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Book Review - Textbook of Research Ethics: Theory and Practice

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TEXTBOOK OF RESEARCH ETHICS: THEORY AND PRACTICE

SANA LOUE (Kluwer Academic/Plenum Publishers, New York, 2000),
247 pages, $55.

*Reviewed by Elizabeth A. Pendo, J.D., Miami, Florida.**

INTRODUCTION

An intense and deeply divided debate is taking place over the testing of a short course of AZT to prevent maternal-fetal transmission of HIV in the developing world.[1] A long course of AZT—administered to HIV-infected pregnant women during their pregnancy and immediately before labor, and then to their newborn children for six weeks—is generally accepted in the United States as providing extensive protection against maternal-fetal transmission of HIV. Given the expense and lengthy administration of the long course, American researchers in the developing world designed studies to test the efficacy of a shorter course of AZT administered during late pregnancy and labor. Significantly, the studies tested the short course of AZT against a placebo, rather than against the long course of AZT. It is undisputed that these studies would not be approved for implementation in the United States because they deny some of the subjects a treatment of known efficacy—the long course of AZT that is the accepted standard of care in the United States—which could result in the transmission of a fatal disease from the subjects to their children. However, as medical research and study increasingly take place on an international basis, many researchers, ethicists, and others are revisiting the question of whether it is ethical to give subjects a placebo when effective treatment is available in principle, but not in practice, due to the relative standard of care otherwise available to the subjects.

If you want to know more about the historical, theoretical, and legal context of ethical issues in human-subject research, such as those raised by the

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[1] Discussion of the AZT trials is based on David J. Rothman, *The Shame of Medical Research*, NEW YORK REVIEW OF BOOKS, Nov. 30, 2000, at 60.

AZT tests in the developing world, read this new book by Sana Loue, a professor of epidemiology and biostatistics at Case Western Reserve University School of Medicine. Loue's stated and laudable goal is to educate researchers about the historical context of human-subject research, provide a framework for understanding the various theories of ethics from which various guidelines have been derived, and offer a detailed outline of ethical issues within the context of designing, implementing, and reporting on human-subject studies. Although clearly aimed at conscientious researchers, laboratory personnel, research administrators, and others involved in human-subject research, Loue's straightforward and comprehensive book will appeal to anyone interested in the ethical issues raised by such research.

A DISTURBING HISTORY

It is common knowledge that well into the twentieth century, medical experiments and research in the United States were conducted using its most marginalized and vulnerable populations, including the poor, the disabled, children, people of color, and prisoners. In the first section of her book, Loue provides a concise historical account of human experimentation and research, focusing mainly on studies conducted in the United States. She summarizes each study, identifying its stated purpose, structure and specific historical context, with special attention to the vulnerable status of the subjects. Her evident interest and knowledge regarding treatment of and research on vulnerable populations lends strength and credibility to the section.[2] This section is not intended to be a comprehensive or complete account of all human-subject research or even of the selected studies, but instead serves as an introduction to the major events and issues in such research and as historical grounding for Loue's later sections.

A Variety of Cases

Loue opens the first chapter with the Nazi experiments in eugenics and racial hygiene and the Tuskegee Experiment, but goes beyond these most (in)famous examples to sketch out a range of cases and circumstances. For instance, she deftly summarizes the thousands of human radiation experiments conducted during the Cold War, often using the poor, the sick, and other similarly marginalized subjects. She recounts that, beginning in the 1940s and, in some cases, continuing until 1962, soldiers, conscientious objectors, pregnant women, institutionalized cognitively impaired children, and

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[2] *See* SANA LOUE, LEGAL & ETHICAL ASPECTS OF HIV-RELATED RESEARCH (1995), GENDER, ETHNICITY & HEALTH RESEARCH (1999), ASSESSMENT OF IMMIGRATION STATUS IN HEALTH RESEARCH (1999), and IMMIGRATION LAW & HEALTH: PATIENTS AND PROVIDERS (1993).

elderly African-American cancer patients were intentionally exposed to radiation without their knowledge or consent.

Loue also reviews a series of medical experiments on prisoners conducted during the mid-1900s at several United States prisons, such as those explored in Allen M. Hornblum's book, *Acres of Skin.*[3] Perhaps most well known are the skin "patch tests" conducted at Holmsburg Prison in Philadelphia, in which researchers directly and intentionally exposed prisoners to untested lotions, creams, and moisturizers. Loue also notes other experiments in which prisoners were exposed to and, in some cases, intentionally inflicted with, various diseases including ringworm, herpes simplex and herpes zoster, malaria, and leukemia, as well as a combination of phototoxic drugs and ultraviolet rays, an experimental polio vaccine, injections of live cancer cells, and psychotropic drugs. She notes that the level of fully informed and freely given consent varied dramatically among these studies—and was totally absent in some cases.

Loue recounts the 1950s experiments at the University of Chicago involving the synthetic estrogen DES (diethylstilbestrol) and its effects on miscarriage and premature birth. The studies exposed the pregnant subjects to DES without their knowledge or consent, and the offspring of the pregnant subjects who took DES later experienced conditions such as vaginal and cervical dysplasia, structural abnormalities of the uterus, breast and reproductive-tract cancers, penile bleeding, testicular masses, hypoplastic testes, infertility and sterility, and fetal death and premature birth. She also includes the 1950s hepatitis experiments at Willowbrook, a state funded, licensed and operated institution for the severely mentally retarded, during which institutionalized children were deliberately infected with hepatitis for a natural history study without the fully informed consent of the parents.

Finally, Loue relates the Tearoom trade experiments, a natural history study in which a researcher anonymously observed men participating in sex at "tearooms" in the Washington area in the late 1960s. The researcher covertly followed the men, recorded their license plate numbers, and later visited their homes posing as a health service worker to collect detailed information about their sexual practices. Loue notes that, due to the use of the technique of deception, the subjects did not know the nature of the research, or even that it was research, and that their confidentiality and privacy were compromised.

The strength of the historical section is two-fold. First, it presents a wide range of situations to draw upon as illustrative examples in the later sections. Loue goes beyond the more obvious cases involving malicious malfeasance and deliberate harm without any form of knowledge or consent, and presents cases in which some amount of notice was given, or some degree of consent was secured, as well as cases of natural history or

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[3] ALLEN M. HORNBLUM, ACRES OF SKIN (1998).

observational studies. The diversity of the cases presented reveals the multiplicity of ethical issues present in, among other things, providing truthful and complete information to potential subjects about the studies and in securing their freely given consent, particularly in institutional settings. Second, it affords an opportunity to explore how the history of human-subject research in the United States impacts current research projects, in particular, projects involving vulnerable populations. For example, Loue draws out the lasting effects of the Tuskegee Experiment and its impact on current attempts to study HIV in the African-American population: "[E]ducation programs designed to combat HIV in black communities have been met with distrust and a belief that AIDS and AIDS prevention and care present forms of racial genocide."[4]

The Subsequent Development of Codes and Guidelines

Beginning with the observation that the existing guidelines are aspirational and without the force of law, and that there is a lack of universal agreement regarding human rights and their implementation in the research context, Loue sketches the development of international codes and guidelines and national regulations relating to human-subject research.

She introduces the principal instruments applicable to human-subject research, including the Nuremberg Code, the Helsinki Declaration, the International Covenant on Civil and Political Rights, the International Guidelines for Ethical Review of Epidemiological Studies advanced by the Council for International Organizations of Medical Sciences, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects and Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products advanced by the World Health Organization. She also provides a section on United States regulations relating to human-subject research.

Again, her style is clear and succinct. She introduces the main themes of the international codes and guidelines and draws adeptly upon the historical outline provided in the first chapter to demonstrate the concerns and events that motivated the development of international guidelines.

DIVERSE APPROACHES TO ETHICAL ANALYSIS

The second section of the book is an outline and brief review of key approaches to ethical analysis. Loue introduces and briefly evaluates the strengths and weaknesses of casuistry, communitarianism, feminine and feminist ethics, principlism, deontology, utilitarianism, contract-based ethics, virtue ethics, and pragmatism, all in the context of human-subject research.

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[4] SANA LOUE, TEXTBOOK OF RESEARCH ETHICS: THEORY AND PRACTICE 8 (2000).

While her analysis is straightforward and accessible, she presents and evaluates each theory separately. The lack of a comparative analysis suggests that each theory is equally valid or appropriate in application to issues of human-subject research and experimentation, which is troubling. Although Loue acknowledges that "[e]ach approach has its strengths and weaknesses, and it is possible that the resolution of different situations may call for different approaches,"[5] she provides no guidance for resolving the difficult and potentially dangerous situations in which the theories come into conflict. While not obligatory in a work like this, such guidance surely would be welcomed by many of the book's readers.

As Loue's historical sketches in the first section make plain, the failure to appropriately resolve the clash of ethical approaches in human-subject research—in particular, the clash between the Kantian ideal of respect for individuals embedded within principlism, deontology, and contract-based ethics, among others, and an understanding of the utilitarian ideal as maximizing health for the greatest number even if at the expense of the welfare of a minority—has led to intolerable results. Indeed, as David J. Rothman has observed within the context of the AZT trials debate, "the source of ethical dilemmas in human experimentation was not 'bad' researchers but a system that was thoroughly utilitarian in its ethic."[6]

A ROADMAP TO PRACTICAL APPLICATION

In the remaining three chapters of her book, Loue puts her historical and theoretical mapping exercises to work. Having laid out the history of human-subject research, the major international guidelines and codes as well as national regulations and a brief synopsis of major ethical approaches, she then provides a thoughtful and detailed inventory of ethical issues at every stage of a human-subject study. Not surprisingly, she goes beyond the typical focus on informed consent to consider a broad range of issues that may arise before, during, or after the study, and in connection with the legal process. Loue's approach is broad and flexible and not limited to any specific type or types of study or experimentation.

She takes a practical, interactive approach designed to alert researchers to possible ethical issues at all phases of human-subject research, and to provide the resources necessary to work through those issues. Loue's style is direct, accessible, and engaging. She peppers the text with lists of questions and exercises that challenge conventional wisdom and invite the reader to think through and apply the ideas and theories presented.

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[5] *Id.* at 66.

[6] David J. Rothman, *Reply to Letter to Editor by Barry R. Bloom*, NEW YORK REVIEW OF BOOKS, Mar. 8, 2001, at 57.

In her words: "The reader is challenged to examine research situations presenting ethical issues for resolution, to devise creative strategies for the integration of science, ethics, and, where relevant, law."[7] These chapters are an effective and meaningful discussion of ethical issues at various stages of research because she has provided historical and theoretical context.

Ethical Issues Before, During, and After the Study

Loue details ethical issues before the study begins, starting with study design, which includes issues of assembling the research team, formulating inclusion and exclusion criteria, special issues regarding working with vulnerable populations, selecting a comparison treatment or intervention, and balancing the risks and benefits. She then discusses ethical review committees, including the purpose and function of review committees, and ethics review in the United States and internationally. She closes the chapter by addressing conflicts of interest, financial and otherwise, to be examined prior to beginning the study. In the next chapter, she addresses potential ethical issues during and after the study, beginning with issues to be considered in designing an informed consent process, recruitment of subjects, and explanation of the study. She then considers confidentiality and privacy concerns, monitoring the study, and disclosure.

The tone of these chapters is practical, engaging, and educational. Throughout, she provides detailed lists of questions, exercises, and strategies to address potential ethical issues. She also effectively draws upon the historical examples sketched out in the first chapter to illustrate her points, and provide the factual basis for exercises. She makes frequent reference to the various theories mapped in the previous section. However, as before, each theory is presented as equally germane and there is little guidance as to what to do when the theories are in conflict.

Legal Issues in Research

Loue concludes with a chapter devoted to legal issues in research, including the potential consequences of misuse of human participants, scientific misconduct, misconduct in regulated research, and issues relating to the use and release of data in a legal context. In particular, she skillfully elucidates how various legal obligations relating to the release of data, such as an FOIA (Freedom of Information Act) request for materials relating to a study, clash with other ethical obligations, such as confidentiality and maintenance of privacy, and she provides suggestions to resolve the potential conflicts.

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[7] LOUE, *supra* note 4, at viii.

This section is particularly strong and informative, as Loue holds a J.D. degree, and has written on the application of science to certain legal concepts, and the appropriate role of science and scientists within the formal legal system.[8]

THE GLOBALIZATION OF HUMAN-SUBJECT RESEARCH

Loue's guide to the historical, theoretical, and practical aspects of ethical issues in human-subject research is quite timely, as evidenced by the explosion of writing in the medical literature on the subject,[9] and the vigorous debate spawned by the AZT trials in the developing world.

As American researchers increasingly conduct human-subject research in the developing world, the applicability of existing international instruments, thought to embody primarily Western principles, to such research will remain the subject of heated debate. The relevant international codes and guidelines were not designed with the developing world in mind and are not universally applicable or enforceable. For example, the Helsinki Declaration, first adopted by the World Medical Association in 1964, provides in pertinent part that the well-being of human subjects must always take precedence, and that members of control groups should always receive the "best proven diagnostic and therapeutic method."[10] However, some have argued that, in the exceptional context of AIDS research conducted in developing countries, this maxim should not be interpreted to mean the best diagnostic and therapeutic method otherwise available at any location, at any cost, anywhere in the world.[11] At the center of the debate is the question of whether a standard of care is or should be merely a description of care actually available to that particular subject or subjects or, instead, be a normative standard of effective medical treatment, whether or not it is provided to a particular community.

Moreover, the international pressure brought to bear against multinational pharmaceutical companies to increase availability of drug therapies for AIDS in sub-Saharan Africa, where an estimated 70% of the world's

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[8] *See* SANA LOUE, FORENSIC EPIDEMIOLOGY (1998) (exploring the concepts of legal and epidemiological causation and the use of epidemiological information including experts in the legal system).

[9] *See, e.g.*, ETHICAL ISSUES IN RESEARCH INVOLVING HUMAN PARTICIPANTS, CURRENT BIBLIOGRAPHIES IN MEDICINE 99-3, *available at* http://www.nlm.nih.gov/pubs/cbm/hum_exp.html (visited May 24, 2001) (listing 4,650 citations for the period January of 1989 through November of 1998).

[10] World Medical Association Declaration of Helsinki *as amended by* the 48th World Medical Assembly, Somerset West, Republic of South Africa, Oct. 1996.

[11] Robert J. Levine, *The Need to Revise the Declaration of Helsinki*, 341 NEW ENG. J. MED. 351 (1999). Some have argued that the Helsinki Declaration should be amended to provide for "the best diagnostic and therapeutic treatment *that would otherwise be available to [the subject.]*" *See* Troyen A. Brennan, *Proposed Revisions to the Declaration of Helsinki—Will They Weaken the Ethical Principles Underlying Human Research?*, 341 NEW ENG. J. MED. 527 (1999).

AIDS-afflicted people reside,[12] will not resolve the debate surrounding the AZT trials. Although several companies have agreed to provide the multiple drugs used to treat AIDS in developed countries at a greatly reduced price, only a handful of African counties have negotiated for the drugs, and fundamental obstacles—such as the lack of an adequate health care system to deliver and support the combination drug therapy, famine and drought which prevents the taking of the drugs with food and/or water as required, and extreme poverty, which puts even the greatly reduced price out of reach of the majority of the afflicted—severely diminish the promise of the drugs.[13]

Undoubtedly, the history of human-subject research in the United States illustrates the peril of a relativistic approach because it creates a troubling double standard and an incentive to use the poorest and most vulnerable populations as research subjects because they have the least access to health care. In that sense, the AZT trials can be analogized to the Tuskegee Experiments, which were defended into the 1970s with a similar set of arguments: first, the information regarding the progression of syphilis was very valuable, in particular to the African-American population to which the subjects belonged; and second, the denial and even prevention of treatment—even after the advent of penicillin as an effective treatment in the 1940s—did not present an ethical issue because the poor, rural subjects probably would not have been treated for syphilis even in the absence of the study.[14]

CONCLUSION

These questions will not be easily answered and, as American researchers increasingly look to the developing world, the controversy is likely to grow. In this context, Loue's underlying theme, that "educating the public and researchers about research ethics is critical for the full protection of research participants," is particularly appropriate.

As a practical matter, Sana Loue's book provides a valuable set of tools with which to identify, analyze, and resolve a range of ethical issues that can arise in human-subject research. As the unfolding controversy surrounding AZT testing in the developing world illustrates, no system of rules or

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[12] John Christensen, *AIDS in Africa: Dying by the Numbers*, CNN In-Depth Specials 2000, *available at* http://www.cnn.com/SPECIALS/2000/aids/stories/overview (visited May 24, 2001) (figure cited by UNAIDS, an umbrella group for five United Nations agencies, the World Bank, and the World Health Organization).

[13] *Mali Gets Deal on Western HIV Drugs*, N.Y. TIMES, Apr. 8, 2001, at 1, *available at* http://www.nytimes.com/aponline/world (reporting Mali negotiated with four major Western drug companies to reduce the price of AIDS drugs by 89%, from $485 to $85 per person per month, which is still greater than the monthly minimum wage in Mali).

[14] Marcia Angell drew this provocative analogy in her now-famous editorial in the *New England Journal of Medicine*. Marcia Angell, *The Ethics of Clinical Research in the Third World*, 337 NEW ENG. J. MED. 847 (1997).

guidelines can anticipate all possible ethical issues. For that reason, while Loue does identify and thoroughly analyze a wide range of ethical issues, the real strength of her book is that it provides a historical context and a theoretical framework for dealing with new issues as they arise. The flexible and functional nature of the book also harmonizes with Loue's larger themes of searching out and addressing the less obvious ethical issues involved in human-subject research, and of providing a framework in which to raise and address questions on which reasonable people can, do, and will disagree.