Responsible conduct of research:  
A view from America  

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Abstract: With the definition of "brain death" in 1968, and the many refinements in interpretations of the beginning of life, it is clear that biomedical research has contributed to the redefinition of birth and death, the "bookends" of life. Developments in the Human Genome Project, cloning, and human embryonic stem cell research increase the complexity. It is no wonder that these changes are disturbing to ordinary people. They threaten traditional values, and increasingly involve government officials in setting or limiting the scientific research agenda. In this context, it is more important than ever that fundamental research is trustworthy. American universities, governmental agencies, and professional organizations have undertaken formal programs to instruct and guide future scientists about the responsible conduct of research and about ethical dilemmas that may arise from their work. This paper will describe the programs, which include discussions of interpersonal relations in the laboratory, conflict of interest, the challenges of collaborative efforts (often interdisciplin ary and cross cultural), and the honest conduct and publication of research, as well as basic issues facing scientists today.
With the definition of "brain death" in 1968, and the many refinements in interpretations of the beginning of life, it is clear that biomedical research has contributed to the redefinition of birth and death, the "bookends" of life. Developments in the Human Genome Project, cloning, and human embryonic stem cell research increase the complexity. It is no wonder that these changes are disturbing to ordinary people. They threaten traditional values, and increasingly involve government officials in setting or limiting the scientific research agenda. In this context, it is more important than ever that fundamental research is trustworthy. American universities, governmental agencies, and professional organizations have undertaken formal programs to instruct and guide future scientists about the responsible conduct of research and about ethical dilemmas that may arise from their work. This paper will describe the programs, which include discussions of interpersonal relations in the laboratory, conflict of interest, the challenges of collaborative efforts (often interdisciplinary and cross cultural), and the honest conduct and publication of research, as well as basic issues facing scientists today.

Introduction

In the United States today there are vigorous efforts to address ethical issues associated with research in the life sciences. The diversity, complexity and interrelatedness of these problems staggers the mind. I have given you a handout that reflects the range and specificity of current ethical quandaries associated with research in the life sciences. They include theoretically simple issues: "Do not lie, cheat or steal!"; and manifestly complex ones: "In what respects does a living cell monoculture differ from an, as yet, undifferentiated cell cluster derived from nuclear transplantation or stem cells?" Hundreds of problems of less (but sufficient) complexity lie between these extremes.

We, in America have an appetite for identifying and worrying over bioethical dilemmas. What accounts for this interest? How are its goals defined? What chance do we have of achieving outcomes that justify these efforts?
It could be that our history of ethical failures (e.g. Tuskegee experiments in which elderly black syphilitic men were not given drugs so that doctors could study the unmedicated history of the disease). Similarly, experiments using radioactive isotopes in misguided medical treatments) has heightened our awareness of human fallibility. It could be a fixation on social and political process that makes it much more difficult to arrive at conclusions in our heterogeneous and opinionated culture.

It could be because, as a nation, we tend to look for trouble, often in the naïve belief that we can provide solutions. Sometimes we strive for answers even before the problems are widely known. Other reasons suggest themselves: the large federal budget for health-related research (and resultant Congressional oversight); democratic traditions that encourage public participation and debate even in technical matters; journalistic interest in scientific scandals; public safety and fear of the unknown in potential scientific dangers.

Non-scientist members of the public now serve on several NIH grant evaluation panels. Vociferous opponents to scientific research have forced scientific organizations to respond and proactively explain and defend the rationale for research programs. The Human Genome Project has a section devoted to the Ethical Legal and Social Impacts of its work.

I shall describe three streams of influence that contributed to the interest that now manifests itself in lively institutional responses. They are:

- 1. Protection of Human Subjects in Medical Research (Medical ethics into bioethics into research ethics.)
- 2. Scientists’ Self-Regulation; Recombinant DNA Moratorium
- 3. Dishonest Research Scandals (untrustworthy practices)

Each of these streams generated periods of intense critical interest that attracted the attention of doctors and scientists, and then to governmental responses; and later as they became part of the cultural landscape, faded from direct public attention. Government interest has on occasion been unnecessarily intrusive and burdensome as scientists were called to testify before Congress, serve on panels of inquiry and conform to rules and regulations that limit the autonomy that scientists believe is necessary to their work. Nonprofessional interests, especially religious interests, have played a significant role and influenced decisions to limit the sphere of scientific investigations.

*Protection of Human Research Subjects. Medical Ethics. Bioethics*
Medical ethics, deeply engrained in the practice of medicine traditionally focused on the rights of individual patients. The advent of modern medical research (20th Century) changed the focus from care for single patients to considerations of how medical knowledge gathered from many individuals could serve the interests of other sick people, now and in the future. Horrifying instances of mistreatment allegedly in the interest of science led to the Nuremberg Code, the Helsinki Code, the US Presidents Commission and enriched medical ethics to include protecting the needs of human (and other animal) research subjects.

Research conducted to test the safety and efficacy of drugs and medical devices, also expanded the scope of interest in medical ethics. Protecting human subjects led to the establishment of Institutional Review Boards (IRBs) which required the participation of non-scientists.

As compelling as these issues of traditional bioethics were, they did not command the attention of most scientists conducting basic research. There were few course offerings in American universities

*Scientists' Self-Regulation: Recombinant DNA, Promise and Hazards*

Another source of interest in the ethics of scientific research stemmed from the development of controlled genetic engineering experiments in the early 1970s. The prompt actions of scientists to verify the safety of these research procedures resulted in a self-imposed moratorium on recombinant DNA experiments until any potential hazards could be addressed and resolved. In 1975, an International Conference on Recombinant DNA was held at the Asilomar State Park in California to recommend controls that would protect against laboratory hazards. Instead of reassuring the public that scientists were mindful of dangers and would protect the public, these actions attracted public attention and protests in several university towns (including Cambridge and Princeton.) The NIH controls resulted in oversight by the Recombinant DNA Advisory Committee (known as RAC). As fail-safe techniques were developed the RAC was kept in place, but in 1978 and 1980 revisions weakened the controls. The safety issue has largely disappeared as a matter of public concern in the United States, but it (safety) provided a platform for public interest and another precedent for public participation in science policy.

It can also be argued, however, that the focus on public safety preempted concerns about larger and more subtle ethical issues, issues that have become more vivid and compelling since the cloning of Dolly and the controversies about the utilization of human (embryonic) stem cells, another complicated facet of reproductive technologies.
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**Research Misconduct. Untrustworthy Research Practices**

Prior to 1980, reported instances of research fraud were rare. Only the "painted mouse" of Dr. William Summerlin had drawn public attention as it made the front page of the New York Times in 1975. Although many scientists knew of one or two cases of suspected dishonesty in research, these situations were handled secretly within the institutions where they occurred, and most often the perpetrator was allowed to leave quietly. The fewer questions asked, the better! In the summer of 1980 that changed, with the disclosure of four cases (Alsabti, Long, Soman, and Straus) of dishonest research. The publicity and the eminence of the institutions at which they occurred (Yale, Columbia) initiated a spate of public interest, of other allegations, and eventually of (US) Congressional hearings, court cases, prosecutions (and some exonerations), and significant and diverse efforts at reform within the research community. The Congressional hearings were largely conducted under two themes (1) waste, fraud and abuse (squandering public money) and (2) public health, and safety (e.g. "Are Scientific Misconduct and Conflicts of Interest Harmful to Our Health?"). It also became clear that when high-profile scientists (such as Noble Prize winner, David Baltimore, and Robert Gallo, who claimed to have discovered the AIDS virus) were accused, Congressmen could get favorable publicity as effective "watchdogs" of the public interest.

Independent professional organizations, and research institutions focused on the responsibility of scientists. [A list of some of the initiatives and their publications is attached.] They were certainly mindful of the NIH as the source of most financial support for biomedical research.

**(US) Government Responses**

In each of the three illustrative streams, government agencies or legislative bodies entered the discussions alleging that there was a need for official oversight because some doctors, or scientists, were not meeting their professional responsibilities. The most frequent justifications were those of public safety, and those of waste, fraud, and abuse.

In all cases there were arguments and evidence that risks needed to be controlled by someone other than those who benefited from public funding. There was an implicit, and sometimes an explicit mistrust of professionalscientists. In the US government most frequently
influences the course of events by investigation and regulation. (Regulation can precede legislation.) But a case has always to be made that the people currently in charge (scientists and doctors) are unwilling or unable to conduct their affairs in a responsible manner. We are currently witnessing government oversight of financial markets (also growing out of a parallel mistrust of professionals) that are reminiscent of the investigations of scientists in the 1980s.

Once government agencies or the US Congress are alerted, there is a concerted effort on the part of the target group to detect and clean up any problems before the official scrutiny ruins the enterprise with draconic reform measures.

In the case of scientific misconduct, it almost seemed like a contest between professional organizations and universities to preempt the moral high ground. There is little doubt that government actions and bad publicity got the attention of most scientists. Investigations and prosecutions failed to improve the laboratory practices, but they drew attention to negligent and opportunistic practices.

In 1989, and again in 1990, the NIH Guide for Grants and Contracts announced a requirement that all applications for National Research Service Award (NRSA) Research Training Grants include a description of a "program to provide instruction in the responsible conduct of research." The requirement was honored in many different ways, from single lectures to full course requirements. In 1994, the requirement was reinforced with the following language: "Applications without plans for instruction in the responsible conduct of research will be considered incomplete and will be returned to the applicant without review." The NRSA offered the following guidance: "Although the NIH will not establish specific curriculum or format requirements, all programs are strongly encouraged to consider instruction in the following areas: conflict of interest, responsible authorship, policies for handling misconduct, policies regarding the use of human and animal subjects, and data management."¹

**Challenges**

Students prefer to be conducting research. Their supervisors concur.

Professors do not want to teach research ethics. Philosophers typically disdain "applied" ethics. The cadre of potential teachers was not obvious.

Bioethics had dealt with a limited number of complex individual cases, but not with issues raised in fundamental expectations of scientific research. Those lessons were supposed to be taught by PI's, but they themselves had not often been trained to think about those issues.

It is difficult to engage students in discussions of philosophical issues when they are reluctant or unwilling to read basic texts. There were usually no teeth in the requirements. Teaching had to be more persuasion/ seduction.

Genetic engineering is not just a national issue: gene therapy that results in germ cell alterations will affect the heritage of the human race.

The complexity of living systems

The mandate requires instruction in the responsible conduct of research and does not refer to "ethics" or "bioethics" per se. I believe that is because scientists have traditionally believed that science is ethically neutral. The pursuit of knowledge is considered to be good. Scientists enjoyed the luxury of regarding the misuse or unanticipated adverse consequences as not their fault. And yet the Chairman of our department refers informally to our course as "the ethics course."

Princeton Course

I was invited to teach such a course at Princeton in collaboration with a series of principal investigators from the department.

The content of our course was initially developed by three molecular biologists (including the Chairman of the Department and the Director of Graduate Studies) and myself. We agreed that the instruction should be directed primarily toward fostering sound professional behavior, not toward the improvement of character. We decided on a course of six lectures, approximately half a semester, in the period just after their formal scientific course work, when they were beginning their independent research.

Topics were chosen to help students become better scientists (i.e. to adhere to professional standards) (using what are now called "best practices"), not better human beings. Much of what governs professional behavior in research has developed informally in an apprentice system and scientists resist codification of the implicit values and norms that they feel have served them well.

With the internationalization of science and collaborations across disciplinary boundaries, however, there are many opportunities for misunderstanding and disagreement.

We initially focused on ethical issues that were a direct result of the controversies growing out of research falsification and Congressional inquiries into matters of public safety, conflict of interest and waste fraud and abuse. The course was divided into six units:

- Review of public interest in science and financial support for research. Because this course was the result of Congressional pressure on the National Institutes of Health (NIH), we began by considering why the public supports research, and the mechanisms for allocating research funds in
the United States. We questioned whether those who pay for research should be able to influence the research agenda and examined the rationale for "investigator-initiated" research programs. Faculty members who have served on NIH panels provided a detailed review of the grant application, evaluation and funding procedures at the National Institutes of Health.

- Examination of the principles of intellectual property, and its protection in law and tradition (custom), including copyrights, and patents. We discussed specific intellectual property issues that arise in proposing, conducting and reporting research in scientific journals. These issues led naturally to considerations of confidentiality in the review process of awarding grants and contracts and in decisions with regard to publication.

- Dissemination of scientific information, publication in scientific journals. Publication is a necessary step in maintaining scientific community, in furthering scientific progress, and in manifesting the work-product resulting from public financial support. Because it is so important to professional advancement, and because authorship of scientific articles is often a contentious area, one that challenges mature as well as young scientists. The criteria for granting authorship in collaborative efforts had not been codified in 1990; they differed from specialty to specialty, and even from institution to institution. As collaborative research became more and more important, the number of authors on each paper grew, and disputes arose about who should be an author, and the order of authorship. The International Committee of Medical Journal Editors addressed this issue, and there is now more agreement on standards, but it is by no means universal. Discussions of the problems and benefits of collaboration, secrecy and protectionism, and openness in scientific exchanges of information and biological materials. Collaboration takes place within laboratories, between different departments in the same university, and with scientists in other institutions, disciplines and countries.

- Authorship: Research misconduct: how to recognize it and avoid it. Falsification, fabrication and plagiarism in proposing conducting and reporting research.

- Misconduct is the term now officially used to describe research that is dishonest or deliberately misleading. Although critics think the term trivializes the worst offense scientists can commit, it was chosen after many days of conferences and committees. Even today, after years of wrangling, the definitions of "misconduct" are neither uniform (across federal agencies) nor fundamentally agreed upon by all scientists. Three instances of dishonest research were discovered and disclosed in the summer of 1980. Two were cases of plagiarism and one was a situation in which the scientist made up his data and then altered his notebooks to cover up the lie. This was followed by a decade in which there were accusations against many well-known biomedical scientists, many of whom worked at our most prestigious universities. In France you
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may be familiar with accusations against Robert Gallo whose work on isolation of the AIDS/SIDA virus drew heavily on that of Dr. Luc Montagnier at the Pasteur Institute.

- Reciprocal obligations of senior scientists as mentors and students as apprentices.

Moral theory

Our hopes for the course Integrity in the Practice of Molecular Biology are that it will familiarize future scientists with attitudes that include the ethical impact of their research should it succeed, and give them skills in practical reasoning about the right course of action.

As the issues become more complex and more consequential, we came to believe that the language of "rights" and "choice" that so often have characterized medical ethics must yield to a broader perspective: that of the welfare of communities and the future of human kind.

Evaluation of RCR Courses

There have been several studies of the effectiveness of programs in the Responsible Conduct of Research (RCR). They touch on changes in attitude and practices. For whatever reason, the initial studies of the earliest programs did not show noticeable effects in any of the measured parameters. It became clear that lectures, and case studies were not convincing.

Evaluation of Princeton Course

In the first year we failed to realize our goals: students seemed not to learn very much; they were "turned off" largely because they resented the loss of time in the laboratory. Alas, this mirrored our early experience at Princeton. Young scientists are apt to regard any distraction from their laboratory work as an intrusion and are not likely to think that philosophical explorations will aid their scientific work. After several years of frustrating experience we changed the content of the course, and put the burden of classroom discussion on the students themselves. Postig that the most effective entry points would be when they could see clear danger to their own research program, we used techniques that highlighted the risks and disruptions associated with misconduct, authorship disputes, sloppy data management, and laboratory unrest. In order to transfer responsibility for discussions to the students, we required that all students participate as a leaders for a chosen topic; faculty met with the students (often on several hour-long occasions) to steer them to sources of information, help them shape their arguments, and above all teach them how to engage every member of the class in each discussion.

We minimized issues of "right and wrong" and shifted the emphasis to choice of action: "What would you do in a particular situation? " "How would you choose among the following
"What would be the consequences of various courses of action?" "If this situation "sucks" (to use the students' word) how would you change it?"

However the most significant change in our efforts at Princeton, and in universities around the country has been that we have undertaken in including discussion of the social legal and ethical consequences of reproductive technologies, cloning and stem cells (human embryonic and other.).

In the future these research opportunities and their attendant problems will bring public sentiment and public discourse closer than ever to the heart of the research enterprise in molecular biology. We have been dealing for some time with the consequences of commercialization, but now the issues are closer to the definition of life itself and the very nature of human beings, as it becomes possible to change the genetic heritage of future generations.

We did not intend, and will never succeed in making natural scientists into philosophers, historian, or ethicists. Arguably it would not be in the best interests of society to do so. However, these courses of instructions in Responsible Conduct of Research and the social consequences thereof have made vast numbers of young scientists more amenable to participate in interdisciplinary and public discussions of the consequences of the work they do.

We now measure our success by the amount of time students discuss the issues after the class is over, standing out in the hall. Our course evaluations within the university have improved, and we look forward to the comprehensive review planned by the NIH. A contract for evaluating the effectiveness of programs nation-wide has just been let; initial stages are underway, and results are expected in the next few years.

Meanwhile, approximately 16,000 research training positions are funded every year in xxx research institutions/ settings. Budget of $600 million. Formal instruction in the responsible conduct of research (RCR) is given not only to these individuals, but to their fellow trainees. The faculty members who teach these courses have, in turn, studied significant issues from Bioethics, as it grew out of medical ethics was originally focused on the protection of patients in life and death situations, on human and animal research subjects; environmental ethics on protection of natural resources, and on safety issues such as risk to persons and the environment growing out of recombinant DNA research.

These programs have contributed to the establishment of a cadre of active scientific investigators who are willing and prepared to discuss ethical aspects of their work with an increasingly interested public.