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George J. Annas

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# HEALTH MATRIX

## The Journal of Law-Medicine

### THE CHANGING LANDSCAPE OF HUMAN EXPERIMENTATION: NUREMBERG, HELSINKI, AND BEYOND

*George J. Annas* †

SINCE WORLD WAR II there have been persistent efforts at both the national and international level to develop rules to protect the rights and welfare of subjects of human experimentation.<sup>1</sup> These efforts have focused primarily on codifying the rights of subjects, and protecting their welfare by prior peer review of research protocols. In recent years research regulations have been under attack by politicians, drug companies, researchers, and advocacy groups. In less than half a century, human experimentation has been transformed from a suspect activity into a presumptively beneficial activity. With this transformation, traditional distinctions be-

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† Edward R. Utey Professor and Chair, Health Law Department, and Director, Law, Medicine & Ethics Program, Boston University Schools of Medicine and Public Health; A.B., Harvard College, 1967; J.D., Harvard Law School, 1970; M.P.H., Harvard School of Public Health, 1972.

This article is based on a lecture Professor Annas gave as the Schroeder Scholar-in-Residence at Case Western Reserve University School of Law. The Schroeder Scholar-in-Residence program honors the founder of the Case Western Reserve University Law-Medicine Center, Professor Emeritus Oliver C. Schroeder, Jr., by bringing to the law school each year a distinguished scholar who conducts faculty workshops, meets with students, and delivers a formal public address, known as the Schroeder Lecture. Copyright 1992 by George J. Annas.

1. See generally *THE NAZI DOCTORS AND THE NUREMBERG CODE: HUMAN RIGHTS IN HUMAN EXPERIMENTATION* (George J. Annas & Michael A. Grodin eds., 1992), [hereinafter *NAZI DOCTORS*]; Bernard M. Dickens, et al., *Editor's Introduction to Research on Human Populations: National and International Ethical Guidelines*, 19 *LAW MED. & HEALTH CARE* 157 (1991).

tween experimentation and therapy, subject and patient, and researcher and physician have become discouragingly blurred. Issues of power, money, control, and fear of death have often been more central than protection of the rights and welfare of research subjects.

Special problems regarding rights and welfare of subjects have been recognized in research involving vulnerable populations, including pregnant women and fetuses, children, prisoners, and mentally-impaired people. But as premature death becomes a rarity in developed countries, and death itself becomes more alien and feared, the most vulnerable research subject, the one most consistently transformed into an object (a mere means to an end), has become the terminally ill patient. How did terminally ill patients come to be so sought-after as research subjects? Can current international research guidelines protect their rights and welfare in research trials? And if not, what additional steps are required to protect the rights and welfare of this uniquely vulnerable population?

A careful examination of the international research guidelines set forth during the past fifty years leads to the conclusion that a project that began as one to protect both the rights and welfare of human research subjects is now concentrated on rights protection in the developed nations, and on welfare protection in the developing nations. In both settings the basic rationale for these two diverging models is the same: desperation fueled by fear of death.<sup>2</sup>

### The Nuremberg Code

The Nuremberg Code was formulated by United States judges sitting in judgment of Nazi physician-experimenters following

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2. The most quoted words in experimental medicine are not from any legal or ethical canon, but from *Hamlet*: "Diseases desperate grown By desperate appliance are relieved, Or not at all." WILLIAM SHAKESPEARE, *HAMLET*, act 4, sc. 2 (Edward Hubler ed., Signet Classic 1963). As with terminal illnesses such as cancer and AIDS, the best strategy regarding the protection of research subjects is prevention. The King's "desperate diseases" speech begins with his musings on Hamlet, as he says,

How dangerous is it that this man goes loose!  
Yet must not we put the strong law on him:  
He's loved of the distracted multitude,  
Who like not in their judgment, but their eyes.

*Id.*

The same thing may be said about human experimentation. It is loved by the public, but primarily because it is little understood, and its promise of "miracle" cures seems real. Nonetheless, the dangers to human rights and welfare of research subjects are such that we must "put the strong law on him" and develop and enforce reasonable research regulations.

World War II. The Nazi experiments involved systematic and barbarous interventions in which death was the planned endpoint. The subjects of these experiments were concentration camp prisoners, mostly Jews, Gypsies and Slavs.<sup>3</sup> The judges at Nuremberg viewed human experimentation as suspect, and the Nuremberg Code itself resulted from horrendous non-therapeutic, nonconsensual prison research.

The Nuremberg Code, despite its inherent limitations, remains the most authoritative legal and ethical document governing international research standards, and one of the premier human rights documents in world history. The judges based the Nuremberg Code on a natural law theory, deriving it from universal moral, ethical, and legal concepts. The Code protects individual subjects first by protecting their rights. Voluntary, informed, competent, and understanding consent is required by the first principle of the Code, and principle 9 gives the subject the right to withdraw from the experiment. The consent of the subject is necessary under the Nuremberg Code, although consent alone is not sufficient. The other eight provisions of the Code are related to the welfare of subjects, and must be satisfied *before* consent is even sought from the subject. The subject cannot waive these provisions. The requirements of the provisions include a valid research design to procure information important for the good of society that cannot be obtained in other ways; the avoidance of unnecessary physical and mental suffering and injury; the absence of any *a priori* reason to believe that death or disabling injury will occur; risks that never exceed benefits; and the presence of a qualified researcher who is prepared to terminate the experiment if it "is likely to result in the injury, disability, or death of the experimental subject."<sup>4</sup>

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3. NAZI DOCTORS, *supra* note 1.

4. The Nuremberg Code:

1. The voluntary consent of the human subject is absolutely essential.

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each

### The Declaration(s) of Helsinki

Physician-researchers viewed the Nuremberg Code as confining and inapplicable to their practices, because it was promulgated as a human rights document by judges at a criminal trial, and because the judges made no attempt to deal with clinical research on children, patients, or mentally-impaired people. The World Medical Association has consistently tried to marginalize the Code by devising The Declaration of Helsinki, a more permissive alternative document, first promulgated in 1964, and amended three times since. This document is subtitled "recommendations guiding doctors in clinical research" and is just that, recommendations by physicians to physicians. The Declaration's goal is to replace the human rights-based agenda of the Nuremberg Code with a more lenient medical ethics model that permits paternalism. U.S. researcher Henry Beecher probably best expressed medicine's delight with the Declaration of Helsinki's ascendancy when he said in 1970: "The Nuremberg Code presents a rigid act of legalistic demands . . . The Declaration of Helsinki, on the other hand, presents a set of guides. It is an ethical as opposed to a legalistic document and is thus more

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individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

NAZI DOCTORS, *supra* note 1, at 2.

broadly useful than the one formulated at Nuremberg . . . .<sup>5</sup>

The core of the Declaration of Helsinki divides research into therapeutic ("Medical Research Combined with Professional Care") and non-therapeutic, eliminating the necessity for subject consent in some cases.<sup>6</sup> The major addition to the 1975 version (mirroring developments in the United States and elsewhere) was the encouragement of formal peer review of research protocols. For example, a new "basic principle" provided that: "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance."<sup>7</sup>

The movement to displace the consent requirement of the Nuremberg Code with prior peer review by a medical committee found its greatest success in the 1975 Declaration. For example, the physician need not obtain the subject's informed consent to medical research combined with professional care if he submits his reasons for not obtaining consent to the independent review committee.<sup>8</sup>

#### Council for International Organizations of Medical Sciences and the World Health Organization

Scientific organizations were even more hostile to the Nuremberg Code than were the world's physicians. In 1967 the president of the Council for International Organizations of Medical Sciences (CIOMS), for example, said that, "On the whole [the 1964 Declaration of Helsinki] corrects what in the Nuremberg Rules was circumstantial, related to Nazi crimes, and places these Rules more correctly in the context of generally accepted medical traditions."<sup>9</sup> Shortly thereafter, officials in the World Health Organization

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5. Quoted in W. Refshauge, *The Place for International Standards in Conducting Research for Humans*, 55 BULL. WORLD HEALTH ORG. 133-35 (Supp. 1977). See also the comparison made by the world's leading liver transplant experimenter, Thomas Starzl: "The Helsinki Declaration was shorter [sic] and easier to read." THOMAS STARZL, *THE PUZZLE PEOPLE: MEMOIRS OF A TRANSPLANT SURGEON* 146 (1992).

6. NAZI DOCTORS, *supra* note 1, at 335-36.

7. NAZI DOCTORS, *supra* note 1, at 334.

Principle I.2 of the 1989 revision of the Declaration (Helsinki IV) provides that the experimental protocol "should be transmitted for consideration, comment and guidance to a specifically appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed."

*Id.* at 159.

8. Sharon Perley, et al., *The Nuremberg Code: An International Overview*, in NAZI DOCTORS, *supra* note 1, at 159.

9. Refshauge, *supra* note 5, at 137.

(WHO) were informed by officials at the National Institutes of Health that WHO grant proposals would not be considered unless they were approved by a WHO ethical review committee. WHO had no such peer review committee, and set about to form one. This was followed by a 1978 agreement between WHO and CIOMS to "develop guidelines to assist developing countries in evolving mechanisms that would ensure the observance of principles of medical ethics in biomedical research."<sup>10</sup> The result was an 1982 document (currently under revision) designed to provide guidance to developing countries.

Remarkably, the 1982 Guidelines contain the statement: "Both the Nuremberg Code and the original Declaration of Helsinki of 1964 have been superseded by Helsinki II [1975]."<sup>11</sup> Helsinki II did supersede Helsinki I, but it could not, of course, supersede the judgment at Nuremberg. The Nuremberg Code is based on international natural law and ethics that even the prior positive law to the contrary in Nazi Germany could not supersede. Thus the Nuremberg Code is *the* basis for international law and ethics in the area of human experimentation, and lowering its standards can be accomplished neither by a vote of a group of researchers, nor by legal rule in any individual country. In this regard, individual countries can only legitimately *add* protections to the Nuremberg Code.

Nonetheless, the heart of the WHO/CIOMS project seems to compromise the Nuremberg Code's requirement for consent of the research subject as an integral part of international law and ethics. Instead, the 1982 Guidelines rely heavily on "an independent impartial prospective review of all protocols."<sup>12</sup> For the first time in an international document, special attention is given to children, pregnant and nursing women, and mentally ill and mentally-impaired people. However, adults in developing countries, perhaps unintentionally, are given the same uncomprehending status as children and the mentally ill.<sup>13</sup> For example, the rights of subjects are subordinated to the view that researchers and community leaders have of their welfare. Thus in developing countries it is suggested:

[W]here individual members of a community often do not have

10. Michael Grodin, *Historical Origins of the Nuremberg Code*, in NAZI DOCTORS, *supra* note 1, at 135-160.

11. WHO/CIOMS, *Proposed International Guidelines for Biomedical Research Involving Human Subjects*, CIOMS, Geneva (1982) at 23 [hereinafter *Proposed Guidelines*]. This language was deleted from the August 1992 redraft of the revisions.

12. *Id.* at 15.

13. Carel B. IJsselmuiden & Ruth R. Faden, *Research and Informed Consent in Africa; Another Look*, 326 NEW ENG. J. MED. 830, 832 (1992).

the necessary awareness of the implications of participation in an experiment so as to adequately give informed consent, the Guidelines suggest that the decision on whether or not to participate should be elicited through the intermediary of a trusted community leader . . . [T]he intermediary should make it clear . . . that participation is entirely voluntary and that he may abstain or withdraw from the experiment at any time.<sup>14</sup>

On the other hand, the standards for "externally sponsored research" done in developing countries are appropriately strict. Such research must meet not only the ethical standards of the host country, but also the ethical standards of the initiating country.<sup>15</sup> If this standard (No. 28) is taken seriously, following the rights and welfare requirements of the Nuremberg Code would be required in most instances of United States and European-sponsored research in developing countries. Nonetheless, CIOMS greatly confuses the very concept of international law and ethics, seemingly encouraging countries to find their lowest common denominator in subject protection.

A 1992 draft revision of the 1982 Guidelines opens with a recharacterization of human research project in developing countries. It states that there is a "positive duty to do good," and that "Research is being seen as a good in itself, and as the discharge of an ethical responsibility."<sup>16</sup> This is, to my knowledge, the first time research has been privileged over treatment, and virtually no explanation is presented in the document for this radical assertion. If the developed countries have ethical responsibilities to the developing countries (and I believe they do), then the responsibilities of providing food, clothing, housing, education, and basic medical care must all have a much higher priority than providing research protocols. Thus, what seems at the center of this reconceptualization of research is not the "discharge" of an "ethical obligation," but gaining access to a population of research subjects for research that will primarily benefit citizens in the developed world.<sup>17</sup>

In summary, although the concept of vulnerable populations has been recognized, there are no international research guidelines that provide special rules or protections for the terminally ill, and there

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14. *Id.* at 26-27. See also Perley et al, *supra* note 8, at 163. Substantially similar language remains in the August 1992 redraft.

15. *Proposed Guidelines*, *supra* note 11 at 31-32.

16. This April 1992 draft language was dropped in the August 1992 redraft, and hopefully will not be resurrected in the final document.

17. See, e.g., Lawrence K. Altman, *AIDS Vaccine to be Tested on Human Volunteers, Bypassing Animal Trials*, N.Y. TIMES, Nov. 11, 1991, at A7.



are no specific rules for research on terminal illnesses such as cancer and AIDS. We have witnessed a general trend away from the Nuremberg Code toward considering the protection of *either* rights (consent) or welfare (prior peer review) sufficient for human subject protection. With regard to research on terminal illnesses such as AIDS and cancer in the developed countries, this usually means that the research will be seen as therapy, and patients (subjects) who have the disease will be expected to protect themselves through the mechanism of informed consent. In developing countries, on the other hand, research on AIDS may be characterized as "community-based," and prior ethical review seen as sufficient protection for the rights and welfare of community members. In both cases the primary justification for research on terminal illnesses is the same: desperation in the face of death.

### Research on Dying Patients: AIDS and Cancer

Perhaps the primary reason that existing national and international research guidelines have little practical relevance for individuals with terminal illnesses is that the terminal diagnosis itself determines both what researchers and physicians deem "reasonable", and what the subjects (patients) themselves find acceptable — even desirable. Many researchers themselves fear death, and believe that terminally ill patients really can't be hurt (they are "going to die anyway") and therefore have "nothing to lose." Prior peer review of protocols under such circumstances becomes pro forma and provides no meaningful protections for subjects. Likewise, terminally ill patients who are told that medicine has "nothing to offer" them have come to view experimental protocols as treatment. Therefore, instead of being suspicious of experimentation, patients may *demand* access to experimental interventions as their right. Under such circumstances informed consent alone provides no meaningful protection.

Psychiatrist Jay Katz has noted that when medicine seems impotent to fight the claims of nature, "all kinds of senseless interventions are tried in an unconscious effort to cure the incurable magically through a 'wonder drug,' a novel surgical procedure, or a penetrating psychological interpretation."<sup>18</sup> Although physicians often justify such interventions as simply being responsive to patient needs, "they may turn out to be a projection of their own needs

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18. JAY KATZ, *THE SILENT WORLD OF DOCTOR AND PATIENT* 151 (1984).

onto patients."<sup>19</sup> Similarly, transplant surgeon Francis Moore has observed of transplant experiments based on the "desperate remedies" rationale: "There must be some likelihood of success before the desperate remedy becomes more than a desperate search for an opportunity to try a new procedure awaiting trial."<sup>20</sup> AIDS activist Rebecca Pringle Smith put it similarly, "Even if you have a supply of compliant martyrs, trials must have some ethical validity."<sup>21</sup>

Susan Sontag has noted that cancer and AIDS have become linked as perhaps the two most feared ways to die in the developed world. In her words, "AIDS, like cancer, leads to a hard death . . . The most terrifying illnesses are those perceived not just as lethal but as dehumanizing, literally so."<sup>22</sup> And although philosopher Michel Foucault was not speaking of the medicalization of death by cancer and AIDS, he could have been when he chronicled how the power of government over life and death has shifted in the past two centuries. "Now it is over life, throughout its unfolding, that power establishes its domination; death is power's limit, the moment that escapes it . . . ."<sup>23</sup> In human experimentation on the terminally ill we have Foucault's vision of public power played out in private: researchers take charge of the bodies of the dying in an attempt to take charge of the patient's lives and prevent their own personal deaths, and death itself.<sup>24</sup>

The Nazi doctors' chief defense at Nuremberg was that experimentation was necessary to support the war effort. Now combatting disease has itself become a "war," as we speak of a "war on cancer" and a "war on AIDS." And in that war, patients, especially terminally ill patients, are conscripted as soldiers. As former editor of the *New England Journal of Medicine*, Franz Ingelfinger, put it: "[T]he thumb screws of coercion are most relentlessly applied" to "the most used and useful of all experimental subjects, the patient with disease."<sup>25</sup> But as Sontag reminds us, war metaphors

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19. *Id.*

20. Francis D. Moore, *The Desperate Case: CARE (Costs, Applicability, Research, Ethics)*, 261 JAMA 1483, 1484 (1989).

21. Quoted in Joseph Palca, *AIDS Drug Trials Enter New Age*, 246 SCI. 19, 20 (1989).

22. SUSAN SONTAG, *ILLNESS AS METAPHOR; AND, AIDS AND ITS METAPHORS* 126 (1989).

23. MICHEL FOUCAULT, *THE HISTORY OF SEXUALITY* 138 (Robert Hurley trans., 1990).

24. *Id.* at 143.

25. F.J. Ingelfinger, *Informed (But Uneducated) Consent*, 287 NEW ENG. J. MED. 465, 466 (1972).

are dangerous in disease because they encourage authoritarianism, overmobilization, and stigmatization. In her words:

No, it is not desirable for medicine, any more than for war, to be "total." Neither is the crisis created by AIDS a "total" anything. We are not being invaded. The body is not a battlefield. The ill are neither unavoidable casualties nor the enemy. We—medicine, society—are not authorized to fight back by any means whatever . . . .<sup>26</sup>

### Cancer

In the early 1980s the President's Commission for the Study of Ethical Problems in Medicine and Behavioral Research attempted to get agreement on categorizing Phase 1 drug studies with anti-cancer agents. Are they research or therapy? Federal Food and Drug Administration (FDA) regulations state that Phase 1 studies are intended to have no therapeutic content, but are to determine "toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range."<sup>27</sup> Nonetheless, National Cancer Institute (NCI) researchers insisted that Phase 1 cancer studies, using cancer patients as subjects, should be described as therapeutic. The Assistant Secretary of the Department of Health and Human Services (HHS) wrote to Congress in 1981:

Notwithstanding the fact that some individuals within HHS may not concur, the official position of the Department, including NCI, NIH, and FDA, is to regard Phase 1 trials of anti-cancer drugs as *potentially* therapeutic. The often small, but real possibility of benefit must be weighed against the nearly 100 percent probability of death if experimental therapy is not attempted for the advanced cancer patients who participate in Phase 1 studies.<sup>28</sup>

The President's Commission never received a better answer to its inquiry, and this answer is not helpful. In a sick person, virtually any intervention, even a placebo, can be described as "potentially therapeutic," and once this misleading label is applied, the nonbeneficial Phase 1 study is de facto eliminated and transformed into "experimental therapy." Any distinction between experimen-

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26. SONTAG, *supra* note 22, at 182-183.

27. PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH, PROTECTING HUMAN SUBJECTS, 65 (1981) [hereinafter President's Commission].

28. *Id.* (quoting letter from Edward N. Brandt, Jr., Assistant Sec. for Health, Dept. of Health and Human Services, to the Hon. Henry A. Waxman, Chairman, Subcomm. on Health & Environment (Nov. 20, 1981, at 3-4)).

tation and therapy is lost. Under these circumstances the President's Commission could only bow weakly to informed consent: "It is important that patients who are asked to participate in tests of new anti-cancer drugs not be misled about the likelihood (or remoteness) of any therapeutic benefit they might derive from such participation."<sup>29</sup>

American oncologists use so many approved drugs for unapproved uses that it seems fair to conclude that for most cancers there are no standard treatments, and sound scientific studies are needed. A 1990 survey, for example, found that fully one-third of all the drugs used on cancer patients are of unproven safety and efficacy for the purpose for which they are given; and unapproved use is even more prevalent for malignancies that have metastasized than for earlier cancers.<sup>30</sup> Unapproved chemotherapy for patients being treated with palliative intent is twice the rate for curative intent, indicating an appropriately higher degree of risk-taking for quality of life enhancement. Oncologist Charles Moertel, commenting on the study, noted that the major beneficiaries of such an approach to cancer treatment are the "appointment book of the oncologist" and "the pharmaceutical companies and their stockholders."<sup>31</sup> In short, business ethics seem to be supplanting medical ethics. As to the argument that oncologists are just responding to the demand of dying patients, Moertel responded: "This argument abandons the scientific basis for medical practice and could just as well be used to justify quackery. Also, one wonders how many patients with advanced pancreatic cancer, for example, would really demand cytotoxic drugs if the sheer futility of such therapy was honestly explained."<sup>32</sup>

If we accept patient demand as sufficient justification to mistreat them, it is a short step to say that the patient should have the right to demand to be killed by his physician. In fact, this very argument was made in early 1992 in the *New England Journal of Medicine*, where another oncologist noted that cancer chemotherapy, while it can prolong life, often makes the patient's dying "unbearable."<sup>33</sup>

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29. PRESIDENT'S COMMISSION, *supra* note 27, at 43.

30. Thomas Laetz & George Silberman, *Reimbursement Policies Constrain the Practice of Oncology*, 266 JAMA 2996, 2997 (1991).

31. Charles G. Moertel, *Off-Label Drug Use for Cancer Therapy and National Health Care Priorities*, 266 JAMA 3031 (1991).

32. *Id.* See also Cornelius O. Granai, *Ovarian Cancer—Unrealistic Expectations*, 327 NEW ENG. J. MED. 197 (1992).

33. Guy I. Benrubi, *Euthanasia: The Need for Procedural Safeguards*, 326 NEW ENG. J. MED. 197 (1992).

He went on to argue that, "since we physicians brought the patient [subject] to the state she is in, we cannot abandon her by saying that euthanasia violates the purpose of our profession."<sup>34</sup> The use of killing as "damage control" for a physician-created harm to patients is chilling. It is far better to avoid the harm than to use it to justify killing. The quest to master terminal illness may, however, make killing by physicians seem reasonable.<sup>35</sup>

The "desperate remedies" rationale used to justify experimentation on the terminally ill is seriously flawed. There are fates worse than death, and many Americans have written living wills and health care proxies to *prevent* their lives from being prolonged under certain circumstances.<sup>36</sup> Likewise, the horrible and prolonged deaths of Barney Clark and William Schroder on the permanent artificial heart insured the end of all further experiments with the Jarvik 7.<sup>37</sup> Although the device can obviously prolong life, it cannot do so at an acceptable level of quality. The conclusion is clear: dying patients are real people, not objects, who value quality over quantity of life, and cannot be legally or ethically used simply as a means to an end. Individuals do have a right to refuse *any* treatment or experiment. But respecting patient autonomy does *not* require that we accept demands for mistreatment, experimentation, torture, or whatever the dying might want, anymore than we must accede to demands for illegal (but effective) drugs like heroin and LSD, unlicensed practitioners, or a physician-induced death.

Closely related to the difficulty of distinguishing research from treatment is distinguishing the role of the researcher from the role of the physician when these two conflicting roles are merged in one person. For example, in a 1992 article on cancer and AIDS research two prominent commentators seem to assume that "cancer researchers" are properly seen as doctors providing "treatment" to "patients."<sup>38</sup> Little attention has been paid to the researcher's inherent conflict of interest. It is unlikely that patients can ever draw

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34. *Id.* at 198.

35. See, e.g., Physician-philosopher Leon Kass, who has argued "We do not yet understand that the project for the mastery of nature and the conquest of death leads only to dehumanization; that any attempt to gain the tree of life by means of the tree of knowledge leads inevitably also to the hemlock . . ." Leon R. Kass, *Suicide Made Easy: The Evil of "Rational" Humaneness*, COMMENTARY, Dec. 1991, at 19, 24.

36. See NANCY M.P. KING, MAKING SENSE OF ADVANCE DIRECTIVES (1991).

37. George J. Annas, *Death and the Magic Machine: Informed Consent to the Artificial Heart*, 9 W. NEW ENG. L. REV. 89 (1987).

38. David J. Rothman & Harold Edgar, *Scientific Rigor and Medical Realities: Placebo Trials in Cancer and AIDS Research*, in AIDS: THE MAKING OF A CHRONIC DISEASE 194-206 (E. Fee & D. Fox eds., 1992).

the distinction between physician and researcher, because most simply do not believe that their physician would either knowingly do something harmful to them, or would knowingly use them simply as a means for their own ends. Cancer researchers, however, know better. James F. Holland, for example, has said simply, "Patients have to be subsidiaries of the trial . . . I'm not interested in holding patients' hands. I'm interested in curing cancer . . . Every patient becomes a piece of scientific data."<sup>39</sup> As candid as Holland is, it seems almost certain that his patients come to him for a cure, and look upon him as their physician — not as simply a researcher. In such a circumstance, the Helsinki Declaration's theoretical division between therapeutic and non-therapeutic research is meaningless.

Finally, we should emphasize that which has generally been marginalized: most studies on the terminally ill, including cancer and AIDS clinical trials, are funded by private drug companies that have tremendous financial stakes in their success. Clinical investigators may even "own equity interest in the company that produces the product or may serve as paid consultants and scientific advisers," roles that at least call their objectivity into question.<sup>40</sup> Medical ethics is being eroded by a new commercialism in medicine. This fact has led most leading medical journals in the United States to require financial disclosure prior to publication of research results. However, neither Institutional Review Boards (IRBs) nor individual subjects are routinely informed of the financial aspects of proposed clinical trials, even though the finances often create major potential conflicts of interest among the sponsor, the researcher, and the patient-subject.

One need not search far for examples. In early February, 1992, the stock of U.S. Bioscience lost \$550 million in value in one day after the FDA review panel refused to recommend approval of its drug, Ethyl (a drug said to protect healthy cells from the toxic effects of cancer chemotherapy).<sup>41</sup> One week later another United States biotechnology company lost half of its value in one day when a clinical trial of one of its cancer drugs was halted because of adverse effects on the subjects.<sup>42</sup> Financing may be *the* major change

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39. Dena Kleiman, *In Search for Cancer Cure, Patients Come Second*, N.Y. TIMES, Feb. 18, 1986, at B1, B7.

40. Arnold Relman, *What Market Values are Doing to Medicine*, THE ATLANTIC MONTHLY 99, 103 (Mar. 1992).

41. Michael Waldholz, *U.S. Bioscience Holders Are Latest to Get Costly Lesson*, WALL ST. J., Feb. 4, 1992, at B6.

42. Floyd Norris, *Drug's Test Pains MGI Investors*, N.Y. TIMES, Feb. 11, 1992, at C1;

in clinical trials over the past two decades, and this change has not been mirrored in research regulations. New research findings are often reported first on the financial pages of newspapers, and only later in the medical literature. It thus came as little surprise in March 1992, when Dow Corning openly declared that its decision to discontinue the manufacture of silicone breast implants was made strictly on "the basis of business."<sup>43</sup>

## AIDS

AIDS has always been perceived as the disease in which there literally is *no* distinction between treatment and experimentation. This is because there is no cure for AIDS. The disease primarily strikes the young, leading to a death that is premature by virtually any calculation, and existing treatments that can prolong life are far from satisfactory. In addition, many people with the disease have no access to health care, so the only way they can obtain medical care is to enroll in an experimental drug trial. Thus, although theoretically wrong, ACT-UP's (AIDS Coalition to Unleash Power) political slogan, "A Drug Trial is Health Care Too," tragically is factually correct in many U.S. settings. However, the slogan serves to wrongly conflate experimentation with therapy, and to encourage people with AIDS to seek out experimentation as treatment, and physician-researchers to see AIDS patients as potential subjects who have "nothing to lose."

As the *Wall Street Journal* editorialized in 1988, supporting a loosening of FDA testing procedures for people with cancer, Alzheimer's disease, and AIDS: "AIDS patients have driven home to the U.S. medical and political establishment what enormous risks human beings in death's grip will take to gain relief or respite."<sup>44</sup> This editorial identified the *problem* and illustrated why regulation is necessary. The FDA is not in the business of regulating "hope" for "relief or respite" but of determining whether "relief or respite" from particular drugs and devices is likely. Deregulation of human experimentation cannot produce new drugs or treatments. Money

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James P. Miller, *MGI Pharma Suffers 52% Fall in Stockprice*, WALL ST. J. Feb. 11, 1992, at B3.

43. Philip J. Hilts, *As It Quits Implant Business, Maker Says Product is Safe*, N.Y. TIMES, March 20, 1992, at A12. See also Michael Waldholz, *An Unapproved Drug for Alzheimer's Gets a Big Marketing Push*, WALL ST. J., Aug. 25, 1992, at A1.

44. *New Ideas for New Drugs*, WALL ST. J., Dec. 28, 1988, at A16. See also Andrew Pollack, *Gene Therapy Gets the Go-Ahead*, N.Y. TIMES, Feb. 14, 1992, at D1; Mireya Navarro, *Into the Unknown: AIDS Patients Test Drugs*, N.Y. TIMES, Feb. 29, 1992, at 1, 29. See also Rothman & Edgar, *supra* note 38 at 205.

can, however, be made by pharmaceutical companies by exploiting our fear of death and desperation. It seems fair to conclude that virtually all of the drugs that have been developed for AIDS treatment have been over-priced, and financially exploitative of those with AIDS.<sup>45</sup> Again, business ethics seem to be supplanting medical ethics.

Although the cover story is compassion, the movement to loosen FDA's research rules should be seen for what it is: a political strategy by a free market administration bent not on helping people with AIDS, but on exploiting the AIDS epidemic to loosen drug regulations and maximize profits for the pharmaceutical industry.<sup>46</sup> For example, Jay Plager, counselor to the former Undersecretary of the Department of Health and Human Services, asserted that one purpose of early drug release regulations is to give "desperately ill patients the opportunity to decide for themselves whether they would rather take an experimental drug or die of the disease untreated."<sup>47</sup> And former FDA Commissioner Frank Young said of AIDS that, "there is such a degree of desperation, and people are going to die, that I'm not going to be the Commissioner that robs them of hope."<sup>48</sup> The FDA must concentrate on using science to identify beneficial treatments, not on using faith healing to promote hope that an unproven drug might be beneficial. There is some evidence that AIDS activists now recognize this. At the July 1992 International AIDS conference in Amsterdam, for example, ACT-UP member Mark Harrington said he believed that regulatory reforms often "go for naught." In his words, "What is the point of streamlining access and approval when the result is merely to replace AZT [with] mediocre, toxic, expensive" drugs.<sup>49</sup> Harrington urged others to follow his example and volunteer for experiments involving basic science.<sup>50</sup>

Of course, it remains unethical to conduct a clinical trial in a

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45. See, e.g., *Forcing Poverty on AIDS Patients*, N.Y. TIMES, Aug. 30, 1988 at A18 (editorial); Maher, *Pitiless Scourge: Separating Out the Hype from the Hope on AIDS*, BARRON'S, March 13, 1989, at 6, 22; Eric Savitz, *No Magic Cure: The War on AIDS Produces Few Gains, Except on Wall Street*, BARRON'S, Dec. 16, 1991, at 10.

46. See generally George J. Annas, *Faith (Healing), Hope and Charity at the FDA: The Politics of AIDS Drug Trials*, 34 VILL. L. REV. 771 (1989).

47. Robert Pear, *U.S. to Allow Use of Trial Drugs for AIDS and other Terminal Ills*, N.Y. TIMES, May 21, 1987, at A1.

48. Phillip M. Boffey, *FDA Will Allow AIDS Patients to Import Unapproved Medicines*, N.Y. TIMES, July 24, 1988, at A1, A19.

49. Quoted in Lawrence K. Altman, *At AIDS Talks, Reality Weighs Down Hope*, N.Y. TIMES, July 26, 1992, at A1.

50. *Id.*



manner in which no reliable data can be generated. As Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, has properly noted, the primary goal of clinical trials is "not to deliver therapy. It's to answer a scientific question so that the drug can be available for everybody once you've established safety and efficacy."<sup>51</sup> On the other hand, community activists have made some important points regarding AIDS, and some rules for AIDS research in the United States are appropriately changing. Three are of note: (1) Representatives of the gay rights and AIDS communities are being asked to join governmental scientific advisory panels which set research priorities; (2) people with AIDS are being placed on local IRBs to evaluate community-based AIDS research protocols; and (3) end points involving quality of life instead of death are being explored in evaluating the results of AIDS drug trials.<sup>52</sup> Emphasis on quality of life measures seems especially relevant in diseases like AIDS and cancer where brief increases in longevity may be possible only at the cost of severe suffering.<sup>53</sup>

Strategies such as promoting unproven AIDS drugs by press conference and press release, and changing research rules for political gain, foster false hope and financial exploitation. Terminally ill AIDS and cancer patients can be harmed, misused, and exploited. It has even been persuasively argued that we as a society have developed a "cure or kill" attitude that permits us to use the terminally ill as "volunteers" for our experiments designed to banish death:

Our quest for a formula that will banish death seems to make it acceptable to try questionable regimens on the aged and terminally ill . . . Those who insist on using the dying as experimental subjects . . . see death as abnormal and dying patients as subhuman. We cast the terminally ill in modern rites of sacrifice, putting patients of experiments . . . through what one might see as torture in the hope of postponing the inevitable.<sup>54</sup>

Of course, consent is no justification for the torture or inhumane treatment of human beings. We must stop treating terminally ill

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51. Joseph Palca, *AIDS Drug Trials Enter New Age*, 246 SCI. 19 (1989).

52. Carol Levine et al., *Building a New Consensus: Ethical Principles and Policies for Clinical Research on HIV/AIDS*, IRB, 1-22 (report which indicates an emerging consensus of the formation and conduct of clinical trials for AIDS research) (Jan.-Apr., 1991), and see Vanessa Merton, *Community-Based AIDS Research*, 14 EVALUATION REV. 502 (1990) (discusses the development and design of the Community Research Initiative of New York City, an IRB that reviews community-based AIDS research).

53. OFFICE OF TECHNOLOGY ASSESSMENT, CONGRESS OF THE UNITED STATES, UNCONVENTIONAL CANCER TREATMENTS 228 (1990).

54. Ralph Brauer, *The Promise that Failed*, N.Y. TIMES, Aug. 28, 1988 sec. 6 (magazine) at 34, 76.

cancer and AIDS patients as subhuman by offering them questionable experiments in the guise of treatment. We cannot justify this behavior on the basis of either their demand for it or our belief that the ultimate good of mankind will be served by it. Researchers who believe their subjects cannot be hurt by experimental interventions *should be disqualified* from doing research on human subjects on the basis that they cannot appropriately protect their subjects' welfare with such a view. Likewise, subjects who believe they have "nothing to lose" and are desperate because of their terminal illness should also be disqualified as potential research subjects because they are unable to provide voluntary, competent, informed or understanding consent to the experimental intervention with such a view. It should be emphasized that these are proposed *research* rules that would not necessarily apply to treatment in a doctor-patient relationship untainted by conflicts of interest.

### What Should be Done Generally?

Action to protect research subjects in our new age of cancer and AIDS seems reasonable on both the international and national levels. On the international level we have already seen that the Nuremberg Code, the Helsinki Declaration, and WHO/CIOMS guidelines are almost universally seen as advisory and ethical only. They have no legal status in most individual countries, and they provide no mechanism for accountability or sanction of researchers who disregard their precepts. Moreover, the content and structure of medical research has changed radically in the past decade, as we have moved away from medical ethics, towards commerce and business ethics. It would therefore seem reasonable at this time to seek more definitive action or international research rules from the United Nations. Although the United Nations never formally adopted the Nuremberg Code, its consent principle did become an important part of the United Nations International Covenant on Civil and Political Rights, which was promulgated in 1966 and adopted by the United Nations General Assembly in 1974.<sup>55</sup> Article 7 of this covenant states: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation."<sup>56</sup>

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55. Perley et al., *supra* note 8, at 153.

56. G.A. Res. 2200 A, U.N. GAOR, 21st Sess., Supp. No. 16, at 49, U.N. Doc. A/0316 (1966).

Most physicians would, of course, be shocked at having anything they do to patients considered "torture or cruel, inhuman or degrading treatment." They would thus view the Covenant's provisions much the same way they view the Nuremberg Code: as a criminal law document not applicable to anything done in the doctor-patient relationship. It should be noted, however, that in Nazi Germany no distinction between torture and experimentation was possible and many contemporary experiments produce "unbearable" suffering.

Because none of the existing conventions of the United Nations deal in a detailed manner with human experimentation, M. Cheriff Bassiouni has proposed that the United Nations adopt a specific criminal Covenant on Human Experimentation:

Section 1. Acts of Unlawful Medical Experimentation

1.0 The crime of unlawful medical experimentation consists of any physical and/or psychological alterations by means of surgical operations or injections, ingestion or inhalation of substances inflicted by or at the instigation of a public official, or for which a public official is responsible and to which the person subject to such experiment does not grant consent as described in Section 2.

Section 2. Defense of Consent

2.1 For the purpose of this Article a person shall not be deemed to have consented to medical experimentation unless he or she has the capacity to consent and does so freely after being fully informed of the nature of the experiment and its possible consequences.

2.2 A person may withdraw his or her consent at any time and shall be deemed to have done so if he or she is not kept fully informed within a reasonable time of the progress of the experiment and any development concerning its possible consequences.<sup>57</sup>

Professor Bassiouni believes this draft Code was rejected because some member countries thought it might impinge upon the practices of their pharmaceuticals industry.<sup>58</sup> If true, this is a serious condemnation of the drug companies involved. It also makes clear the need to include privately funded research in the Code as well. The Code's purpose is to articulate *human* rights that *all* members of the human community share by virtue of being human.<sup>59</sup> Human rights are more important than either medical or business ethics, and are *not* a matter of "internal affairs." Because

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57. M. Cheriff Bassiouni, et al., *An Appraisal of Human Experimentation in International Law and Practice*, 72 J. CRIM. LAW & CRIMINOLOGY 1597-1666 (1981).

58. Perley, *supra* note 8 at 166.

59. Ruth Macklin, *Universality of the Nuremberg Code*, in NAZI DOCTORS, *supra* note 1, at 240-257.

the United Nations is the only credible international body capable of articulating an international code of conduct for human experimentation, an international Covenant on Human Experimentation based on the Nuremberg Code, covering all non-therapeutic research, and all therapeutic research on competent individuals, should be adopted. Additional provisions regarding children, the mentally impaired, and the terminally ill [see *infra*.] should be included.

An international tribunal for human experimentation should also be established. Such a tribunal could be established to enforce a United Nations-adopted Code, initially limited to civil sanctions, and financed with a small percentage of the human research budget of member states. Without an international tribunal with the authority to judge and punish violators of international norms of human experimentation, we are left where we began: international norms of human experimentation are relegated to the domain of ethics, and are ignored or subverted in that domain. This is because without the possibility of judgment and punishment, there is no international law worthy of the name, only international ethics.

An international tribunal will not be established overnight; therefore, we should agree to voluntarily take some steps immediately. With regard to human rights, we should insist on informed consent from all potential subjects capable of giving it. With regard to human welfare, we must be much more insistent that nonresearchers and nonphysicians make up a significant proportion (at least half) of all ethical review committees. This step will not solve the power problems inherent in expertise, but will help expose the extent to which the agenda of the researcher/scientist diverges from that of the nonexpert citizen. In addition, all research protocols should be made public, and the financial arrangements and sources must be made available to both review committees and subjects to expose (and hopefully curtail) conflicts of interest. All meetings of such review committees should be open to the public, because openness helps to dilute the power of expertise and democratically enfranchise the public.

### The Special Problems of Terminally Ill Research Subjects

Because the voluntary and understanding nature of consent of the terminally ill subject is compromised, and because this population is especially subject to exploitation by researchers who are often unrealistically optimistic in their expectations and believe

their subjects cannot be harmed, adoption of the following additional safeguards is suggested. The primary goals of these safeguards should be to protect the quality of life of conscious patients, and to protect the unconscious from being used simply as objects for the ends of others.

### Proposed Regulations Governing Research on Terminally Ill Patients

1. For the purpose of these regulations a "terminally ill patient" is one whose death is reasonably expected to occur within six months even if currently accepted and available medical treatment is used.
2. In addition to all other legal and ethical requirements for the approval of a research protocol by national and local scientific and ethical review boards (including IRBs), research in which terminally ill patients participate as research subjects shall be approved only if the review board specifically finds that:
  - (a) The research, if it carries any risk, has the intent and *reasonable probability* (based on scientific data) of improving the health or well-being of the subject, or of significantly increasing the subject's length of life without significantly decreasing its quality;
  - (b) There is no *a priori* reason to believe that the research intervention will significantly decrease the subject's quality of life because of suffering, pain, or indignity attributable to the research; and,
  - (c) Written informed consent will be required of all research participants over the age of sixteen in research involving any risk, and such consent may be solicited only by a physician acting as a *patient rights advocate* who is appointed by the review committee, is independent of the researcher, and whose duty it is to fully and objectively inform the potential subject of all reasonably foreseeable risks and benefits inherent in the research protocol. The patient rights advocate will also be empowered to monitor the actual research itself.
- (3) The vote on and basis for each of the findings in subpart (2) shall be set forth in writing by the review board, and be available to all potential subjects and the public.
- (4) All research protocols (including the financial arrangements between the sponsor and the researcher) involving terminally ill subject shall be available to the public, and the meetings of the scientific and ethical review boards on these protocols shall be open to the public.

The major features of this proposal are worth emphasizing. The first is that so-called non-therapeutic research may not be per-

formed on terminally ill patients at all unless there is no risk to the patient. Nor may "potentially," or "hopefully," or "possibly" therapeutic research be performed — the research must have "the intent and *reasonable probability* (based on scientific data) of improving the health or well-being of the subject . . . ." The fact that there is no treatment for the condition does *not* make any intervention "therapeutic" or even "probably" therapeutic. Phase 1 cancer drug research, for example, may not be performed on terminally ill subjects under these guidelines because there is no reasonable probability that it will benefit the subjects. Second, for subjects over the age of sixteen, only the subjects themselves are permitted to give consent for any research that involves any risk. Unless the condition is unique to children, no experimentation should be done on children until it has been demonstrated to meet the "reasonable probability" standard in adults. Proxy consent is acceptable only for *no risk* research (such as observation and monitoring studies, blood sampling, and research involving comatose patients). Third, the researcher is disqualified from obtaining the subject's consent. This task must be performed by an independent physician acting as a patient rights advocate, and whose primary obligation is to protect the rights and welfare of the potential research subject. Finally, the protocols, their financing, votes on them, and meetings concerning them, shall be open to the public.

These steps should help to protect both the rights and welfare of the terminally ill. Changes in codes and procedures alone, however, will not be sufficient to clarify societal goals for research and the practice of medicine, to define the meaning of progress, or to delineate the appropriate content of the practice of medicine. Resolving these central questions requires a recognition on the part of both society and medical practitioners that immortality is not a reasonable goal for medicine or humanity,<sup>60</sup> that there are fates worse than death, and that quality of life is more important than quantity of life.<sup>61</sup>

We can harm the terminally ill by treating them as objects with nothing to lose. They are our most vulnerable population, and need much more protection than they are currently afforded. It will take reality-based care for the dying, rather than fantasy-based experiments on the dying, to reclaim medicine's commitment in The Dec-

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60. See, e.g. Hans Jonas, *The Burden and Blessing of Mortality*, HASTINGS CENTER REP., Jan.-Feb. 1992, at 34, 39.

61. See, e.g., DANIEL CALLAHAN, *WHAT KIND OF LIFE: THE LIMITS OF MEDICAL PROGRESS* (1990).

laration of Geneva: "The health of my patient will be my first consideration."<sup>62</sup>

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62. World Medical Association, Declaration at Geneva, 1948.