PROTECTING HUMAN SUBJECTS

Office of Biological and Environmental Research U.S. Department of Energy

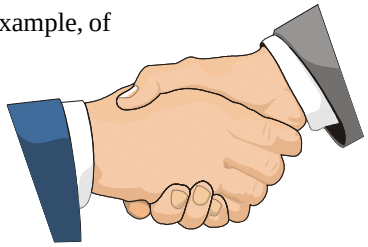
Protecting Research Integrity: An Update on the Issues

? What is scientific or research integrity and what is scientific misconduct?
? Who is responsibility for dealing with scientific misconduct?
? What protections must surround the accused and the accusers?
? Is there really much of a problem?

These questions have engaged researchers, administrators, ethicists, journalists, and the public since 1981 when the House Science and Technology Committee held a hearing on scientific misconduct following reports of several misconduct cases at major universities. Instances where allegations of data fabrication or falsification were ignored, or where whistleblowers suffered retaliation, rallied advocates of better investigations and stronger oversight of research, suggesting that the traditional "self-policing" of science by research groups, institutions, peer reviewers, and professional societies was inadequate.

Although the debates intensified in the 1980s, the issue was not new. Clear instances of data tampering and outright fraud dot the history of modern science. Some famous events, such as the "Piltdown man" archeological forgery of the early 1900s, continue to stimulate public interest.[1] But the "gray areas," in which honest error or acceptable (if uncommon) practices are difficult to separate from misrepresentation, also have a long history.

Adding to the difficulty is the fact that new ways of looking at data and even error—deliberate or not—have sometimes stimulated fruitful new explorations. Much has been made, for example, of evidence that physicist Robert Millikan discarded discrepant data in the oil droplet experiments he performed in 1909 to study the charge on electrons.[2] However, decades of replication yield the value Millikan derived, and his process for selecting data has been defended by modern physicists. [3]



These complexities moved to the background as the scandals of the 1980s drove demand for more rigorous processes for dealing with misconduct. In the 1985 Health Research Extension Act, Congress directed the Department of Health and Human Services (HHS) to develop new policies and rules on scientific misconduct. The HHS Public Health Service (PHS), which includes the National Institutes of Health (NIH), is the largest source of biological and medical research dollars in many universities. In 1998, PHS funding for research and development exceeded $13 billion, supporting research by more than 50,000 investigators affiliated with about 2,000 universities, hospitals, and other research institutions as well as more than 9,000 research staff at NIH.[4]

Rules on Misconduct

In 1989, HHS published a final rule on scientific misconduct that covered all PHS-funded research.[5] The rule assigned primary responsibility to universities, hospitals, and other research institutions

Continued on page 2

Contents

Continued from page 1

applying for PHS grants, fellowships, or cooperative agreements to establish formal policies and procedures to address allegations of scientific misconduct. After January 1, 1990, no research proposal was accepted from any institution that lacked a formal process. To handle investigations and reports, HHS established an Office of Scientific Integrity (OSI) in the National Institutes of Health and an Office of Scientific Integrity Review (OSIR) in the Office of the Assistant Secretary for Health. In 1992, these offices were merged in the Office of Research Integrity (ORI), which reports to the Assistant Secretary. The Departmental Appeals Board, or Research Integrity Adjudications Panel, took on the independent review of appealed findings.

Other funding agencies were also developing more formal processes: for example, the National Science Foundation and the U.S. Department of Agriculture adopted similar policies and procedures for addressing scientific misconduct. The HHS function, however, remains the largest and most visible in public debates about research integrity.

The new requirements and the implementing procedures at HHS and in the research institutions it funded dealt with many of the concerns raised during the 1980s. Allegations could no longer be ignored. Whistleblowers were to be protected from retaliation. And uniform procedures and definitions were established, including one for "scientific misconduct" itself (see box).

The Commission on Research Integrity

But the new processes generated new controversies and complaints. According to critics, protections were not adequate for either the accused respondent or the accusing whistleblower. Prolonged and aggressive investigations that ended in no charges could ruin careers of respondent and whistleblower alike. Broad interpretation of what constituted "serious" deviation "from commonly accepted practices" could frighten young researchers away from novel experiments.

In the 1993 NIH Revitalization Act (Section 162, Public Law 103-43), Congress directed a new examination of the definitions and of policies and procedures for assuring compliance, conducting investigations, and protecting both accused scientists and whistleblowers. The Act mandated a Commission on Research Integrity (CRI), under the leadership of Harvard Medical School Professor Kenneth Ryan to re-visit definitions, whistleblower protection, and related matters. The Commission submitted its final report in November 1995.[6]

The CRI Report contained seven recommendations to HHS, summarized as follows (p. ix):

- Adopt a new federal definition of research misconduct and other professional misconduct related to research. The proposed definition specifies offenses that by themselves constitute research misconduct: misappropriation, interference, and misrepresentation (MIM). Each is a form of dishonesty or unfairness that, if sufficiently serious, violates the principles on which the definition is based. The definition clarifies the role of intent in research misconduct, and distinguishes such behavior from other defined forms of research-related professional misconduct, including obstruction of investigations of research misconduct and noncompliance with research regulations.
- Form an interagency task force to develop a common federal definition of research misconduct and other forms of professional misconduct related to research.
- Expand existing institutional assurances to require that research institutions

provide research integrity education for all individuals supported by PHS research funds.

- Develop a regulation guaranteeing appropriate standards for protection of whistleblowers, based on "Responsible Whistleblowing: A Whistleblower's Bill of Rights."
- Require that intramural research programs of the PHS be subject to requirements concerning assurances, annual reports, and monitoring that parallel requirements for research institutions.
- Streamline DHHS administrative requirements and mechanisms concerning investigation and adjudication of research misconduct allegations, federal intervention in institutional misconduct proceedings, and the imposition of federal sanctions.
- Focus federal oversight of institutional research integrity and research misconduct activities.

The CRI also encouraged scientific and professional societies to "adopt and apply codes of ethics in research to educate their membership and to help ensure that all scientists follow professional ethical standards for their particular disciplines," and research institutions "to develop and disseminate specific guidelines for good scientific practices."

Continuing Disagreement on Defining Scientific Misconduct

Not surprisingly, the CRI's recommendations were not universally endorsed by the scientific community. The revised definition of scientific misconduct, in particular, drew criticism from several major groups.

The Council of the National Academy of Sciences objected to the definition as "open-ended," "broad," and "vague" and called the "case law" approach for refining its specificity to be "totally alien to scientists and the scientific process." The Council went on to criticize the "legalistic" approach in specific examples of misconduct delineated in the report, arguing that "aside from the clearly defined infractions of fabrication, falsification, and plagiarism, which cannot be tolerated at any stage of a scientific project, no single code can define how all science should be performed." [7]

The Federation of American Societies for Experimental Biology (FASEB) raised similar issues. In a letters to HHS, FASEB and 50 of its affiliated societies opposed the CRI definition, calling it "overly broad, legalistic, and open-ended" and capable of "opening scientists up to unpredictable and ill-defined charges of misconduct." FASEB President Ralph Bradshaw advocated a definition of scientific research misconduct "sufficiently precise to provide an unambiguous basis for investigating and adjudicating cases of alleged misconduct, and serve as a clear guide for practicing scientists, teachers and administrators." [8]

Other commentators have recommended even narrower definitions of "misconduct," that clearly exclude acts covered by existing laws whether or not they occur in a scientific setting. For example, CalTech philosopher James Woodward and physicist David Goodstein propose corralling *scientific* misconduct off from plagiarism, theft, and other behaviors for which clear legal definitions and penalties already exist. Woodward and Goodstein recommend instead that the scientific community focus on cases "that require a detailed understanding of the nature of the experiments, the instrument used, accepted norms for presenting data and so on…." [9]

The definition controversy arises from fundamental questions about how science is done and how reports of findings relates to the scientific process. In the essay cited above, Woodward and Goodstein explore some of the philosophical, social, and

Continued on page 4

Three Recent Definitions of Scientific Misconduct

Public Health Service (adopted 1989):

"'Misconduct' or 'misconduct in science' means fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. It does not include honest error or honest differences in interpretations or judgments of data."

National Science Foundation (adopted 1991):

"'Misconduct' means (1) fabrication, falsification, plagiarism, or other serious deviation from accepted practices in proposing, carrying out, or reporting results from activities funded by NSF; or (2) retaliation of any kind against a person who reported or provided information about suspected or alleged misconduct and who has not acted in bad faith."

Commission on Research Integrity (proposed 1995):

"Research misconduct is significant misbehavior that improperly appropriates the intellectual property or contributions of others, that intentionally impedes the progress of research, or that risks corrupting the scientific record or compromising the integrity of scientific practices. Such behaviors are unethical and unacceptable in proposing, conducting, or reporting research, or in reviewing the proposals or research reports of others.

"Examples of research misconduct include, but are not limited to, the following:

"Misappropriation: An investigator or reviewer shall not intentionally or recklessly a. plagiarize . . .; or b. make use of any information in breach of any duty of confidentiality associated with the review of any manuscript or grant application.

"Interference: An investigator or reviewer shall not intentionally and without authorization take or sequester or materially damage any research-related property of another . . . .

"Misrepresentation: An investigator or reviewer shall not with intent to deceive, or in reckless disregard for the truth, (a) state or present a material or significant falsehood; or (b) omit a fact so that what is stated or presented as a whole states or presents a material or significant falsehood."

Continued from page 3

psychological explanations of the processes researchers follow and their implications for defining misconduct. They observe that flawed ideas about "scientific method" can lead to "formulating plausible-sounding ethical principles that would be unworkable or even damaging to the scientific enterprise."

In a similar vein, Virginia Tech chemistry and science studies professor Henry Bauer has studied the ways many scientists mingle theorizing and empiricism in their work, following pathways far removed from the inductive process identified with "The" scientific method.[10] Researchers working in what Bauer calls "frontier science," where experimental craft, intuition, and creativity are most important, may face special hardships in having their work understood and accepted as real science. Protecting these pioneers, while demanding honesty and openness, is the balance point that most scientists and ethicists recognize as essential but difficult to maintain.

Current Status of the Issues

In 1996 an implementation work group reviewed the CRI recommendations and advised that HHS adopt most of them. Consideration of the scientific misconduct definition was deferred and still awaits possible government-wide action through the White House Office of Science and Technology Policy. The work group proposed that the CRI whistleblower recommendation be the basis for a new HHS rulemaking.

Reports since 1996 suggest that the definitions and rulemakings are not the only areas where consensus has been hard to reach. Dispute and uncertainty continue about how much scientific misconduct does occur and the approaches universities and other research centers can take to prevention and to punishment and rehabilitation of offenders.

Is There Really a Problem?

One of the thornier problems is that, regardless of how misconduct is construed, no one is really sure how many of the million or so researchers in the U.S. today have engaged in acts, such as plagiarism or data fabrication, that tend to be universally acknowledged as unethical. This question is important because participants in the dialog tend to align into two (metaphorically) opposing camps: the "tip of the iceberg" versus a "few bad apples."

The data reported by ORI suggest a problem large enough to warrant vigilance, but not overwhelming. Between 1992 and 1996, ORI closed 1500 allegations and 200 cases where allegations led to inquiries and investigations by research institutions, which then reported them to ORI. Of these 200, 68 resulted in a finding of misconduct. In 1997, 64 new scientific misconduct cases were opened.[11]

These numbers appear small given the 50,000 research personnel and the thousands of institutions subject to the HHS rules. But some scientists and administrators caution that we cannot be complacent about these numbers because they may only be that iceberg tip. For example, C. Kristina Gunsalus, associate provost of the University of Illinois at Urbana-Champaign and a member of the CRI, argues that "we have no direct data on the accuracy of the scientific literature. We simply do not know whether a lot or just a little untruthful information is published." [12]

One NSF-funded survey of perceptions of faculty and doctoral candidates about the incidence in their disciplines of 15 different kinds of questionable activities found alarmingly high numbers reporting that they had observed plagiarism (9%) data falsification (6%), and other unacceptable behavior.[13] However, the study has been criticized for "self-selection bias" among respondents, since only 2600 of the 4000 surveys were returned.[14] Moreover, the study queried *perceived* misconduct, which may or may not equate to *actual* misconduct (consider the 1500:68 ratio of allegations to findings of misconduct in the ORI data).

Researchers at the University of California recently reported the results of a survey of 606 NSF investigators in molecular or cell biology and 91 representatives from their institutions (69% of the sample contacted) who were asked to determine whether acts described in 12 scenarios were unethical, how unethical the act was, and what responses and punishments were appropriate.[15] The study found that scientist and administrators ranked the acts in a similar way, giving equally high "malfeasance ratings" to data fabrication and falsification, for example. The two groups differed the most in their approaches to punishing unethical acts, with the administrators proposing stiffer penalties, using university sanctions (such as a letter of reprimand) while the scientists chose "social constraints and peer pressure" (such as requiring retraction of the publication). The authors speculate that these differences in focus (administrators on the institution and scientists on their peer community) may underlie many of the controversies that surround the CRI recommendations.

Managing Research Integrity: Whose Responsibility?

Despite these ongoing disagreements, one of the benefits of the changes since 1989 is the clearer delineation of responsibility for research integrity, and greater acceptance by research organizations of their role in maintaining integrity. Institutions now routinely appoint a Research Integrity Officer (RIO), publish policies and procedures, educate staff and students on research ethics, and report investigations to ORI.

ORI, in turn, reports both better quality and greater speed in its handling of its case investigations. The office is also making a

Continued on page 6

Continued from page 5

strong outreach effort. The ORI home page offers model policies and procedures, quarterly newsletters, annual reports, a handbook for RIOs, and reports and white papers on various topics. To request ORI documents or to inquire about other topics, contact:

Division of Policy and Education
The Office of Research Integrity
5515 Security Lane, Suite 700
Rockville, MD 20852
Telephone: 301-443-5300
Fax: 301-443-5351
E-mail: requests@osophs.dhhs.gov
Internet: *http://ori.dhhs.gov/*

Research Integrity and Human Subjects Protection

Several of the emerging issues in research integrity also concern the protection of human research subjects. In a February 1998 workshop sponsored by ORI and the University of Michigan, participants identified two such concerns:

- Potential liability of institutional committee members
- Conflict of interest issues, such as IRB access to "insider information" or to information on a patentable technology

Even more basic to the role of the IRB is the responsibility for determining that the research to be conducted is ethical. In its 1995 report, the Advisory Committee on Human Radiation Experiments (ACHRE) recommended national efforts the "ensure the centrality of ethics in the conduct of scientists whose research involves human subjects," observing that "a national understanding of the ethical principles underlying research and agreement about their importance is essential to the research enterprise and the advancement of the health of the nation. The historical record makes clear that the rights and interests of research subjects cannot be protected if researchers fail to appreciate sufficiently the moral aspects of human subject research and the value of institutional oversight." [16]

Given their overlapping responsibilities, RIOs, Ethics Committees, and IRBs share a concern about improving researchers' basic understanding of and adherence to all ethical standards including conflict of interest, human and animal rights, and the values of honesty, openness, and collegiality in performing and reporting work.

To explore these topics and their relevance to the needs of their own institutions, IRB members can examine the resources provided by the Office of Research Integrity or by their own RIOs. Additional sources include the many professional organizations, publishers, and universities that offer teaching guides, case studies, videos and other valuable materials researchers and administrators can use to improve understanding of key ethical issues.

The American Association for the Advancement of Science sponsors or co-sponsor several projects on science and ethics and maintains many resources including a quarterly newsletter, *Professional Ethics Report*. Contact:

The Scientific Freedom, Responsibility and Law Program
AAAS
1200 New York Avenue, NW
Washington, DC 20005
Phone: 202-326-6600
Internet: *http://www.aaas.org/spp/dspp/sfrl/sfrl.htm*

The American Association of Medical Colleges (AAMC) is an association of the accredited U.S. and Canadian medical schools, the major teaching hospitals, and health and academic and professional societies representing 75,000 faculty members. In 1997 the AAMC Committee on Research Integrity published *Developing a Code of Ethics in Research: A Guide for Scientific Societies.*

To order this or other AAMC publications, phone 202-828-0416, or fax 202-828-1123. For more information on the AAMC, contact:
Association of American Medical Colleges
2450 N Street, NW
Washington, DC 20037-1126
Phone: 202-828-0400
Fax: 202-828-1125
Internet: *http://www.aamc.org*

Michigan State University's Graduate School publishes a semi-annual newsletter on research integrity. Read the newsletter on-line at: *http://www.msu.edu/~gradschl/gradstudy/newslett/Research/rihome.htm,* or contact:
Research Integrity
119 Linton Hall
Michigan State University
East Lansing, MI 48824
Phone: 517-353-3262

Virginia Tech maintains an extensive, current bibliography of readings on ethics in science. Download the bibliography from: *http://www.chem.vt.edu/ethics/vinny/ethxbibl.html,* or contact:
Ethics in Science
Department of Chemistry
Virginia Polytechnic Institute and State University
Blacksburg, VA 24061-0212

Notes

[1]See, for example, John Evangelist Walsh, *Unraveling Piltdown: The Science Fraud of the Century and Its Solution* (New York: Random House, 1996).

[2] An analysis of Millikan's "data selectivity," is included in an appendix entitled "Known or Suspected Cases of Scientific Fraud," in William Broad and Nicholas Wade's controversial 1982 book, *Betrayers of the Truth* (New York: Simon & Schuster).

[3] See Caltech physicist David Goodstein's argument for the legitimacy of Millikan's method in "What DO We Mean When We Use the Term 'Scientific Fraud,'" first published in Texas A&M's *Windows* (Fall 1991, p.7) and excerpted in *The Scientist*, 6(5), March 2, 1992.

[4] Data from the HHS 1999 Budget documents presented by Secretary Donna Shalala on February 2, 1998.

[5] 42 Code of Federal Regulations 50, Subpart A. Similar requirements appear in the National Science Foundation's rules for its grantees. The Department of Energy laboratories are subject to the rules of agencies funding their work.

[6] *Integrity and Misconduct in Research: Report of the Commission on Research Integrity to the Secretary of Health and Human Services, the House Committee on Commerce, and the Senate Committee on Labor and Human Resources*. 1995. Washington, DC: U.S. Department of Health and Human Services.

[7] Bruce Alberts et al., Council of the National Academy of Sciences, letter to Dr. William Raub, Science Advisor, HHS, March 15, 1996.

[8] FASEB letter endorsed by 50 scientific societies, to Dr. William Raub, Science Advisor, HHS, May 13, 1996.

[9] James Woodward and David Goodstein. 1996. "Conduct, Misconduct and the Structure of Science," *American Scientist* 84(5):479-490

[10]*Scientific Literacy and the Myth of the Scientific Method*. Chicago: University of Illinois Press, 1992.

[11] ORI Annual Report for 1996 and ORI Newsletter for June 1998.

[12] From a presentation at "Science in Crisis at the Millennium," a symposium at George Washington University; published in *The Chronicle of Higher Education*, March 28, 1997, p. B4.

[13] Judith P. Swazey, Melissa S. Anderson, and Karen Seashore Lewis. 1993. "Ethical Problems in Academic Research." *American Scientist* 81 (Nov./Dec.): 542-553.

[14] Christopher Anderson. 1993. "Study Tracks Misconduct, to an Extent." *Science* 262 (19 Nov.): 1203-1204.

[15] Stanley G, Korenman, Richard Berk, Neil S. Wenger, and Vivian Lew. 1998. "Evaluation of the Research Norms of Scientists and Administrators Responsible for Academic Research Integrity." *Journal of the American Medical Association* 279 (1): 41-47,

[16] Recommendation 9, Chapter 18, of ACHRE's *Final Report* , October 1995. This report may be found online at www.ohre.doe.gov/roadmap/achre/.html.

IRB Profile: Education, Outreach, and Ethics at the University of Texas Houston Health Science Center

Contributed by Paula Knudson, Executive Coordinator, Committee for the Protection of Human Subjects, University of Texas, Houston

A native of Manhattan, Paula Knudson has resided in Houston since 1969 and has worked with the IRB at the University of Texas Houston Health Science Center since 1977. Her office also supports the Animal Welfare Committee and the Radioactive Drug Research Committee. She became a member of the Board of Directors of PRIM&R (Public Responsibility in Medicine and Research) in 1982 and actively aids in the planning of their national conferences.

Her personal as well as professional interests are in the ethical issues associated with both human and animal experimentation; particularly research with vulnerable populations; research in women's health; overcoming the barriers to research participation by ethnic minorities and, providing a bridge between investigators in the social and behavioral sciences and those IRB members solidly based in the biomedical mode.

The IRB at the University of Texas Houston Health Science Center is known as the Committee for the Protection of Human Subjects (CPHS) and takes this as its mission. The CPHS was established in 1974 following the attachment to the National Research Act of that year which stated that institutions receiving federal funds for research would be required to have an "institutional review board" (IRB) to review research specifically to see to the protection of the human subjects who would be enrolled. The Health Science Center was very new at that time, and consequently there was little in the way of research going on. This situation changed rapidly over the following years as did the understanding by CPHS members of how best to implement the ethical principles of autonomy, beneficence, and justice enunciated in the Belmont Report. My role with the CPHS began in 1976, and my current title is Executive Coordinator.

Our CPHS is made up of 26 regular members and 23 alternate members. Members are drawn from all branches of our faculty, our Chaplain service, our legal department, and our social work department. We also have five outside members who represent community interests. We are responsible for reviewing research that takes place in all of our component units or is conducted by faculty and staff of the Medical School, Dental School, Graduate School, Nursing School, School of Public Health, Allied Health Sciences School, and our three teaching hospitals. We are currently responsible for approximately 500 new studies a year and approximately 900 ongoing studies. To meet these responsibilities, our committee meets once a month.

Almost from the very beginning, it was clear that our major emphasis needed to be on our role as educators. It became a fundamental belief of the CPHS that, until all of the players in the research enterprise were aware of and able to internalize the ethical principles of the Belmont Report, our role as IRB members would amount to little more than paper checks and balances. We therefore offer lectures in research ethics to students in research classes at all of the schools. We also lecture in the nursing units at the hospitals—specifically in the intensive care units (ICUs), which are heavy targets of research these days. Additionally, we also lecture in the University's research integrity curriculum and at Grand Rounds or faculty meetings of the medical school departments.

In addition to our external teaching commitments, we provide continuing education for our IRB members by spending approximately 15 minutes at the beginning of each meeting discussing a particularly perplexing or new and emerging problem for IRBs. Topics are selected by the Chairperson and the coordinator, and the discussion is generally led by the Chair with open and lively participation by the membership. Papers and newspaper articles dealing with ethical dilemmas in research are circulated to the membership as well.

Our IRB has been proactive in establishing written policies to help members and investigators deal with the issues and problems associated with incorporating women and children in research, including minorities in research, maintaining confidentiality of computer databases, remunerating subjects in research projects, and developing a glossary of research terms for the lay public, among others. Ad hoc subcommittees, appointed by the Chairperson and working with the Executive Coordinator, formulate and write these policy documents.

Another part of the mission of our IRB has been outreach to the Houston community. When the 1993 directive came down from the National Institutes of Health that women and minorities were to be included in research studies, the CPHS began a program called Ethnic Diversity in Research. Members of the CPHS and staff regularly (approximately three times a month) give talks to community groups about current and past research and the role of the IRB

committee. In addition, we solicit information from community members as to what they perceive to be barriers to research participation. This information enables the CPHS to attempt to solve some of these problems. Of equal importance, we ask community members to identify the kinds of research they would like to see take place, and carry this information back to our faculty.

The CPHS makes these presentations at health fairs held at local churches and health clinics, at breakfast and service clubs, at senior citizen meetings, and to community groups of many different types. The outreach effort has been fully supported by the Health Science Center administration and is leading to valuable spin-offs.

One spin-off has been the realization that the words "research" and "study" do not have significant meaning for lay persons. However, when the word "experiment" is used, there is instant recognition.

We also have learned the importance of when and how individuals receive information on informed consent. For example, we found that a patient had been placed in a study when that patient and family had specifically requested that the patient not be included. The circumstance under which this occurred were as follows: the informed consent form for the study had been included with the consent for treatment and the consent for surgery, all of which were signed at the same time. We have used this incident as a great learning experience for our investigators and have cautioned them to assure that it does not happen again. Having a community outreach program in place was of great assistance when we were given permission by the Department of Health and Human Services (DHHS) to proceed with an emergency medicine study of traumatic head injury which required waiver of consent because the intervention had to be performed within a very short window of time—long before family members could be found and permission requested from them. As part of the DHHS approval, we were mandated to obtain community consultation and consent for the abandonment of that sacred tenet of research ethics: the autonomy of the individual (or responsible relative) to provide informed consent before enrollment in a research study. We were quickly able to fold this information into our community presentations and obtain feedback for our researchers and the DHHS.

Because many of our members were concerned about vulnerable populations enrolled in research studies as well as about what happens to consent over time, we developed a staff position we call the "Research Intermediary," whose main responsibility concerns our psychiatric hospital. Although she is not part of the consent process, the Research Intermediary sees each patient who has been enrolled in any study taking place at the psychiatric hospital within 12 hours of enrollment and then maintains contact with that patient at least three times a week. Her encounters with the patient are designed to elicit their understanding about the research and the consent form, and to assure liaison between the patient/subject and the research team. The Research Intermediary in turn, brings subject concerns to CPHS meetings for discussion. This keeps the membership apprised of problems that subjects encounter so that, if necessary, changes can be suggested to the particular protocol or, kept in mind for future protocols.

All of these measures are designed to maintain a dialogue between our research community and the community on whom the research focuses—the research subjects. This dialogue enables us to stay aware of and sensitive to subject needs. We can then communicate these needs to our investigators and administrators, which makes the protection of human subjects a meaningful process.

The University of Texas, Houston, CPHS Hears a New Proposal?

DOE Human Subjects Protection Update

On January 20, 1998, Secretary of Energy Federico Peña signed an updated policy statement on the Department of Energy's position on the types of studies in which human subjects must be afforded protection. The following is the full text of Secretary Peña's memo:

MEMORANDUM FOR ALL DEPARTMENTAL EMPLOYEES

FROM: FEDERICO PEÑA, SECRETARY OF ENERGY

SUBJECT: Update on Departmental Policy for the Protection of Human Subjects in Research

All DOE employees, contractors, and grantees must be mindful of the importance of protecting the rights and welfare of human subject research volunteers. In a world of rapidly advancing medical technology, revolutionary genetics research, and ever-increasing threats to personal privacy, the protection of human subjects in research is paramount. All research conducted at DOE, supported with DOE funds, or performed by DOE employees, including classified and proprietary, must comply with Federal regulations and DOE Orders to protect human subjects. These requirements must be met before work is initiated. Responsibility for the ethical conduct of research begins with researchers, extends to their institutions and local Institutional Review Boards (IRBs), and includes DOE field and program officials. Research using human subjects encompasses a broader range of research than many investigators, program managers, and government officials often realize. In addition to traditional biomedical and clinical studies, human subjects research includes, but is not limited to, studies that use:

- identifiable or high risk data, including surveys, collected through direct intervention or interaction with individuals;
- private information readily identifiable with individuals, including genetic information and medical and exposure records, such as in worker surveillance studies;
- worker populations or subgroups;
- humans to test devices, products, or materials developed through research; to examine human-machine interfaces; or to evaluate environmental alterations; and,
- bodily materials such as cells, blood, tissues, or urine that are identifiable with individuals.

Within the Department, the Office of Energy Research is responsible for making final decisions as to what constitutes DOE-related human subject research and how human research subject protection must be implemented. Questions or uncertainties regarding the applicability of human subject protection regulations to research studies should be addressed to:

Dr. Susan L. Rose, DOE Human Subjects Protection Program Manager
Office of Biological and Environmental Research, ER-72
U.S. Department of Energy
Germantown, MD 20874-1290
Phone: 301-903-5468
Fax: 301-903-8521
E-mail: susan.l.rose@oer.doe.gov

Dr. Rose should be consulted when a project is under development, if local administrative support is unable to evaluate or meet protection requirements, and when referrals to other resources are needed. The DOE Human Subjects Protection Program has a wide variety of educational and technical resources available for investigators, administrators, and IRBs.

Thank you for helping make DOE a leader in the protection of human subjects in research.

DOE/VA/NIH Jointly Fund Research on Informed Consent

A grant program sponsored by DOE, the Department of Veterans Affairs, and a number of National Institutes of Health components is supporting 11 projects of "Informed Consent Research Involving Human Participants." Grant recipients are conducting research on components of informed consent and testing innovative approaches to the process in an effort to find ways to enhance the understanding research subjects must have in order to give truly informed consent to their participation. The 11 projects were selected from 82 applications submitted in response to a request for applications issued in 1997.

In one project, Jon Merz, research assistant professor of bioethics, and his colleagues at the University of Pennsylvania are attempting to answer such questions as "How can the informed consent for tissue and blood donation be made more effective? What format and content will assure that research subjects adequately understand what they are agreeing to?" in a study comparing different methods of presenting information to patient donors.

During the study, approximately 2000 patients in University of Pennsylvania's General Clinical Research Center will be asked to contribute blood samples to a DNA bank for research purposes only. Each patient will be randomly assigned to one of two groups. One group will receive a standard consent form developed for the DNA bank. The second will receive the same form but will also be presented with several "vignettes" or brief sketches that illustrate risks and benefits of the choices they are asked to make. Patients in both groups will then be surveyed on their perception of the process and on their understanding of the issues introduced. The research team's hypothesis is that patients who work through the vignettes will demonstrate better comprehension of what they are asked to consent to.

Study results will help shape the informed consent process for Pennsylvania's new DNA bank. Dr. Merz notes that the issues surrounding donation to a DNA bank for future research are complex. For example, the bank is not the researcher, but a "trustee," mediating between donors, who may wish to limit access to information about themselves, and researchers, who may want to know more about the donors' backgrounds and lives. Donors may have preferences about the types of research they want their DNA to be part of. Donors may also differ in their interest in feedback from the studies and in their level of concern about third-party access to data that can be linked to them personally.

The grant program reflects concerns voiced by the 11 projects are funded for three years with each sponsoring agency contributing $2.25M annually to the effort. The program is the first large is the first program on informed consent research to be sponsored by multiple federal agencies and multiple NIH institutes. The directive for the program originated in an interagency response to recommendations of the Advisory Committee on Human Radiation Experiments. Committee members had found that many of the consent forms they reviewed "to be overly optimistic in portraying the likely benefits of research, to inadequately explain the impact of research procedures on quality of life and personal finances, and to be incomprehensible to lay people." (ACHRE, *Final Report*, Executive Summary, October 1995).

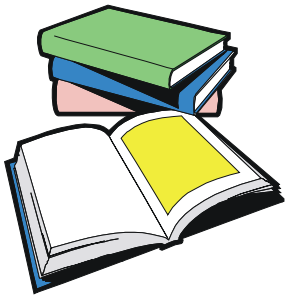
On March 17-18, 1998, the sponsoring agencies convened all the principal investigators and federal staff in Rockville, MD, for the first of three planned annual meetings to share information about their projects. The sponsoring agencies and the grantees will use these annual meetings and the associated networking as a way of encouraging investigators to communicate progress with one another and to seek one another's help in addressing problems that arise in the course of their projects. Jon Merz hopes that "figuring out how we work together" will assure that the program's "end result is coherent."

Continued on page 12

Continued from page 11

The full list of projects and principal investigators funded for the three-year program follows:

- "An Experimental Study to Improve Risk/Benefit Appraisal," James Sorenson, University of North Carolina
- "Therapeutic Research Consent: Empirical/Ethical Analysis," Laura Siminoff, Case Western Reserve University
- "Dynamics of Informed Consent in AIDS Clinical Trials," Mary-Rose Mueller, University of California at San Francisco
- "Dementia Research: Informed, Proxy, and Advance Consent," Greg Sachs, University of Chicago
- "Vulnerability and Informed Consent in Clinical Research," Laura Roberts, University of New Mexico
- "Improving Understanding in Early Phase Clinical Trials," Nancy Kass, Johns Hopkins University
- "Enhancing Autonomy of Vulnerable Subjects of Research," Laurence McCullough, Baylor College of Medicine
- "Improving the Consent Process for Low-Literacy Parents," Frances Campbell, University of North Carolina, Chapel Hill
- "Minors at Risk of Future Disease: Their Role in Research," Gail Geller, Johns Hopkins University
- "Evaluating Informed Consent in BRCA1 and BRCA2 Screening," James Gribble Research Triangle Institute, North Carolina
- "Informed Consent to DNA Banking for Research," Jon Frederick Merz, University of Pennsylvania



Book Review—Cloning and Religion Intersect

Ted Peters. 1997. *Playing God? Genetic Determinism and Human Freedom*. New York: Routledge Press. Foreword by Francis S. Collins, M.D., Director, National Center for Human Genome Research.

Reviewed by the Reverend Bill Nebo, Senior Pastor, First Presbyterian Church, Livermore, California, and Community Member, Lawrence Livermore National Laboratory IRB

When Dolly the lamb brought the issue of cloning out of science fiction and established it as scientific fact the philosophical and theological implications were not lost on religious people in the United States and elsewhere. In religious circles throughout the country people were concerned about who was about to "play God," resting their thoughts on the old familiar assumptions that certain actions of life were not the prerogatives of mere mortals. And certainly making exact, physical duplicates of animals without the aid of sex, seemed a God like task, the far reaching implications seeming beyond the grasp of human intellects.

Though lacking a discussion of cloning in particular, this concern about humans taking God's prerogatives in creation is the major source of concern of Dr. Ted Peter's book *Playing God? Genetic Determinism and Human Freedom*. Dr. Peters is Professor of Systematic Theology at the Pacific Lutheran Theological Seminary and the Graduate Theological Union in Berkeley, California and also Associate at The Center for Theology and the Natural Sciences in Berkeley. In both capacities Dr. Peters has made the discussion of the relationship between scientific thought and religious thought his specialty.

"Playing God?" is not written for the casual lay reader. In many respects it is a way for those who are more seriously interested in theological thought about the impact of genetic research and development to touch the major bases uncovered by the winds of challenge blowing on religious life from the quarter of the biological sciences. It is also not poetically written and its blunt style often seems a bit awkward.

In short it is not great literature, but then it was not written to be a literary work. Its purpose is to accurately, and clearly cover issues which Dr. Peters feels that religious individuals, and Christians in particular, must address both morally and theologically if they are to fully grasp the implications of genetic research and development.

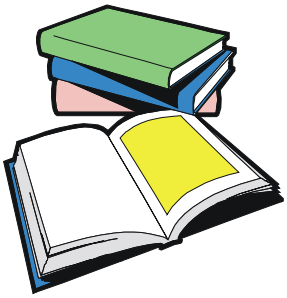
Dr. Peters is passionate in his thesis that Protestant theological thought needs to embrace the challenges given to it by the biological sciences with a view of humans as co-creators with God. He spends much time developing his thesis, which is essentially that humans are invited to play God by God him/herself. As a result, Dr. Peters sees it as cowardly for Christians to simply impede exploration of the good that genetics is bringing within human grasp. This is not to say that Dr. Peters is unaware of the need for caution and a great deal of reflection upon the long-term consequences of genetic alteration and enhancement.

What concerns Dr. Peters most in his writing is the way genetic information impacts how humans think of themselves, their place in the cosmos, and their attitudes toward their behavior. In his opening sentences he asks," will new discoveries in genetic science so completely explain human behavior that the freedom we previously thought we had will turn out to be delusion?"

"Playing God?" shows us how what Peters calls "the genetic myth" bears upon the issue of moral pronouncements about and therapeutic attitudes toward homosexuality. The myth impacts the way Christians doctrine of original sin and free will as well as its views about crime and punishment. In his more theological chapters Peters takes a crack at unpacking these issues so that they reshape and harmonize his Lutheran theology with the moving tide of scientific thought. One should be warned that these theological chapters are not easy to grasp, or particularly fun to read. But if one is truly seeking to understand how modern Protestant thinkers can honestly deal with the way that modern genetics changes our view of our selves and the universe, then slogging through these chapters will be useful and rewarding.

It is refreshing to read a theological work about genetics which is not interested in political correctness or filled with populist hysteria based on misinformation about science. Ted Peters may not win any literary prizes for *Playing God?* but he deserves great praise for his dedication to being informed, considering all points of view rationally, and building his conclusions independently and compassionately.

Other Recent Books of Interest



Arthur L. Caplan. 1997. *Am I My Brother's Keeper? The Ethical Frontiers of Biomedicine*. Bloomington, Indiana: Indiana University Press.

This volume collects 19 essays by Arthur Caplan, Director of the Center for Bioethics at the University of Pennsylvania. Dr. Caplan explores a variety of current issues in bioethics. His chief concern is the moral cynicism and distrust that have accompanied rapid changes in what is medically possible (in vitro fertilization, organ transplants) and how medical care is delivered (managed care, definitions of disease and disability). Researchers will find useful perspectives on gene therapy, the use of data obtained from unethical work, and the debate on fetal tissue in research. Anyone who participates in

Continued on page 14

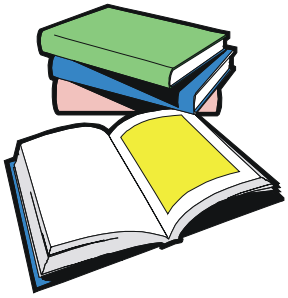
Continued from page 13

bioethical debates will appreciate Dr. Caplan's argument in Chapter Six for the power of analogy and the dangers of comparing every event we find repugnant to the Holocaust. Dr. Caplan clearly believes that we can and must restore balance between individual autonomy and "the need to rely upon one another at moments of weakness, illness, and death." These readable, well-argued essays constitute a valuable resource for a bioethics course or an IRB educational seminar.

Catherine Baker. 1997. *Your Genes, Your Choices: Exploring the Issues Raised by Genetic Research*, a publication of the Science + Literacy for Health project of the American Association for the Advancement of Science, Directorate for Education and Human Resources. Available on-line at *http://erweb.aaas.org/ehr/books/index.html*.

This book, intended for the lay person, uses seven case studies to introduce basic concepts of genetics, genetic testing and counseling, genetic engineering of crops and farm animals, and the social, legal, and ethical issues these topics generate. No case yields a simple, obviously right answer, and each case builds on the information and issues presented in the preceding one. The seven cases in short:

- An albino child's experience of being different is used to introduce heredity and the idea of gene therapy.
- Genetic testing issues are presented through the question of whether the child of a person who has died of Huntington's chorea should be tested for the gene.
- A middle-aged man's questions about his risk for heart disease launch a discussion on the interplay of heredity, environment, and behavior in the disease.
- Prenatal testing is the issue confronting a young couple who know they are at some risk of having a child with cystic fibrosis.



- The police want to use a mass DNA screening of all the workers in a factory where a woman has been murdered. What becomes of their DNA samples? How will donor privacy rights be protected?
- A dairy farm family considers injecting their cows with a drug that increases milk production. Is biotech farming a good idea or not?
- And what about biotechnological solutions in medicine? The last case asks whether a doctor should prescribe treatment with human growth hormone for a child, who will otherwise be much shorter at maturity than his parents.

All or part of this document may be useful to researchers and clinicians looking for accessible explanations of conditions, therapies, and research projects to share with patients or human subjects who are seeking supplemental information.

Raymond DeVries and Janardan Subedi. 1998. *Bioethics and Society: Constructing the Ethical Enterprise*, 1st ed. New York: Prentice-Hall.

This reader, appropriate for a medical ethics or medical sociology course, is organized in four sections: Part One contains four essays on historical sources of concern with ethics in research and medicine, and the second part examines institutional mechanisms and conflicts, both in the U.S. and in other societies. Part Three, "Doing Bioethics," considers how ethical decisions are made and the economic and social changes that affect that process. Part Four and the afterword by Renee Fox and Raymond DeVries look at bioethics in relationship to sociology.

Bioethical Dilemmas—How Would You Decide?

The following case studies are two of eleven compiled to date with contributions from several sources including federal laboratories, academic institutions, and private organizations. The collection was prepared by the DOE Working Group on Human Subjects Protection in Research under the direction of Dr. Susan Rose, Program Manager, Human Subjects Protection Program, Office of Health and Environmental Research.

The goal of these case studies is to develop a simple "user-friendly" way to enhance the understanding of the application of regulations for protection of human subjects in research. The studies can be used by principal investigators, research and contract administrators, Institutional Review Boards, and perhaps even by the news media and general public, both as a guide to good practices and as an educational tool.

The short vignettes provide some insight into the wide variety of circumstances encountered in the protection of human subjects in research. The decisions reached in each case study are not "definitive," that is, they are not absolute— other equally acceptable decisions may be reached by other organizations.

If you have faced similar dilemmas in your organization, please consider sharing your experience and the outcome with the Working Group so that your case study can be included in a future newsletter (you can e-mail your information to either Charles Pietri at cpietri@aol.com, or Lisa Carroll at carrolle@orau.gov; or you can fax it to Lisa at 423-576-9384). Note that identifying language is removed from these cases before they are disseminated.

The decisions made by the IRBs in response to each dilemma are given at the end of each case. But before you look, take a minute to think how *you* believe the question should have been resolved.

Case Study 1. No Scientific Merit, No Study

Description of issue: A researcher at a government agency laboratory proposed to use a small amount of funding to support a graduate student performing research in a related area. Under the agency's policy, the research, which was already approved at the student's university, also became subject to the review process at the agency's facility. Because the study had prior approval at another institution and involved survey research, it was initially submitted to the IRB for exemption from further review. The IRB administrator and the chairman briefly reviewed the project and found it *not* eligible for exemption for two reasons:

1. the subject population (paroled perpetrators of violent crime and their victims) was a sensitive issue and might even be judged vulnerable by the full IRB; and
2. the questions dealt with the subject's perceptions of violent crime and suitable punishment.

In the latter instance, the subjects' responses could be an upsetting subject for victims and could conceivably be used against the parolee subjects should they become known. The fact of prior review was irrelevant.

Both the research administrator and chair were concerned by the lack of peer review, which raised questions about the scientific merit of the study. The student informed the IRB that the study would not be possible without the agency's funding, meaning that denial by the facility would force cancellation of the research.

Bioethical options: The IRB at this facility does not routinely consider review of scientific merit to fall within their purview. They do, however, consider the effect of scientific merit on the benefit aspect of the risk-benefit ratio when the research is considered to be of greater than minimal risk. The IRB further distinguishes between benefit to the subjects personally and benefit to society as a whole in their considerations of the risk-benefit ratio.

Continued on page 16

Prepared by Charles Pietri, consultant and former science program manager, U.S. DOE, Chicago Operations Office

Continued from page 15

In this study, there were two options depending on the perceived vulnerability of the subjects and the risks of participation:

Vulnerability of subjects: Although neither population (victims and their families or parolees) fall into the classic definitions of 10 CFR 745.46.111(a)(7), they might still be found by the IRB to be "likely to be vulnerable to coercion or undue influence." Additional safeguards might then be required to protect the rights and welfare of the subjects (e.g., a certificate of confidentiality to protect the parolees' attitudes on crime and punishment from subpoena by law enforcement officials).

Risk: Is the study of greater than minimal risk? If yes, then the IRB would weigh the expected benefit of the research against the risk. Since faulty design impairs the benefit, the study might be disapproved unless design could be modified to either reduce the risk or improve the benefit – or ideally both. If the research were found to be of minimal risk, the IRB would still consider whether the risk is as low as possible and may recommend ways to reduce the risk (e.g., the certificate of confidentiality).

Decision made: Human subjects review at the facility requires that initial submissions be co-signed by the division director or group leader of the researcher. The signature signifies that the research has been reviewed by the division and found compatible with the research mission of the institution. In this case, no formal submission through the divisional process had been made. It was therefore requested that the facility sponsor of the study provide the study to the facility IRB as the researcher with co-signature from the division director.

The division director subsequently approved the study as appropriate to the university's mission.

The IRB at the home institution of the student did not find any of the subject populations to be vulnerable under 10 CFR 745.46.111 and approved the research at a full board review. Whether or not peer review or scientific merit was included in the review is not known. A number of precautions to reduce the risk to victims were already included in the protocol, but the student researcher was advised by the facility human subjects staff to reduce risks to parolees by seeking a certificate of confidentiality.

The facility IRB did not approve the study for the following reasons:

- Although the perceived vulnerability of the subjects and the risks of participation could be adequately addressed, there was not indication of a peer review to validate the scientific merit of the study.
- Although the researcher's division director approved the study as appropriate to the *mission* of the institution, such approval did not, and was not intended to, constitute scientific peer review.
- Although the student's home institution IRB had approved the study, there was no evidence that peer review had taken place.

Case Study 2. Informed Consent in Genetic Investigation

Description of issue: A laboratory holding a Department of Health and Human Services Multiple Project Assurance received a request from an investigator who wished to do additional genetic research on blood samples he had received four years earlier. These samples were from healthy people who had no exposure to ionizing radiation. The samples included blood taken from the umbilical cords of newborn infants at a local hospital. The investigator now wanted to extend his research because of advances in genetic research. In his new research he requested permission to ask people who had donated to his first experiment to donate fresh blood for continued experimentation. He also wanted permission to use the old samples of people who could not be located.

He was not requesting permission to obtain repeat blood samples from any of the cord blood sample children, who would have been 4 years old at the time of his second request.

He also asked permission to obtain blood samples from 65 new donors all of whom are employees or retirees of the laboratory. Finally, he desired clearance to ask the local hospital to provide 75 new cord blood samples from newborns whose parents were willing to have the cord blood of their babies used for the experiment.

The following concerns became evident during the review of this proposal by the IRB:

- The investigator was to do *new* genetic testing on old material without receiving informed consent for new testing. The fact that the donors could not be located seemed to provide adequate confidentiality to allow the testing to proceed. If the donors could not be found, then would it matter if their material was used again in additional tests?
- The IRB was concerned about the impact of the results derived from this additional genetic testing on the parents of the babies. Since the testing could determine whether the legal mother and father were the real parents of the child, should the investigator tell parents of any "discrepancy" the testing revealed? Should the investigator report to the parents results of the testing, such as a tendency toward breast cancer even when such findings were still in many ways speculative? Did the parents have a right to those findings?
- How much information about risk should the IRB place in the consent forms for both adult donors and parents of newborns? Should it reveal that it could not offer an absolute guarantee of confidentiality, but only a very highly probable guarantee? Should it make clear that there was a minimal risk of some present or future employer or health insurance company demanding or somehow receiving the results and acting in ways that were not in the donor's best interests?

Bioethical options: The IRB could request that the investigator receive full, new informed consent, detailing every risk, however unlikely from any donor of old or new material. Donors who could not be located would not have their samples used in any further experimentation. Moreover, it could request that all donors and parents of newborn donors be given the option to receive any or all of the information about outcomes of their tests.

Alternatively, the IRB could consider that participants in the original experiment who could not be located were, de facto, adequately protected by this anonymity and, thus, give the investigator the approval to use these samples in new testing. Furthermore, it could consider that the consent to the first test was adequate consent to genetic testing in the second test, giving the investigator permission to test samples without a full, new consent form being required. All new donors would be given new consent forms detailing all of the risks of genetic testing including hypothetical future risks.

Decision made: The IRB decided that the investigator had to obtain full, new informed consent from all donors, past (when available) and present, for the use of their blood samples. All donors were given the option of knowing the results of their testing after being informed of the risks of knowing these results (e.g., "the baby isn't mine," "I have a tendency toward a certain fatal disease," etc.). The IRB also decided that samples of persons who could not be located from the first test could be used stripped of all identifiers.

Protecting Human Subjects

This bulletin is designed to facilitate communication among those involved in human subjects research and to inform persons interested in human subjects research activities.

DOE Human Research Subjects Program Manager
Dr. Susan L. Rose

Editors
Lisa Carroll
Linda Sharp

Graphic Designers
Mark Longmire
Julie Malicoat

This bulletin is available at no cost to individuals interested or involved in human subjects research at DOE. Please send name and complete address (printed or typed) to the address below. Please indicate whether information is to (1) add new subscriber, (2) change name/address, or (3) remove name from mailing list. Enclose a business card, if possible.

Send suggestions, contributions, and subscription information to—

Dr. Susan L. Rose
Office of Biological & Environmental Research
ER-72
U.S. Department of Energy
19901 Germantown Rd.
Germantown, MD
20874-1290
FAX (301) 903-8521

UNITED STATES
DEPARTMENT OF ENERGY
Office of Energy Research/ ER-72
Germantown, MD 20874-1290