

# THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: Facing the 21st Century

Edited by

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## Introduction and Overview: Ethics, Historical Case Studies, and the Research Enterprise

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Why is so much attention now being given to the ethics of research involving human subjects?<sup>1</sup> What is the nature and content of this ethics? What roles does ethics play or should it play in the conducting of biomedical research?

These questions are unanswerable apart from understanding the purposes and ever-increasing power of biomedical research itself. Research involving human beings has expanded exponentially over the last 60 years as nations, national and international institutions, and groups of researchers have linked their destinies and hopes to medical advances. The nature and influence of this expansion will be explored under the subheading, "The Reach of Research," below.

Studies by historians, sociologists, political scientists, and multi-disciplinary scholars have explored how, when, and by whom this research was and is being conducted. Those who deal with the ethics of clinical research should be acquainted with a number of these important, factually oriented studies, many of which are referenced in this book. Ethical judgments about the rightness or wrongness of a research protocol or some aspect of that protocol are null and void apart from a precise understanding of the research in question.

ETHICS

While necessarily relying upon its sister disciplines in the humanities and the social sciences, ethics focuses not on what individuals and groups do and how they behave, but on,

what they *ought* to do and how they *ought* to behave. Ethics asks about what is right or good or virtuous; it seeks to identify and characterize moral arguments, and to investigate whether and the extent to which these arguments, or the decisions they are intended to justify, are rationally warranted.<sup>2</sup>

Ethics provides the means to identify and critically assess the explicit and implicit reasons for conducting research with human subjects. It also enables us to make judgments about the morality of researcher-subject relationships within the many settings in which research occurs. Ethical scrutiny provides hindsight, assists in oversight, and offers foresight.

How can ethics fulfill these roles? An inventory of the “ingredients” of ethics shows how and why ethics functions as a means for critically assessing both the rationales for human conduct and the morality of human relationships.

Ethics or ethical analysis begins with a straight-forward, jargon-free question: What actions are right or wrong, good or bad, praiseworthy or blameworthy? To ask about “actions” brings into play actors, personal interactions, and relationships. This question immediately calls forth another: By what criteria do we decide whether some action or personal interaction is right or wrong, good or bad?

Regardless of their levels of training or areas of specialization, all who “do ethics” or make ethically discerning decisions can agree on the following criteria: judgments about the morality of actions and relationships are predicated upon logical arguments, accurate facts, and coherent reasons. As we examine difficult issues, we discover that we often cannot arrive at uncontested or conclusively convincing answers, but we can be sure that we are not indulging in serious ethical inquiry if we are not seeking to arrive at answers that are the most convincing and acceptable among alternative possibilities.<sup>3</sup>

The salient features of ethics as a human enterprise arise from this search for coherent and defensible answers. First, ethics is a rational enterprise that endures as a centuries-long search for time-tested arguments and principles that are coherent and applicable.<sup>4</sup> Second, ethical reasoning rests on common and shared experiences and insights, on the facts insofar as they can be ascertained, and on ordinary logical inference. With effort and experience, most persons can become skilled in ethical analysis. Third, as

critical and disciplined inquiry, ethics commissions us to make *judgments* predicated upon thoughtful analysis and deliberation. This contrasts with making assertions or voicing opinions, regardless of the frequency or certitude with which they are asserted or voiced.<sup>5</sup>

What the poet Wallace Stevens says of modern poetry is true for ethics:

It has to be living, to learn the speech of the place.  
It has to face the men of the time and to meet  
The women of the time. It has to think about war  
And it has to find what will suffice.<sup>6</sup>

The criteria and salient features of ethics alert us to common misperceptions about ethics. Ethics should not be equated with regulations and bureaucratic rules, even though ethics informs and shapes many such rules.<sup>7</sup> The interesting and important ways ethics informs regulations of human-subject research will be further explored in this chapter and in the introductions and chapters that follow.

Nor should ethics be equated with all value statements and judgments, even though these judgments characteristically assess things as good or bad, right or wrong. This is true because we hold to many types of values that have little or nothing to do with ethics. For example, on the basis of prudential or practical values, we assess wrenches, cars, or human work as good, not so good, or terrible. In like fashion, we commonly make strong and, at times, highly contested judgments about aesthetic, economic, or religious matters. Ethical values are a subset within the universe of human values and valuing, even though ethical values interact in complex and multifaceted ways with other values.<sup>8</sup>

Ethical values and judgments pertain to the following three areas:<sup>9</sup>

1. Judgments about that which is ultimately good, that is, good with respect to the purposes and ends of human action;<sup>10</sup>
2. Judgments of human character—judgments that assign praise or blame to persons and their actions in light of their virtues of character or lack of such;<sup>11</sup>
3. Judgments about moral obligations—what we ought or ought not to do, how we should or should not treat others.

Concerning moral obligations, consequentialists determine the rightness or wrongness of actions according to their outcomes. Actions are judged to be right or obligatory if they will, or probably will, bring into being that which is regarded as ultimately good—human happiness, mutual respect, harmony and peace, and so on. Holding to a version of consequentialism, utilitarians regard happiness as the ultimate human good, and thus equate right or obligatory moral actions with actions that will likely produce the greatest balance of happiness over displeasure or suffering.<sup>12</sup> Nonconsequentialists and nonutilitarians deny that rationally calculated outcomes or consequences serve as the ultimate criterion or standard of morality. Nonutilitarians include deontologists and casuists. Deontologists equate morality with basic rules and principles of action—the principle of respecting the autonomy of others, the duty to tell the truth, certain principles of justice, and so on. Regarded as obligatory in and of themselves, these duties generate principles of procedure,<sup>13</sup> for example, the principle of never using persons as a means toward an end, but rather, respecting persons as end-choosing or self-choosing agents.<sup>14</sup> Some deontologists view these principles as multiple and interacting norms that must be played off against one another before the morality of specific acts can be determined.<sup>15</sup> Critical of those who equate ethics with theory-based rules of procedure and universal ethical principles, casuists accent practical moral reasoning and decision making about particular, morally troubling situations.<sup>16</sup>

These brief points indicate how ethics serves as a disciplined, reasoned way to identify, criticize, discover, and defend arguments and rationales that justify how humans should relate to and behave toward one another. Additional features about the nature and functions of moral inquiry will be discussed in the pages and chapters that follow. These features will be examined when they offer essential and useful ways to understand and critically assess the morality of clinical research involving human subjects.

#### CASE STUDIES IN THE CHECKERED HISTORY OF RESEARCH ETHICS

Discussions over the morality of deliberate medical experiments on human beings extend from Greek and Roman antiquity,

to the writings of Moses Maimonides (1135-1204) and Francis Bacon (1214-1294), to debates over smallpox inoculations in the 18th century, to numerous controversies over reported abuses of human subjects after 1870, to a host of 20th century developments.<sup>17</sup> While many case studies of the ethics of research involving human subjects could be drawn from this long history, the brief case-sketches that follow represent notable chapters over the course of the last 60 years. Comprising the darkest and brightest periods in the history of human experimentation, these episodes continue to serve as positive and negative standards for evaluating research ethics and regulation.

Concerning ethics, episodes in the history of research with human subjects serve as cases, as heuristic devices, for thinking about the nature and function of ethics as applied to research. By using them as case examples, readers individually and in study groups can identify ethical principles that will more likely protect or permit—unwittingly or by intention—abuses of human subjects. This can be done by reflecting on the interplay between (1) types of experiments, (2) the reasons or rationales for these experiments, and (3) the ethical assumptions underlying these reasons and rationales.

The phrase “ethical assumptions” may be confusing. For example, since the sketches below include experiments conducted under Nazi supervision, should not some of them be viewed as grievously *unethical*? This question points to a distinction between two subdivisions of moral inquiry. The first is called descriptive ethics—the *nonjudgmental* task of describing and charting the many assumptions and modes of reasoning used as justifications or rationales for human behavior.<sup>18</sup> This involves exploring “ethical assumptions” in the social scientific sense of discovering their types and variety. Ethicists have shown that social practices and policies are never devoid of assumptions and rationales that function as moral justifications.<sup>19</sup> For good or ill, these systems of value shape how humans deal with war, commerce, family relationships, medical care, and biomedical research.

In addition to descriptive ethics, ethical inquiry includes normative ethics, the task of identifying and rationally justifying the grounds for determining which courses of action are right or

wrong, ethical or unethical.<sup>20</sup> The foregoing discussion under the subheading “Ethics” dealt with some of the salient features of normative ethics. Ethical norms and theories of moral obligation function (1) as personal guides, (2) as grounds for assessing or judging others’ actions, and (3) as vantage points for criticizing assumptions and modes of moral reasoning identified via descriptive ethics.<sup>21</sup>

The following episodes challenge us to think both descriptively and normatively. Descriptively: What assumptions and modes of reasoning served as rationales for these experiments? And what assumptions and forms of reasoning are *we* using to assess the morality of these experiments? Normatively: What ethical assumptions and modes of reasoning should we be using to assess past (and present) actions as right or wrong?

#### NAZI EXPERIMENTATION

During World War II, National Socialist (Nazi) German investigators experimented on unwilling and unsuspecting civilians and political prisoners for the purposes of advancing the state’s goals of national and racial superiority and, more immediately, to enable Germany’s fighting forces to cope with disease, injury, and life-threatening battle conditions.<sup>22</sup> The ideological justifications of Nazi physician-experimentalists included contributing to scientific progress—particularly, the science/pseudoscience of advancing human evolution by destroying those deemed genetically inferior and worthless.<sup>23</sup> The career of the infamous Dr. Sigmund Rascher exemplifies how some Nazis used their work to gain political favor and secure appointments within academic medicine.<sup>24</sup> Extensive, willfully harmful experiments included subjecting concentration camp internees to extreme hypothermia, high altitude decompression, mutilative wounds, typhus and other infections, toxic substances, experimental drugs, massive bleeding, and vivisections, all often ending in death.<sup>25</sup> Most, if not all, of these experiments were without scientific merit.<sup>26</sup> They were conducted in spite of and in opposition to laudable and visionary ethical guidelines on medical experimentation promulgated by the German Minister of the Interior in 1931.<sup>27</sup>

#### U.S. WORLD WAR II RESEARCH

During the Second World War medical research was planned, coordinated, and extensively funded at the federal level for the first time in U.S. history. To increase combat effectiveness while the nation was mobilized for war, this research centered on the medical problems of America’s troops—dysentery, malaria, gas warfare, wounds, and wartime climatic conditions.<sup>28</sup> Research subjects included nonconsenting orphaned children in their teens and retarded and mentally ill persons and ward patients, as well as consenting and informed prisoners and conscientious objectors. This research was predicated upon the rationale that,

All citizens were—or were supposed to be—contributing to the war effort. . . . Some people were ordered to face bullets and storm a hill; others were told to take an injection and test a vaccine. No one ever said that war was fair, or that it should be fairer for the incompetent than the competent.<sup>29</sup>

Usually healthy when they volunteered or were obligingly used, most of those experimented upon endured moderate or serious sickness, and some died.<sup>30</sup> Unaware, nonconsenting, and deceived servicemen also suffered moderate to severe short-term and long-term injuries from mustard gas experiments in gas chambers and field tests.<sup>31</sup> While a number of these experiments failed to uncover useful cures, this research produced an effective influenza vaccine, developed highly effective and valuable synthetic antimalarial drugs, and discovered ways to suspend penicillin in beeswax and peanut oil so as to make it less costly and more widely used.

#### THE NUREMBERG TRIAL AND CODE

In its concluding decision on the war crimes of Nazi physicians and scientists, the Nuremberg Military Tribunal set forth 10 ethical principles regarding human experimentation. Replicated as free-standing principles, they are now known as the *Nuremberg Code*. Declared to be “basic principles [that] must be observed in order to satisfy moral, ethical and legal concepts,” these principles stipulate that the “voluntary consent of the human subject is absolutely essential”; and that experiments must “yield fruitful results for the good of society,” must “protect the experimental

subject against even remote possibilities of injury, disability, or death," must "be conducted only by scientifically qualified persons," and should be terminated when there is "probable cause to believe" that "a continuation of the experiment" will likely result in harm.<sup>32</sup> Beyond previous codes of research ethics, the *Nuremberg Code's* consent requirements were remarkably specific—the necessity of free choice without "any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion"; sufficient knowledge "to make an understanding and enlightened decision" in light of "the nature, duration, and purpose of the experiment" supplied by the person "who initiates, directs or engages in the experiment"; and the right to withdraw when the experiment's continuation seems "to be impossible" physically or mentally. Although this code influenced the formation of many professional and governmental codes thereafter,<sup>33</sup> it has been viewed as politically naive and unduly restrictive with respect to research involving children and other populations of patients.<sup>34</sup> The *Nuremberg Code* nevertheless continues to be regarded by some as the gold standard for all research with competent adults, a standard that "can guide us in eliminating all unconsented-to research on competent persons throughout the world."<sup>35</sup>

## TWO DECADES OF NONFEDERALLY REGULATED RESEARCH

Believing that the Nazi atrocities were a world apart from the work they were doing, biomedical researchers in the U.S. between 1946 and 1966 resisted ethical and regulatory oversight as intrusive to their relationships with patients-subjects and as adequately handled at the discretion of investigators.<sup>36</sup> Surveys of the practices and thinking of research institutions in 1960 and 1962 revealed that this trust in the conscience of investigators resulted in sporadic internal regulation and oversight.<sup>37</sup> Through an article published by the *New England Journal of Medicine* in 1966, Henry K. Beecher undercut the moral complacency and hands-off policies of many American physician-researchers. Beecher's exposé included 22 examples of unethical research conducted between 1948 and 1965.<sup>38</sup> His examples dealt with research by well-known, highly funded investigators who worked in leading medical schools and government institutions and

published their findings in prestigious medical journals. Beecher showed how the research experiments he reviewed "risked the health or the life of their subjects" often without their knowledge or consent. Examples 16 and 17 became famous, widely debated cases—the injecting of live cancer cells under the skin of unsuspecting patients at the Jewish Chronic Disease Hospital in Brooklyn, New York, and the infecting of retarded children in the Willowbrook State School on Staten Island with a mild strain of infectious hepatitis.<sup>39</sup> The impact of Beecher's article was all the more confounding because it probed the actions and assumptions of recognized cultural benefactors, those who in a few years' time had discovered "an array of antibiotics. . . a cure for tuberculosis; a variety of drugs for treating cardiac abnormalities; a new understanding of hepatitis."<sup>40</sup> A disturbing number of these advances relied on research that disregarded basic principles of research ethics as set forth by the World Medical Association's *Declaration of Helsinki*, Appendix B of this book.

## TUSKEGEE, 1932-1972

Yet another exposé occurred before the present-day world of research ethics and regulation was born. In July 1972, the headlines of a story by Jean Heller revealed, "Syphilis Victims in U.S. Study Went Untreated for 40 Years."<sup>41</sup> News stories and an *ad hoc* government panel commissioned to investigate what happened decried the way the U.S. Public Health Service had conducted a study it initiated in 1932. The study charted the many, at times devastating, effects of untreated syphilis on some 400 black men in the county seat of Tuskegee, Alabama. Finding "no evidence that informed consent was gained from the human participants in this study," the *ad hoc* panel declared that this experiment was "ethically unjustified" at its inception in 1932, not to speak of the subjects' being kept unaware and uninformed for another 40 years. Compounding its moral problems, "penicillin therapy should have been made available to the participants . . . not later than 1953," when penicillin became generally available. In a separate memo, one of the panelists, Jay Katz, recalled the Nuremberg Military Tribunal, whose decision rendered the harms and violations of the Tuskegee Syphilis Study "intolerable in this country or anywhere in the civilized world."<sup>42</sup> In the face of criticisms about the study's scientific reliability and questionable

therapeutic value, its scientific defenders maintained that it contributed to a first-hand knowledge of the pathological sequelae of advanced syphilis and was useful in the development of new serologic tests. In December 1974 the U.S. government agreed to pay a \$10 million out-of-court settlement to subjects-plaintiffs and their survivors. In addition, the U.S. Department of Health and Human Services (DHHS) has been making yearly payments to cover the medical, nursing care, and other expenses of the research subjects, their spouses, and their progeny—payments that exceeded \$1.8 million in 1994.<sup>43</sup>

#### FEDERAL REFORM, 1973-1981

Contemporary research ethics and regulation in the U.S. evolved step by step in response to the exposés between 1966 and 1972 as well as to other controversies in medical ethics and momentous changes in civil rights and the law.<sup>44</sup> In response to the turmoil over Beecher's article, the Food and Drug Administration (FDA) (1966) and the National Institutes of Health (NIH) (1971) developed internal policy guidelines. These were codified as federal *regulations* by the U.S. Department of Health, Education, and Welfare in 1974.<sup>45</sup> In response to the recommendations of a congressionally created National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974 - 1978), these regulations were revised in 1981 then, in turn, formulated as "Common Federal Policy" for additional federal agencies in 1991.<sup>46</sup> The institutions and dynamics of present day biomedical research regulations were thus assembled:

- Peer review by local review committees, commonly called IRBs (institutional review boards) in the U.S.;<sup>47</sup>
- Assurance of compliance contracts between local institutions and federal agencies;<sup>48</sup>
- Detailed federal and local regulations;<sup>49</sup>
- Officially sanctioned ethical principles set forth as guides for the resolution of ethical problems;<sup>50</sup>
- Updated instructions with respect to interpreting and following all of the above.<sup>51</sup>

In spite of ongoing criticisms over the ethical flaws, bureaucratic complexities, and time-consuming costs of these

developments, they have been effective, perhaps greatly effective, in reducing harmful injuries to research subjects.<sup>52</sup> Meanwhile, this research resulted in dramatically increased knowledge about the nature of human disease and disability, and it has generated a vast array of new diagnostic and therapeutic modalities.<sup>53</sup>

#### AFTER 1981

Following the revisions of the U.S. federal regulations in 1981, a decade of calm ensued, during which time many persons naively assumed that the ethics of research involving human subjects had become settled and noncontroversial. Beginning in 1992, this calm was shattered by new revelations about abusive and denigrating mustard gas experiments during World War II, alarming radiation experiments on unaware subjects thereafter, and nightmarish harms to persons in an NIH drug trial.<sup>54</sup> The 1990s have also given rise to a host of new problems and concerns, such as initiatives favoring the inclusion of far greater numbers of women and minorities in biomedical research. These initiatives led to the recent adoption of sweeping guidelines by the NIH, *The Inclusion of Women and Minorities as Subjects in Clinical Research*. These guidelines apply to all NIH-sponsored research, and are reproduced in this volume's Appendix E.

Each of the chapters in this collection identifies and discusses the many, ever-continuing, and changing concerns over the ethics and regulations of research involving human subjects at the present time. Altogether, they comprise not one, but numerous case studies on the nature and import of research ethics. An overview of the topics in these chapters is given in the last subheading of this chapter, entitled "This Book's Imperatives."

#### THE REACH OF RESEARCH

Thousands of researchers and administrators, hundreds of thousands of research subjects, billions of dollars, reputations, profits, and promise: these are the markings of contemporary biomedical research involving humans. Although the full-scale reach of this research is not known, my research confirms the following profiles.

Presently, the DHHS awards approximately \$5.5 billion per year for research involving human subjects.<sup>55</sup> Its ethics-oversight

branch, the Office for Protection from Research Risks (OPRR), has multiple project-assurance contracts with 420 institutions in North America, including the 127 U.S. medical schools. A survey of several major medical centers reveals that, on average, each center's IRB has between 1,300 and 1,600 research projects/protocols under active and/or continuing review.<sup>56</sup> These include projects subject to both expedited review and full IRB review.<sup>57</sup> Each medical school surveyed reviews 350 to 540 new research protocols per year, which call for the recruitment of between 10,000 and 20,000 subjects for the institution's biomedical research.<sup>58</sup> It is likely that the 25 U.S. medical schools that are receiving the highest levels of extramural grant funding from the NIH are recruiting some 250,000 research subjects each year. In 1993 the NIH granted the U.S.'s 127 medical schools \$3.9 billion for extramural research for some 15,240 protocols, not all of which is for clinical research involving human subjects.<sup>59</sup>

Notably, Henry K. Beecher predicated the "urgency" of his 1966 exposé on the remarkable growth of federally funded biomedical research and on a growing emphasis on research in medical schools and university hospitals "increasingly dominated by investigators."<sup>60</sup> Beecher indicated that NIH funding had risen to \$436 million in 1965. That year the NIH funded between 1,500 and 2,000 research projects.<sup>61</sup> To begin to grasp the extent of biomedical research in the U.S. at the present time, one should note that, allowing for inflation, the NIH now grants the equivalent of its entire 1965 budget to its top 22 grant-receiving medical centers.<sup>62</sup> Medical schools, however, comprise only 30 percent of the institutions that now have multiple project-assurance agreements with the OPRR. In addition, the OPRR has single-project-assurance contracts with at least 1,000 other groups and institutions.

The FDA is responsible for regulating a somewhat separate solar system of research involving human subjects. Paul Goebel, chief of the Institutional Review Branch of the FDA, reports that the FDA is responsible for the oversight of 1,200 IRBs, many of which are also regulated by the NIH through multiple project-assurance agreements. In addition, the FDA exercises exclusive oversight over another approximately 5,000 IRBs that focus on intraocular-lens research. The FDA's database of 1,200 IRBs includes hospitals, geographically based nonprofit committees, and

a number of free-standing, for-profit IRBs.<sup>63</sup> This last group contracts with various researchers, many of whom work for and with pharmaceutical, medical device, and biotech companies.

Goebel comments that "most of the research in the U.S. is conducted under the purview of the FDA, not the OPRR," because "most studies are funded by drug companies that fall outside of the OPRR's auspices."<sup>64</sup> He estimates that *industry*-sponsored research with human subjects is more than twice that of universities, and this research likely involves at least 1 million subjects each year.<sup>65</sup>

For-profit IRB companies that operate under FDA oversight include eight to 10 companies that focus solely on approving or disapproving research protocols according to the regulatory guidelines of the DHHS and FDA.<sup>66</sup> One of these companies employs 18 full-time staff members and reviews an estimated 3,500 research projects per year throughout the world.<sup>67</sup>

Altogether, funding for biomedical research from federal, state, local, philanthropic, and industry sources had reached the amazing sum of \$22.5 billion by 1990.<sup>68</sup>

Behind these statistics are increasingly powerful and symbiotic linkages between researchers, academia, industry, and the government, linkages that comprise a medical-industrial, research-industrial complex.<sup>69</sup> As Beecher indicated 30 years ago, the academic careers and fame of physician-investigators are inextricably linked to their publications as well as to their expertise in securing grant support. In turn, the financial stability and reputations of researchers' medical institutions are rooted in their abilities to develop notable programs of research, to attract top-notch investigators, and, increasingly, to develop commercial, technology-transfer ventures with industry.<sup>70</sup> Complementing these, the long-term needs of pharmaceutical, drug-device, and biotech industries are based on "the five Ps" of medical centers: patients, prestige, patents, publications, and personnel.<sup>71</sup> To complete the circle, the U.S. government and the governments of other developed nations, view innovative medical technology and a strong biomedical industry as essential to favorable balances of trade, economic competitiveness, and the ability to assure a "fuller life" for citizens.<sup>72</sup>

The ethics of research involving human subjects is the standard-bearer of an awesome responsibility: how to respect and

protect human subjects of research within the framework of these powerful, pro-research initiatives. This responsibility can and should be borne not only by ethicists but by all who seek to examine and apply ethical reasoning to research with human subjects—professionals and nonprofessionals alike. To be relevant and responsible, research ethics must be informed by and appreciative of the ethically justifiable purposes and ends of the institutions and individuals who are expanding the reach of research. The ethics of research must negotiate between the moral interests of protecting and showing respect for the human subjects of research and those of enabling researchers to continue humankind's historic battle against the forces of death, disability, and disease.

### THIS BOOK'S IMPERATIVES

The foregoing discussions of ethics, episodes in the checkered history of research ethics, and the reach of research account for this book's contents. For the sake of clarity and comprehension, its chapters are arranged into four parts, each of which is introduced by a "road map" essay that identifies overarching issues, places its chapters in the context of current regulation and debate, and flags notable issues discussed by each author.

The chapters in Part I serve the following three purposes. First, the chapters by Albert R. Jonsen, Robert M. Veatch, and Terrence F. Ackerman display the continuing debate over whether the benefits of biomedical research should be balanced with, or curtailed by, the principles of respecting and protecting the human subjects of research. As major voices in the debate, these authors identify the basic principles of research ethics, illustrate how they should be applied, and differ over how they should be interpreted and prioritized. Second, Carol Levine indicates how and why the principle of justice has achieved new focus and influence over the last 15 years. Her chapter acquaints readers with some of the recent and dramatic changes in research ethics—in particular, research pertaining to AIDS and women's health. It also forecasts momentous changes adopted in 1994 for all NIH-funded projects regarding the inclusion of women and minorities in research.<sup>73</sup> Third, Charles R. McCarthy charts future challenges that will be faced by IRB members and admin-

istrators, as well as those who assume responsibility for reforming the regulations and ethics of research. The agenda of issues identified by McCarthy is extended by Fletcher and Miller in Chapter 7.

The essays in Part II focus on critical issues of conflict of interest that infest the just-sketched world and reach of research involving human subjects. The chapter by John C. Fletcher and Franklin G. Miller tackles what the stance of the federal government ought to be vis-à-vis controlling, supporting, or forbidding controversial areas of biomedical research. Their chapter critically examines the brief but turbulent career of "public bioethics," that is, bioethics analysis and policy formation at the federal level. They do this for the purpose of defining and shaping federal policy. Stuart E. Lind charts and analyzes the many ways financial issues and incentives influence clinical investigation. Beyond finger pointing on the one hand and defensiveness on the other, Lind challenges readers to reflect on and constructively deal with ethical issues of sponsorship, coercion, and the profit motive in research with human subjects. John La Puma discusses a largely uncharted but emerging and significant topic in the ethics of research with human subjects—physicians' involvements in post-marketing investigation. La Puma wrestles with the critical connections between the biomedical industry's marketing techniques, the laudable goal of assessing the efficacy of new drugs, and physicians' conflicts of interest.

Part III explores issues surrounding a controversy that became public in the late 1980s—the fear that adhering to Western research ethics in developing countries constituted "medical-ethical imperialism."<sup>74</sup> How should research with human subjects be conducted in developing countries? Should the construction and ranking of underlying ethical principles of this research be different from that of the operative principles of the U.S., Canada, and Western Europe? Exploring these issues provides insights regarding the nature and character of ethical inquiry, offers perspectives on how U.S. regulations should be interpreted and applied in non-Western settings, and assists IRB members in their review of Western-sponsored research conducted abroad.<sup>75</sup>

Similar to the chapters in Part I, the essays in Part III display ongoing ethical debates and examine present and developing regulations. Involved for years as a speaker and consultant in the

development of national and international guidelines for research ethics, Robert J. Levine critically examines the adequacy and authority of the three historic codes of research ethics—the *Nuremberg Code*, the *Declaration of Helsinki*, and the *International Ethical Guidelines for Biomedical Research on Human Subjects* developed by the Council for International Organizations of Medical Sciences (CIOMS), each of which is printed in this book's appendices. Levine argues that the *Nuremberg Code* and the *Helsinki Declaration* are far less adequate than CIOMS's *International Ethical Guidelines*—particularly in transcultural research. He believes that damage, confusion, and consternation are caused by those who continue to appeal to the *Nuremberg Code* and the *Helsinki Declaration* as ultimate sources of ethical guidance.

Nicholas A. Christakis (U.S.A.) and Carel B. Ijsselmuiden (South Africa) and Ruth R. Faden (U.S.A.) join the debate initiated by Levine: should ethical principles articulated in the West, including informed consent and its underlying principle of respect for persons' autonomy, be understood as universally required in cross-cultural biomedical research, or should it be subject to multiple (or culturally plural) interpretations and applications? The issues in this debate have long intrigued philosophers and ethicists, but they have only recently achieved urgency in the ethics of human-subject research. Because it explores the time-bound nature, limits, and conceptual problems of Western research ethics, this debate may have important implications for the future shape of research ethics in the West.

Part IV deals with four critical, cutting-edge areas of human research, each one the subject of controversy, ongoing deliberation, and, at times, entire conferences. Benjamin Freedman addresses ethical issues in cancer research. He shows how cancer trials presage ethically infused problems in other clinical arenas, and he raises challenging and innovative issues over the need to expand IRBs' ethical responsibilities. Instead of their present, narrowly defined functions, IRBs should be dealing with no less than a "superset" of ethical issues inherent to clinical trials from their design stage through their application in medical practice.

William G. Bartholome identifies the ethical blind spots in the current U.S. federal regulations involving research with children and makes his own contributions to the ethics of pediatric research. Based upon his mastery of and participation in

explorations of pediatric research since the 1970s, Bartholome critically evaluates the contemporary literature, illustrates how core ethical principles apply to controversial protocols, and forecasts future challenges.

Constance M. Pechura profiles the science, regulations, and ethical issues regarding three hotly contested areas of research—on fetal tissue, on fetuses, and on embryos. With great clarity, she describes the interplay between scientific and technological advancements, ethical debates, and political pressures. Pechura's essay presents an agenda of philosophical and ethical issues for future analysis.

Part IV ends with Eric T. Juengst's chapter on a policy agenda for genome research. His discussion deals with 10 ethical questions that neither current rules nor practices completely address, including how to investigate the inheritance patterns of extended families, how to deal with the social and psychological risks of genetic studies, and when and how to disclose the interim results of such studies.

Altogether, these authors deal with "Critical Issues in Specialized Areas," the title of Part IV. Readers should nevertheless note that this final section does not encompass all the issues and areas that are discussed elsewhere in this volume—research pertaining to women's health, AIDS, post-marketing studies, and so on. The challenges are extensive and continuing.

## NOTES

1. As its title indicates, this book explores the ethics of research *involving*, not *on*, human subjects. Though constantly used past and present, the preposition "on" connotes a position over others, whereas "involving" refers to the many levels of researcher-subject interaction. I thank Robert J. Levine for bringing this wording to my attention, and for his critical and helpful review of this chapter.

2. A.J. Dyck, *On Human Care: An Introduction to Ethics* (Nashville: Abingdon, 1977), 22.

3. H.Y. Vanderpool, "The Ethics of Clinical Experimentation with Anticancer Drugs," in *Cancer Treatment and Research in Humanistic Perspective*, ed. S.C. Gross and S. Garb (New York: Springer, 1985), 16-46, esp. 27-31.

4. A readable and useful discussion of ethical theories and principles vis-à-vis their applications in bioethics is found in T.L. Beauchamp and

J.F. Childress, *Principles of Biomedical Ethics*, 4th ed. (New York: Oxford University Press, 1994), 3-119.

5. As a form of reasoned discourse, ethical inquiry is suspended when persons assert that the rightness or wrongness of an action in question is based on some authority—for example, the authority of self, of a family member, a famous person, or a hallowed book or tradition. Such sources may indeed be, and at times are, wellsprings of moral guidance and insight, but their contributions must be identified and shown to be relevant and convincing before they can carry moral weight.

6. W. Stevens, "Of Modern Poetry," in *The Palm at the End of the Mind*, ed. H. Stevens (New York: Vintage Books, 1972), 174-75.

7. See the humorous and informative article by Andrew Taylor, Jr., who indicates how ethics is not what it is often taken to be, that is, the work of bureaucrats who "have wrapped medical (and animal) ethics with rules and regulations endowing that area of human activity with a rapacious capacity to gobble time and generate reams of paper work." A. Taylor, "Don't Confuse Me with Ethics: I Already Know What's Right," *Journal of Nuclear Medicine* 33 (1992): 296-303.

8. For example, ethical values are often compatible with and/or in conflict with other types of values. H.Y. Vanderpool, "Values, Valuing, and Ethics," in *The Values and Ethics of Medicine*, ed. H.Y. Vanderpool et al. (Galveston, Tex.: The University of Texas Medical Branch, 1994), 1-10.

9. For this outline I am indebted to the discussion of G.C. Graber, A.D. Beasley, and J.A. Eaddy in *Ethical Analysis of Clinical Medicine* (Baltimore: Urban Schwarzenberg, 1985), 99-102.

10. This is another point at which ethics intersects with nonmoral values, because these values are often viewed as the ultimate ends for human action. Consider, for example, the hedonistic value of happiness and/or pleasure, or (for Friedrich Nietzsche) the creative power of the human spirit, or (for Judaism, Christianity, and Islam) faithfulness to God and the holiness of life. See, for example, W. K. Frankena's discussion, "Intrinsic Value and the Good Life," in *Ethics* (Engelwood Cliffs, N.J.: Prentice-Hall, 1973), 79-94.

11. A succinct and clear discussion of virtue or character ethical theories is found in Beauchamp and Childress, *Principles of Biomedical Ethics*, 62-69.

12. This point of view is maintained by only one school of utilitarians. See Frankena, *Ethics*, 34-60; and Beauchamp and Childress, *Principles of Biomedical Ethics*, 47-55.

13. These principles often represent summations of extensive philosophical/moral inquiry. Since the principles or rules themselves are

viewed as determinates of moral obligation or duty, this approach to ethics is technically termed deontological—from the Greek word *deon* (that which is needful or obligatory).

14. Frankena, *Ethics*, 12-33; Beauchamp and Childress, *Principles of Biomedical Ethics*, 56-62; Dyck, *On Human Care*, 54-73, 92-113; and Vanderpool, "Ethics of Clinical Experimentation," 27-31.

15. Drawing upon the work of W.D. Ross, whose thinking is further discussed by Albert R. Jonsen in Chapter 3 of this book, each of these principles is viewed as *prima facie* (at first view) obligatory, as "an obligation that must be fulfilled unless it conflicts on a particular occasion with an equal or stronger [*prima facie*] obligation." Beauchamp and Childress, *Principles of Biomedical Ethics*, 28-40, at 33 (emphasis added). Robert M. Veatch's analysis in this book's Chapter 2 also exemplifies that of a nonconsequentialist who holds to multiple and interacting deontological principles (see especially Veatch's note 10). See also Vanderpool, "Ethics of Clinical Experimentation," 28-29.

16. A.R. Jonsen and S. Toulmin, *The Abuse of Casuistry* (Berkeley, Calif.: University of California Press, 1988), 1-19, 333-43; Beauchamp and Childress, *Principles of Biomedical Ethics*, 92-100; and Jonsen in Chapter 3 of this book.

17. G.H. Brieger, "Human Experimentation: History," *Encyclopedia of Bioethics*, (New York: Macmillan, 1978), 684-92; D.J. Rothman, "Research, Human: Historical Aspects," *Encyclopedia of Bioethics*, revised ed. (New York: Simon & Schuster Macmillan, 1995), 2248-58; and S.E. Lederer, *Subjected to Science: Human Experimentation in America before the Second World War* (Baltimore: Johns Hopkins University, 1995).

The term "experimentation" is ambiguous in that it can refer both to present-day controlled research (including randomized clinical trials) and to testing or trying something new or tentatively (which typified most past medical research and important degrees of patient care at present). To seek to avoid confusion, the terms "experiment" and "experimentation" will be used to refer to research involving human subjects in the past, while the terms "research," "biomedical research," and "clinical trials" will be used for contemporary controlled biomedical research. See the discussion in R. J. Levine, *Ethics and Regulation of Clinical Research*, 2d ed. (Baltimore: Urban and Schwarzenberg, 1986), 8-10.

18. Dictionaries commonly refer to this meaning of "ethics" as the second or third way the term is used. For example, in *Webster's New Collegiate Dictionary* (Springfield, Mass.: G. and C. Merriam, 1981), the second definition of ethics is rendered as "a set of moral principles or values" and "a theory or system of values." The first of the "three kinds

of thinking that relate to morality" listed by Frankena is that of "descriptive empirical inquiry," the goal of which is "to describe or explain the phenomena of morality." Frankena, *Ethics*, 5. Although descriptive ethics dwells on the taxonomy of moral assumptions and modes of reasoning within human culture, it is unavoidably "judgmental" in the weak sense of being value laden or value infested. This is true for all forms of human discourse, including scientific and medical thinking and writing. Provocative discussions of the many values inherent to concepts of health and disease are found in A.L. Caplan, H.T. Engelhardt, Jr., and J.J. McCartney, eds., *Concepts of Health and Disease* (Reading, Mass.: Addison-Wesley, 1981).

19. As soon as politicians and policy makers—including those who overtly appeal only to science and the social sciences—argue why some course of action ought or ought not to be undertaken, moral assumptions and modes of reasoning are brought into play. This appears to be true even for those who expressly discount the influence of moral reasoning. See Dyck, *On Human Care*, 18-23; and H.Y. Vanderpool, "B.F. Skinner on Ethics and the Control of Retarded Persons," *Linacre Quarterly* 45 (1978): 135-51.

20. This task accords with the first and most common definition of "ethic" in many dictionaries: "the discipline dealing with what is good and bad and with moral duty and obligation," (*Webster's*) or "a principle of right or good conduct," in *The American Heritage Dictionary*, 2d college ed. (Boston: Houghton Mifflin, 1982), 467.

21. Frankena, *Ethics*, 12-60.

22. As previously indicated, one area of ethical inquiry explores judgments about that which is ultimately good with respect to the purposes and ends of human action. This ultimate good was and is identified with the hedonistic value of happiness and/or pleasure by many utilitarians. In contrast, Aristotle associated this end (for Aristotle a means-end) with *arete*, the excellence encompassing human virtue (wisdom, courage, temperance, and justice) and intelligence within human communities—which Aristotle believed would result in happiness. The national, racial, and evolutionary ends of the Nazi party constituted a form of consequentialist nation-state tribalism, which is commonly but wrongly equated with utilitarianism. Consequentialists identify right or obligatory moral actions with outcomes or consequences, but they differ greatly with respect to what ultimate end(s) or goal(s) they have in mind. For discussions of the good and good ends, see A.K. Bierman, *Life and Morals: An Introduction to Ethics* (New York: Harcourt Brace Jovanovich, 1980), 380-414; and Frankena, *Ethics*, 79-94. The tradition of associating the Nazi experiments with utilitarianism likely stems from the influential article by Leo Alexander, "Medical Science Under

Dictatorship," *New England Journal of Medicine* 241 (1949): 39-47, esp. 39, 45. For the charge that Nazi physicians "grounded their actions on utilitarian principles," see, for example, F. Rosner *et al.*, "The Ethics of Using Scientific Data Obtained by Immoral Means," *New York State Journal of Medicine* 91 (1991): 54-59, at 55.

23. I. Van Der Sluis, "The Movement for Euthanasia, 1875-1975," *Janus*, 66 (1979): 131-72; and R.J. Lifton, *The Nazi Doctors* (New York: Basic Books, 1986).

24. Currying the favor of Heinrich Himmler, the Reichsführer of the SS (*Schutzstaffel*, or Defense Echelon), and others, Rascher attracted the attention of high officials in the Nazi party. Accused of financial irregularities, the murder of an assistant, and scientific fraud, Rascher was executed, presumably on Himmler's orders. R.L. Berger, "Nazi Science—The Dachau Hypothermia Experiments," *New England Journal of Medicine* 322 (1990): 1435-40, esp. 1438-39.

25. For the text of the charges against Nazi physicians that details these experiments, see Telford Taylor, "Opening Statement of the Prosecution, December 9, 1949," in *The Nazi Doctors and the Nuremberg Code*, ed. G.J. Annas and M.A. Grodin (New York: Oxford University Press, 1992), 67-93. See also Eva Mozes-Kor, "The Mengele Twins and Human Experimentation: A Personal Account," in *Nazi Doctors and the Nuremberg Code*, ed. Annas and Grodin, 53-59; and Rosner *et al.*, "Ethics of Using Scientific Data," 54-59. Similarly brutal experiments were performed by Japanese doctors and scientists during World War II. In exchange for their scientific data and in the name of national security, U.S. authorities did not seek to prosecute these experimenters. See the summary discussions of A.M. Capron, "Human Experimentation," in *Medical Ethics*, ed. R.M. Veatch (Boston: Jones and Bartlett, 1989), 137-38; and P. M. McNeill, *The Ethics and Politics of Human Experimentation* (Melbourne, Vic., Australia: Cambridge University Press, 1993), 24-26; and the recent comprehensive study by S.H. Harris, *Factories of Death: Japanese Biological Warfare 1932-45 and the American Cover-Up* (London: Routledge, 1994).

26. Berger, "Nazi Science," 1435-40.

27. M.A. Grodin, "Historical Origins of the Nuremberg Code" in *Nazi Doctors and the Nuremberg Code*, ed. Annas and Grodin, 121-44. The 1931 regulations specified that "experimentation shall be prohibited in all cases where consent has not been given," that prior experiments on animals must serve to clarify and confirm the validity of human research, that experiments "shall be prohibited if it in any way endangers" the lives of children or young persons, and that no trials should include dying persons. *Ibid.*, 130-31 (which gives the full text of these regulations).

28. This episode in the history of human experimentation has been uncovered by D.J. Rothman, "Ethics and Human Experimentation: Henry Beecher Revisited," *New England Journal of Medicine* 317 (1987): 1195-99; and D.J. Rothman, *Strangers at the Bedside* (New York: Basic Books, 1991), 30-50.

29. Rothman, *Strangers at the Bedside*, 49-50.

30. Rothman indicates that six out of 238 subjects in a sulfonamide treatment protocol died apparently because of kidney damage. He adds that "there is no indication that the subjects or their relatives had any idea that they were part of an experiment." *Ibid.*, 35.

31. C.M. Pechura and D.P. Rall, eds., *Veterans at Risk: The Health Effects of Mustard Gas and Lewisite* (Washington, D.C.: National Academy Press, 1993). Similar experiments were conducted by Australian doctors and physiologists on Aborigines and armed-service personnel. McNeill, *Ethics and Politics*, 29.

32. See the full text of the code in this book's Appendix A. Notably, these principles were included in the 1931 ethical guidelines of the Reich Minister of the Interior (see note 27 above).

33. For example, it influenced the *Declaration of Helsinki* of 1964, and in modified form it was adopted by the Joint Chiefs of Staff of the U.S. Army, Navy, and Air Force in 1953, as indicated by J.R. Taylor and W. Johnson, "Summary of the Department of the Army Report" (1975), in *Veterans at Risk*, ed. Pechura and Rall, 379-438. The complete text of this U.S. armed services code, which was designated "Top Secret," is given in Annas and Grodin, *Nazi Doctors and the Nuremberg Code*, 343-45. In Chapter 10 of the present volume, Robert J. Levine further discusses the influence of the *Nuremberg Code*.

34. In his thoughtful overview of the ethics and regulation of human experimentation, A.M. Capron remarks, "The Nuremberg code in some ways amounted to a retreat from the German regulations [of 1931] which had emphasized institutional and not merely individual responsibility." Capron, "Human Experimentation," 135-72, at 146. See also the discussion of Fletcher and Miller in Chapter 7 at note 10 in the present volume. In the present book's Chapter 10, Levine argues that the *Nuremberg Code* should be viewed as flawed and time-bound. An outstanding discussion of the ways informed consent was defined, altered, and applied to biomedical research after Nuremberg is found in R.R. Faden and T.L. Beauchamp, *A History and Theory of Informed Consent* (New York: Oxford University Press, 1986), 151-232.

35. G.J. Annas and M.A. Grodin, "Where Do We Go from Here?" in *Nazi Doctors and the Nuremberg Code*, 314. Jay Katz concludes his assessment of this code by saying that it is "a remarkable document that stands alone in its unequivocal declaration of the rights, perhaps even

inalienable rights, of subjects to consent to participation in research." J. Katz, "The Consent Principle of the Nuremberg Code: Its Significance Then and Now," in *Nazi Doctors and the Nuremberg Code*, 227-39, at 235. See also J. Katz, "Human Experimentation and Human Rights," *Saint Louis University Law Journal* 38 (1993): 21-25.

36. Rothman, *Strangers at Bedside*, 51-69. In his 1959 review of the history and ethics of research, Henry K. Beecher spoke of the crippling effect of the *Nuremberg Code's* consent requirements on various types of research and in favor of his view against setting down "many rules" in the conducting of research. H.K. Beecher, "Experimentation on Man," *Journal of the American Medical Association* 169 (1959): 461-78.

37. The 1962 survey indicated that only nine of 52 reporting institutions (out of 86 departments of medicine contacted) had a documented procedure for approving research involving human subjects, 16 of 52 had developed consent forms for research subjects, and 22 had review committees that performed advisory functions. See the discussion of W.J. Curran, "Governmental Regulations of the Use of Human Subjects in Medical Research: The Approach of Two Federal Agencies," in *Experimentation with Human Subjects*, ed. P.A. Freund (New York: George Braziller, 1969), 402-54, at 407. Later surveys in 1970 uncovered "inadequate ethical concern" among many American investigators, 28 percent of whom, for example, would willingly approve of very high-risk, low-benefit research. Peer review of protocols was found to be weak and permissive in one-third of the institutions polled, and "the poorer patients in hospitals" were bearing undue burdens of risky research. B. Barber, "The Ethics of Experimentation with Human Subjects," *Scientific American* 234 (1976): 25-31.

38. H.K. Beecher, "Ethics and Clinical Research," *New England Journal of Medicine* 274 (1966): 1354-60. For a discussion of Beecher's career and publications respecting the ethics of research, see Rothman, *Strangers at Bedside*, 70-84.

39. Faden and Beauchamp, *History and Theory*, 161-64; and Levine, *Ethics and Regulation*, 70-71. Lederer indicates that by the 1930s many American physician-researchers had achieved celebrity status and the public's confidence. Lederer, *Subjected to Science*, 126-38.

40. Rothman, *Strangers at Bedside*, 79.

41. J. Heller, "Syphilis Victims in U.S. Study Went Untreated for 40 Years," *New York Times*, 26 July 1972, 1, 8. Heller was alerted to this study by an Associated Press colleague, Edith Lederer. Lederer had been contacted and informed by Peter Buxtun, who, beginning in 1966 as an employee in the Public Health Service, had been lobbying for the study's termination on ethical grounds. See the superb historical narrative by J. H. Jones, *Bad Blood* (New York: Free Press, 1993), esp. 188-205.

42. An abbreviated version of the *Final Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel* (Washington, D.C.: U.S. Public Health Service, 1973), is found in *Ethics in Medicine*, ed. S.J. Reiser, A.J. Dyck, and W.J. Curran (Cambridge, Mass.: MIT Press, 1972), 316-21. See also Faden and Beauchamp, *History and Theory*, 165-67.

43. The court settlement is discussed in Jones, *Bad Blood*, 212-19. The yearly costs are from unpublished remarks by Gary B. Ellis, Director of the Office for the Protection from Research Risks, at an annual conference sponsored by Public Responsibility in Medicine and Research (PRIM & R), 31 October 1994, Boston, Mass.

44. See Faden and Beauchamp, *History and Theory*, 81-234. Rothman's historical account deals with the interplay among the medical-ethics controversies over heart transplantation; congressional hearings on the ethical, legal, and social implications of biomedical advances; the recurring scandals over the Tuskegee Syphilis Study; as well as uncovered scandals over unethical contraceptive research in Tennessee and San Antonio, Texas. Rothman, *Strangers at Bedside*, 168-89.

45. The FDA called for Institutional Review Committees and informed consent in 1971. For developments in the U.S. between 1961 and 1983, see the discussion of Fletcher and Miller in Chapter 7 of the present volume, 158-66. Rothman discusses FDA and NIH responses to Beecher in *Strangers at the Bedside*, 87-100. The completed federal regulations were presented on 30 May 1974 by the Department of Health, Education, and Welfare (now called the Department of Health and Human Services) and were listed as Title 45, *Code of Federal Regulations (CFR)*, part 46.

46. The 1991 regulations are duplicated in this book's Appendix D. They were printed in the *Federal Register* on 18 June 1991 under the titles of 16 U.S. departments, including, as revised, under Title 46 *CFR*, part 46, of the Department of Health and Human Services. These regulations include Subparts B ("Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization"), C ("Involving Prisoners as Subjects"), D ("Protection for Children"), and a final section on "Expedited Review Procedures." Henceforth, I will refer to the National Commission for the Protection of Human Subjects of Biomedical and Behavior Research by the abbreviated title of the National Commission.

47. On the local level, IRBs are called by many names—research ethics committees, local review committees, human investigation committees, and so on. Each local IRB is entrusted with the power to approve, revise, and/or disapprove all human-subject research protocols. Each IRB is responsible for "balancing . . . society's interests in protecting the rights of subjects and in developing knowledge that can benefit the subjects of society as a whole." The National Commission

for the Protection of Human Subjects of Biomedical and Behavioral Research, *Institutional Review Boards: Report and Recommendations* (Washington, D.C.: DHEW Publication No. (OS) 78-0008, 1978), 1. IRB members are to work closely with investigators and in keeping with current federal regulations. See Levine, *Ethics and Regulation*, 321-63, at 325. For a history of the development and use of these committees, see R.J. Levine, "Research Ethics Committees," *Encyclopedia of Bioethics*, revised ed. (New York: Simon & Schuster Macmillan, 1995), 2266-69; and the discussion of Franklin and Miller in this book's Chapter 7, note 10.

48. These agreements require that each institution has a local IRB that must be sure that each research proposal accords with federal regulations. "In effect, having set the standards for approval of projects (including minimal requirements for diversity of IRB membership), the government delegates the execution of its rules to research institutions based on their assurance that they will comply." Capron, "Human Experimentation," 147. Universities, medical centers, and many research institutes secure compliance-with-regulation contracts through the Office for the Protection from Research Risks (OPRR), the regulatory division within the U.S. Department of Health and Human Services. Hospitals and clinics that conduct human research for drug and medical-device companies must either have their own IRBs or utilize the services of for-profit IRB companies. FDA regulations require drug and medical-device sponsors of research to make commitments about the nature of such IRB review. Capron outlines the steps that must be taken to satisfy these assurance contracts. *Ibid.*, 147-48. Levine briefly discusses and contrasts the differing styles of oversight by the FDA and OPRR in *Ethics and Regulation*, 357-59. Perspectives on the functions of the OPRR and the contributions of IRBs are offered by Charles R. McCarthy, "Experience with Boards and Commissions Concerned with Research Ethics in the United States," in *Research Ethics*, ed. K. Berg and K. Tranoy (New York: Alan R. Liss, 1983), 111-22.

49. For current U.S. federal regulations, see note 46 above and Appendix D. The vignette given here on the emergence and character of U.S. regulations is both similar to and different from that of other nations. H. Sass, "Comparative Models and Goals for the Regulation of Human Research"; A. Shapira, "Public Control Over Biomedical Experiments Involving Human Beings: An Israeli Perspective," in *The Use of Human Beings in Research*, ed. S.F. Spiker *et al.* (Boston: Kluwer Academic, 1988), 47-89, 103-19; and P. Riis, "Experiences with Committees and Councils for Research Ethics in Scandinavia," in *Research Ethics*, 123-29.

50. Notably, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, "Belmont Report: Ethical Principles and Guidelines for Research Involving Human Subjects," *Federal Register*, 44 (19 April 1979): 23192-97, which is printed as Appendix C of this book.

51. Guidebooks on understanding and applying federally mandated U.S. policies for biomedical and behavioral research were first produced in the early 1980s. The most recent guide deals with the jurisdiction and administration of IRBs, compares regulations of the FDA and the Department of Health and Human Services, provides an extensive discussion of the ethical dimensions of IRB review, and discusses issues pertinent to special classes of research subjects—women, children, cognitively impaired persons, prisoners, and so on. The Office for the Protection of Research Risks *et al.*, *Protecting Human Research Subjects: Institutional Review Board Guidebook* (Washington, D.C.: U.S. Government Printing Office, 1993). The most thorough-going scholarly discussion of the interplay between these regulations and the work of the National (1974-1978) and the President's (1980-1983) Commissions, as well as the extensive medical ethics literature through 1985, is R.J. Levine, *Ethics and Regulation*.

52. This raises complex questions about the degrees and frequency of injuries to research subjects over time. Upon surveying the literature on injuries to research subjects from the mid-1970s through the early 1980s, R.J. Levine concludes that "the role of research subject is not particularly hazardous in general." Levine nevertheless registers a menu of worries over the various physical, psychological, and social risks and harms inherent to this research. R.J. Levine, *Ethics and Regulation*, 39-54, at 40. Published discussions of harmful experiments that continue to occur remind us that a *reduction* of injuries caused by research still means that hazards and injuries continue. J. Katz, "Human Experimentation and Human Rights," 41-51; B. Freedman, "Multicenter Trials and Subject Eligibility: Should Local IRBs Play a Role?" *IRB: A Review of Human Subjects Research* 16 (January-April 1994): 3; M.K. Cho, "Are Clinical Trials of Cell Transplantation for Duchenne Muscular Dystrophy Ethical?" *IRB: A Review of Human Subjects Research* 16 (January-April 1994): 12-15; and note 54 below.

53. T.E. Malone, "The Moral Imperative for Biomedical Research," in *Biomedical Research: Collaboration and Conflict of Interest*, ed. R.J. Porter and T.E. Malone (Baltimore, Md.: Johns Hopkins University, 1992), 3-32.

54. Addressing the widely held belief that problems in research ethics had been resolved, A.M. Capron commented prophetically in 1989, "today the subject is often naively viewed as one of settled ethical

principles . . . and multifaceted procedures. History suggests that such claims must be viewed skeptically: the principles may be less conclusive and the guidelines less protective than they appear." Capron, "Human Experimentation," 128. As Fletcher and Miller indicate in Chapter 7, pp. 160-66 of the present volume, turmoil continued during the 1980s over research on fetal tissue, human fertilization, genetics, and factors related to human behavior. The mustard gas experiments were brought to light in 1993 by a study conducted by the Institute of Medicine on behalf of the Department of Veterans Affairs. Pechura and Rall, *Veterans at Risk*. An *ad hoc* Advisory Committee on Human Radiation Experiments between 1946 and 1974 was formed by an executive order by President William Clinton in January 1994. The committee's reports indicate that these experiments were far more frequent and widespread than government officials had reported or admitted. The 1993 NIH drug trial on fialuridine (FIAU) resulted in neurological damage, severe toxicity, and liver failure on the part of seven research subjects, two of whom were probably saved from death by liver transplants. In the face of media alarm and investigations by the NIH and FDA, the National Academy of Science's Institute of Medicine (IOM) conducted a review of this and previous FIAU trials. While the IOM Committee found "nothing to suggest that the investigators were negligent," or that, given previous trials on the drug, the tragedy was preventable, it set forth a number of recommendations that would likely control for, but not "absolutely prevent" the recurrence of similar tragedies. Institute of Medicine, *Review of the Fialuridine (FIAU) Clinical Trials* (Washington, D.C.: National Academy Press, 1995), 151. Benjamin Freedman discusses several grim examples of unethical research and the ethical pros and cons of using information derived by immoral means in "Research, Unethical," *Encyclopedia of Bioethics* revised ed. (New York: Simon & Schuster Macmillan, 1995), 2258-60.

55. Gary Ellis, Director of the OPPR, telephone conversation with author, 2 September 1994. Combined with the funding supplied by other branches of the U.S. government—the Alcohol, Drug Abuse, and Mental Health Administration and the Departments of Defense, Energy, and Veterans Affairs—some \$9.5 billion was being used to support biomedical research and development in 1989. An excellent survey of this support is provided by A.K. Dustira, "The Funding of Basic and Clinical Biomedical Research," in *Biomedical Research*, 33-56.

56. This author's survey yielded the following figures: Johns Hopkins, 1,500; the University of Alabama, 2,500; the University of California at San Diego, 2,000; the University of Michigan, 2,000; the University of Pennsylvania, 3,000; the University of Texas, Southwestern (Dallas), 1,600; the University of Washington (Seattle), 3,000; and

Vanderbilt University, 3,100. Like so much of the data on the funding and extent of biomedical research involving human subjects, these figures are not precise in their numbers and meaning. These high numbers likely include newly reviewed protocols, those subject to expedited review (see note 57 below), and research projects that are subject to continuing review (annual reapprovals). The discrepancies between these figures likely indicate that some of these institutions were reporting only their number of biomedical research projects subject to either expedited or full IRB review (as was the case with Southwestern in Dallas), while others were including behavioral and epidemiological studies that dealt with medical issues. Having recently completed an in-house survey of its research programs, the University of Washington reported that its 3,000 figure included all its epidemiological and behavioral research projects, but that its "biomedical" research included approximately 1,400 research projects: 1,000 the subject of full committee review and 400 for expedited review. Southwestern estimated that of its 1,600 active protocols, less than 320 were subject to expedited review.

57. Expedited review is allowable for protocols that involve no more than "minimal risk" to research subjects or for protocols that were previously approved, but that need minor changes. Such review is expedited in that only one or more experienced reviewers designated by the IRB chairperson (not the full IRB) can review and approve the protocol in question. "Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater . . . than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." See the 1991 federal rules and regulations (45 *CFR*, part 46, secs. 102 (i) and 111) in Appendix D of this book. Expedited review was first authorized by the DHHS in 1981.

58. These data are tentative. Executive administrators of IRBs readily state that they "have a good handle" on their total number of protocols but not on the number of research subjects that are being recruited. The University of Washington estimates that its biomedical research probably involves between 15,000 to 20,000 research subjects (a small portion of the approximately 300,000 subject-participants in its combined biomedical, behavioral, and epidemiological research). Other institutions estimate that some 10,000 subjects are being recruited for their biomedical research on a yearly basis.

59. These figures are from NIH's 1993 ranking of extramural awards to medical schools. While they are categorized as "research" funds, they do not indicate the amounts that are targeted for basic research, animal research, or clinical research involving human subjects.

60. Beecher, "Ethics and Clinical Research," 1354.

61. Rothman, *Strangers at Bedside*, 53, 59.

62. Although a separate study would need to be done in regard to the effects of inflation on biomedical research, a rough measure of these effects can be derived from consumer price indexes and estimates of the effect of inflation on the purchasing power of the dollar. These measures indicate that inflation caused the price of goods and services to increase 4.6 times between 1965 and 1993. To be equivalent with present-day purchasing power, the NIH's 1965 budget of \$436 million would thus need to be \$2 billion in 1993. In 1993, the NIH granted \$2.04 billion in extramural research funding (a figure that excludes the NIH's training and fellowship grants) to 22 top-funded U.S. medical schools for some 3,098 research projects. These inflation figures are drawn from the *Statistical Abstract of the United States* (Washington, D.C.: U.S. Government Printing Office, 1994), 466-68.

63. An analysis and overview of one of these committees is provided in S.S. Herman, "A Noninstitutional Review Board Comes of Age," *IRB: A Review of Human Subjects Research* 11 (March-April 1989): 1-6.

64. Paul Goebel, telephone conversation with author, 28 September 1994. It is nevertheless clear that many studies funded by drug companies remain under the OPRR's purview insofar as they occur in institutions that receive federal support and maintain project assurance agreements with the NIH. Goebel added that at the present time more than 1,000 investigational new drugs (INDs)—many with more than one research protocol—are being researched under the sponsorship of drug companies and the oversight of the FDA.

65. As indicated by this figure, and the equally conjectural estimate of 250,000 research subjects for the top 25 U.S. medical schools above, there is little data on the number of research subjects recruited each year, on their socio-economic status, on the levels of risks they face, or on the number of subjects recruited for respective medical specialties.

66. See the 1992 in-house "Guides" of Independent Review Consulting (IRC) Inc., San Anselmo, Calif. For 14 years beginning in the 1970s, IRC's president, Erica Heath, administrated the IRB at the University of California at San Francisco. Heath believes that the OPRR "does a shoddy job" in its review and oversight of university-based IRBs. She has published examples of consent forms "that really honored subject autonomy" and confidentiality. E. Heath, "Improving Confidentiality in Pharmacoeconomic Studies," *Arena Newsletter* 7 (July 1994), 6-7.

67. This company, Western IRB, mostly works for U.S. firms, but each year it conducts protocol reviews in Great Britain, continental Europe, Canada, South America, and India. The company's CEO, Dave Boston, says that Western IRB "keeps its review boards separate from its business" and charges the same fee regardless of whether the protocol in

question is approved or disapproved. D. Boston, telephone conversation with author, 20 September 1994.

68. Dustira, "Funding of Basic and Clinical Biomedical Research," 34-46.

69. These phrases are used by Thomas E. Malone and Jay Katz, respectively. Malone says that medicine and industry are following "in the footsteps of the military, the nuclear, and the space establishments to become part of a medical industrial complex in which the researchers, the health care providers, and the manufacturers who supply them will be closely linked." Malone, "Moral Imperative," 30; and Katz, "Human Experimentation and Human Rights," 38. Concerns over the newly emerging "medical-industrial complex" were registered 15 years ago by Arnold S. Relman, "The New Medical-Industrial Complex," *New England Journal of Medicine* 303 (1980): 963-70.

70. P.G. Waugaman and R.J. Porter, "Mechanisms of Interaction between Industry and the Academic Medical Center," in *Biomedical Research*, 93-118.

71. T. Cooper and M. Novitch, "The Research Needs of Industry: Working with Academia and with the Federal Government," in *Biomedical Research*, 187-98, at 191.

72. C.C. Vaughan *et al.*, "The Contribution of Biomedical Science and Technology to U.S. Economic Competitiveness," in *Biomedical Research*, 57-76.

73. See Appendix E of this book for the 28 March 1994 NIH *Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*.

74. C.B. IJsselmuiden and R.R. Faden, "Research and Informed Consent in Africa—Another Look," *New England Journal of Medicine* 326 (1992): 830-33.

75. The most recent IRB guidebook asks, "Why must foreign sites abide by DHHS regulations?" It answers that this must be done "to ensure that all DHHS-supported or -conducted research involving human subjects provides subjects with protections that are at least equivalent to those afforded by DHHS regulations . . . those required by 45 *CFR* 46." Later this guidebook stipulates that although IRBs in America should be responsive to "local laws" and "population differences," IRBs dealing with "another," presumably non-American geographical or cultural setting, "may not take into account pertinent local factors." OPPR *et al.*, *Protecting Human Research Subjects*, 2-8, 2-11. The apparent discrepancy between researchers having to follow U.S.-equivalent protections of human subjects in non-U.S. settings and their being allowed to adjust Western ethics to the mores of minority populations within their own countries is far from resolved.