with his understanding of bioethics as a social and political movement.

THE INSTITUTIONAL DIMENSION OF RESEARCH ETHICS

The leading innovation in the history of research ethics is prospective independent review of protocols for clinical research. The familiarity of this institutional innovation obscures its vital importance. *The Nuremberg Code* makes no mention of independent review. Nor was it mentioned as a safeguard in the path-breaking 1966 essay by Beecher that exposed abuses of research subjects in studies conducted by leading investigators, mostly in prestigious academic medical centers and often funded by the U.S. government.[20] In

a valuable historical essay on informed consent to research, Fletcher criticized Beecher for emphasizing the integrity of the conscientious investigator as the primary safeguard for protecting human subjects.[21] He rightly argued that oversight by an impartial, independent committee whose members had no vested interest in the particular research project under review was essential both to assure that the rights and well-being of research subjects would be adequately protected, and to provide an institutional mechanism of public accountability for a social practice that exposes some to risks for the benefit of society.

The interests of investigators who seek to promote their professional careers in conducting biomedical research inherently diverge from the interests of patient-subjects who participate in clinical trials to receive potential medical benefits or to contribute altruistically to the improvement of medical care. This divergence opens the door to exploitation, especially insofar as patient-subjects confuse research with medical therapy or feel under pressure from their treating physician to enroll in research. The primary purpose of the IRB is to protect human subjects from exploitation and harm while at the same time permitting valuable research to go forward.

Independent review is, in part, a mechanism of peer review, familiar to the scientific world. But it is more than that, because the federal regulations that mandate review and approval by IRBs require that these committees include at least one member who is not a scientist and at least one member who has no other affiliation with the research institution.[22] In addition to being charged with protecting subjects, these committees must include members who do not bring a professional commitment to biomedical research to the table. Many IRBs also include bioethicists as members.

The IRB can be seen as an example of democratic governance, even though there is no democratic procedure involved in appointing or removing its members. Just as national defense is too important to be left up to the generals, so the design and conduct of medical research should not be left to the discretion of investigators. Ethics is everyone's business. The fact that IRBs make their decision by vote, with a majority determining the outcome, signifies that the voice of each member ultimately counts equally.

The role of bioethicists on IRBs has not received the attention it deserves. The medical world is governed by a culture of expertise. In this world, the bioethicist may be seen as an ethics expert. Long ago, Ruth Macklin distinguished between expertise *about* ethics, which bioethicists possess, and expertise *in* ethics, which is a philosophically dubious concept.[23] Even if expertise in ethics exists, there is no guarantee that it will be possessed by those who have most assiduously cultivated expertise about ethics. Although moral wisdom exists, it is probably a category mistake to understand it as expertise. In any case, bioethicists can make no claim to moral wisdom simply by virtue of long pursuit of ethical scholarship or competence in ethical analysis. Nonetheless, bioethicists may be perceived as experts in ethics, and it behooves them not to cultivate the false impression that this is the case.

Despite a proper humility about the source of their expertise, bioethicists still may find themselves in a position of power or authority. Their voices may carry considerable weight, not based on the transparent rightness of their views or the merits of their arguments, but because they come from a person with the professional credentials of being a bioethicist. Bioethicists should take care, accordingly, that their expressed views have been reflectively validated and that they are backed by cogent arguments. They owe this responsibility, both on the basis of professional integrity, and as a morally appropriate accompaniment to the power they exercise, even when this power derives from a misperceived ascription of expertise.

IRBs work best when their mission is understood to include an educational dimension, in addition to passing judgment on research protocols and assuring compliance with regulatory guidelines. Here bioethicists have an important role to play in sparking moral reflection, elucidating confusions that impede accurate moral judgment (most notably the pervasive tendency to regard clinical trials from a therapeutic perspective that distorts moral reflection and judgment), and making sure that all morally relevant considerations have been articulated and duly weighed. The role calls for a willingness to be a Socratic gadfly. When bioethicists do their homework in coming to appreciate methodological considerations relevant to research design, their educational role is more likely to be respected.

THE ENDURING IMPORTANCE OF INFORMED CONSENT

In the history of research ethics, the moral importance of informed consent has both been exaggerated and underappreciated. The first principle of *The Nuremberg Code* declares, "The voluntary consent of the human subject is absolutely essential."[24] Strictly understood, this cannot be a sound principle for research that involves human subjects, for it would rule out research involving children and incompetent adults, making it impossible to make progress in combating dreaded diseases that afflict these populations. Even in the case of research involving competent adults, it is a mistake to see informed consent as *the* cornerstone of research ethics. Issues of informed consent should not even come into play in evaluating research protocols, unless these studies have been assessed as having adequate potential value, deploying valid methods, selecting subjects fairly, minimizing risks, and offering a favorable risk-benefit ratio.[25]

Putting informed consent in its place, however, also involves giving this moral consideration its due. Recently, some disturbing trends have emerged in the research ethics literature that point to unjustified erosion of commitment to informed consent. Three articles are notable in this respect. Truog and colleagues argued a few years ago that informed consent for participation in research is not ethically necessary in a class of randomized trials that compare two medically indicated treatments for a given disorder that pose comparable risk-benefit profiles, such that the reasonable patient would have no reason to prefer one over the other.[26] In this situation, an informal informed-consent process that is adequate to medical treatment should ethically suffice. Specifically, if this position is sound, there would be no reason to inform patient-subjects of randomized treatment selection. Recently, Sreenivasan has argued that it is a mistake to require that research subjects enrolled in randomized controlled trials (RCTs) possess some minimal degree of understanding about the basic elements of participation in research.[27] As long as trials have been judged by a competent IRB to meet the basic ethical requirements, including a favorable risk-benefit ratio, the duty of obtaining informed consent requires adequate disclosure of relevant information, but not comprehension on the part of subjects. Empirical evidence regarding the understanding of trial participants indicates that many, if not most, fail to understand basic elements disclosed in the informed-consent process, such as randomization, and they confuse the experimentally structured allocation and provision of treatment in RCTs with the patient-centered context of medical care. If comprehension of these features of participation in research were strictly required, many valuable RCTs would be judged ethically invalid. Accordingly, ethical honesty calls for a minimalistic requirement of informed consent. Finally, Evans has recently contended, in an even more-radical article, that we should dispense entirely with voluntary participation in many RCTs.[28] Since all patients benefit from the progress of medical research, they should be subject to a legally enforceable duty to participate in available and clinically appropriate RCTs when they seek care in a public healthcare system. He uses taxation as an analogy to bolster the position that voluntary consent is not a valid requirement.

Each of these positions warrants detailed critique. We limit our discussion here to examining the ethical premises that underlie these provocative but dubious challenges to informed consent. The doctrine of clinical equipoise, criticized above, plays a central role in grounding these positions. It is important to point out that there is no inherent logical connection between clinical equipoise and ethical positions that obviate the need for informed consent. Certainly, it was not part of the agenda of Benjamin Freedman, who developed the concept of clinical equipoise, to promote the sorts of positions advocated by Truog and colleagues, Sreenivasan, and Evans. Nonetheless, the doctrine of clinical equipoise attempts to bring the RCT under the Hippocratic ethical umbrella that covers therapeutic medicine, such that the therapeutic obligations of physicians to their patients can be preserved in the context of participation in trials. Insofar as it is presumed that when clinical equipoise obtains, participation in a trial is ethically congruent with medical care, the stage is set for arguing that no more is needed for informed consent to participate in an ethically justified RCT than to receive medical care. Such a position is explicitly adopted by Truog and colleagues, who emphasize that trials for which informed consent for participation in research is not required must satisfy clinical equipoise. Clinical equipoise is also an explicit background ethical condition for mandatory participation in trials in Evans's argument, and it is implicit in the argument of Sreenivasan.

Contrary to the thrust of the equipoise doctrine, clinical trials must be understood from an ethical perspective as fundamentally different from medical care.[29] Clinical trials are aimed at and designed to produce generalizable knowledge about the safety and efficacy of treatments; in contrast, medical care aims at promoting the best medical interests of particular patients. Consequently, the ethical imperative of respect for persons calls for assuring that research subjects have a minimally adequate understanding of how participation in trials differs from medical therapy. Sreenivasan is right that it is unrealistic and unreasonable to demand full comprehension of all of the ethically relevant aspects of participation in research. It doesn't follow that we should dispense with requiring any level of understanding on the part of research subjects. What constitutes an adequate minimum of understanding and how it is to be assured are tasks for future work in research ethics. However, if we permit the erosion of informed consent as a result of theoretically misguided views about the ethics of clinical trials, or out of despair over evidence that patient-volunteers "just don't get it," then we will have failed to do our part to uphold and maintain the historical legacy of bioethics.

CODA

John Fletcher played a leading role in getting research ethics off the ground. His teaching, including the five maxims around which we have oriented this essay, offers a rich source of enduring moral wisdom regarding the ethics of clinical research. In bioethics almost nothing remains settled. Views that once seemed unassailable are challenged, calling for reconstruction of moral perspectives. Always hard at work in promoting ethics services, doing ethics consultations, teaching, and scholarship, John C. Fletcher used to quip that "bioethics never sleeps." More importantly, his exemplary career teaches us that, in bioethics, there is never a time for "dogmatic slumber."

DISCLAIMER

The opinions expressed are those of the authors and do not necessarily reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

NOTES

1. F.G. Miller, "Dedicatory Essay on John C. Fletcher," *Journal of Contemporary Health Law and Policy* 13 (1996): ix-xiv.

2. J.C. Fletcher, "Realities of Patient Consent to Medical Research," *Hastings Center Studies* 1 (1973): 40-9.

3. J.C. Fletcher, "Deliberating Incrementally on Human Pluripotential Stem Cell Research," National Bioethics Advisory Commission, *Ethical Issues in Human Stem Cell Research* vol. 2, Commissioned Papers (2000): E1-E50.

4. R. Lifton, *The Nazi Doctors* (New York: Basic Books, 1986) R. Proctor, *Racial Hygiene* (Cambridge, Mass.: Harvard University Press, 1988).

5. The Nuremberg Code, *ohsr.od.nih.gov/guidelines/nurember.html.*

6. G. Santayana, "Reason in Common Sense," in *The Life of Reason* (Amhurst, N.Y.: Prometheus Books, 1998).

7. B. Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317 (1987): 141-5.

8. F.G. Miller and H. Brody, "A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials," *Hastings Center Report* 33, no. 3 (2003): 19-28.

9. E.J. Emanuel and F.G. Miller, "The Ethics of Placebo-Controlled Trials—A Middle Ground," *New England Journal of Medicine* 345 (2001): 915-9.

10. R. Macklin, "The Ethical Problem with Sham Surgery in Clinical Research," *New England Journal of Medicine* 341 (1999): 992-6; P.A. Clark, "Placebo Surgery for Parkinson's Disease: Do the Benefits Outweigh the Risks?" *Journal of Law, Medicine & Ethics* 30 (2002): 58-68; A.J. London and J.B. Kadane, "Placebos that Harm: Sham Surgery Controls in Clinical Trials," *Statistical Methods in Medical Research* 11 (2002): 413-27.

11. F.G. Miller, "Sham Surgery: An Ethical Analysis," *American Journal of Bioethics* 3, no. 4 (2003): 41-8.

12. J. Dewey, *The Quest for Certainty,* in *John Dewey: The Later Works, 1925-1953,* ed. J.A. Boydston, vol. 4: 1929 (Carbondale, Ill.: Southern Illinois University Press, 1988).

13. H.J. Silverman and F.G. Miller, "Control Group Selection in Critical Care Randomized Controlled Trials Evaluation Interventional Strategies: An Ethical Assessment," *Critical Care Medicine* 32 (2004): 852-7.

14. E.J. Emanuel, D. Wendler, and C. Grady, "What Makes Clinical Research Ethical?" *Journal of the American Medical Association* 283 (2000): 2701-11.

15. see note 11 above.

16. J. Marks, *The Search for the "Manchurian Candidate": The CIA and Mind Control* (New York: Times Books, 1979), 67n.

17. Advisory Committee on Human Radiation Experiments, *The Human Radiation Experiments* (New York: Oxford University Press, 1996), 79.

18. J.D. Moreno, *Undue Risk: Secret State Experiments on Humans (*New York: Routledge, 2001): 240-3.

19. H.K. Beecher, "Ethics and Clinical Research," *New England Journal of Medicine* 274 (1966): 1354-60.

20. Ibid.

21. J.C. Fletcher, "The Evolution of the Ethics of Informed Consent," ed.K. Berg and K.E. Tranoy *Research Ethics* (New York: Alan Liss, 1983), 187-228.

22. Department of Health and Human Services, Protection of Human Subjects, *Code of Federal Regulations,* 45 *CFR* 46, 1991.

23. R. Macklin, *Mortal Choices* (New York: Houghton Mifflin, 1988), 18.

24. See note 5 above.

25. See note 14 above.

26. R.D. Truog, W. Robinson, and A. Randolph, "Is Informed Consent Always Necessary for Randomized, Controlled Trials?" *New England Journal of Medicine* 340 (1999): 804-7.

27. G. Sreenivasan, "Does Informed Consent to Research Require Comprehension?" *Lancet* 362 (2003): 2016-8.

28. H.M. Evans, "Should Patients be Allowed to Veto their Participation in Clinical Research?" *Journal of Medical Ethics* 30 (2004): 198-203.

29. F.G. Miller and D.L. Rosenstein, "The Therapeutic Orientation to Clinical Trials," *New England Journal of Medicine* 348 (2003): 1383-6.