

Welcoming Remarks

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Welcome to this conference on "Research Integrity: A Professional, Ethical, and Social Obligation." My name is Sandy Hanneman. I am chair of the planning committee for this conference and my role over these next two days is to keep us as close to being on time as is polite and feasible. We have what we hope is an exciting and useful conference, with today's focus being on the professional view of research integrity. We have structured the agenda for today to talk about the ground rules that underlie ethics and biomedical research. Tomorrow's program is a more expansive view. It will look at research from the public's viewpoint.

I would like to particularly welcome those of you who are here from the Midwest and the Northeast. I hope tomorrow we can guarantee you a beautiful spring day with sunshine, but I know that for both days we can guarantee you a temperature at least 50 degrees warmer than where you live. That is an advantage of holding conferences in Houston at any time of the year. We can always guarantee warmth. Without further ado, I would like to introduce Dr. Thomas Burks, who is the Executive Vice President for Research and Academic Affairs at the University of Texas-Houston Health Science Center. Dr. Burks will do a general welcome.

Thomas Burks, Ph.D.

Executive Vice President for Research and Academic Affairs

University of Texas-Houston Health Science Center

Thank you so much, Sandy. Good morning, welcome to all of you. It is my pleasure to welcome you to this conference, to Houston, to the Texas Medical Center, to the University of Texas-Houston Health Science Center, and to the University of Texas-Houston School of Public Health, which is where we are seated. We at the University of Texas-Houston are proud to join in partnership with the United States Public Health Service's Office of Research Integrity and collaborating institutions in the Texas Medical Center - namely, the University of Texas M.D. Anderson Cancer Center, the University of Houston, Texas Woman's University-Houston Center, Texas Southern University, and Prairie View A & M University - in this conference on research integrity.

I want to acknowledge the creativity and organizational skills of Dr. Sandra K. Hanneman, who has done such a good job in understanding the needs for this conference, and the value it will add to our ethical environment, as well as for her thoughtful approach to the structure of our discussion over the next couple of days.

We will enjoy two full days of dialogue about an extremely important aspect of our research environments, including research that is carried out in academic settings, industrial and corporate environments, government laboratories, or wherever research takes place. I think it is important to recognize that we do not generate or participate in conferences about research integrity because we believe that research misconduct is commonplace. It is probably not. Rather, we devote time and energy to conferences such

as this because of the tremendous importance of research and the importance of an accurate, complete, and credible research record.

Our future is based on discovery and application of new knowledge. The health of Americans and people around the world will be affected by the research that we carry out and communicate through the scientific community as well as the research that we apply to the prevention, diagnosis, and treatment of diseases, or optimization of health. There is also, of course, an economic stake as we discover and develop new vaccines, drugs, and devices that will improve health.

We cannot permit our future, even in small ways, to be contaminated by fraudulent data. We cannot confuse the record by misappropriation of intellectual property through plagiarism or other kinds of serious misconduct. We know, or think we know, what constitutes misconduct. But beyond the requirements for truthfulness in science, what specifically are our research ethics? This conference, and others similar to it, will help us think together about these issues, about humans acting human, and about better ways to describe and define research ethics.

Dr. Hanneman and her co-organizers have gathered an impressive amount of brain power together to consider the professional, ethical, and social obligations that require us to ensure integrity in our research. I look forward to lively and productive discussions today and tomorrow. Again, welcome to each of you. We are pleased that you are here, and we look forward to learning from every one of you. Thank you very much.

Dr. Sandra K. Hanneman

The next presenter is Mr. Chris Pascal, who is the Acting Director of the Office of Research Integrity. Chris is going to talk about “Public Health Service Perspective on Scientific Misconduct and Research Integrity.” In the interest of time, please refer to the short biosketch of each of the presenters in the handout so that we can dispense with lengthy introductions.

Chris Pascal, J.D. Acting Director Office of Research Integrity U.S. Public Health Service

Good morning. I want to thank the University of Texas-Houston and the other co-sponsors for putting on this conference. Our office has been looking forward to it.

What are some of our key functions at the Office of Research Integrity (ORI)? One of the primary things I want to cover this morning is the Public Health Service’s definition of scientific misconduct. That is going to be one of the take-home messages I want those not working in this field on a regular basis to learn today. I will talk about handling allegations of misconduct and the breadth of institutional responsibility. Our office does not just deal with scientific misconduct; we also deal with promotion of research integrity. However, institutions have a much larger responsibility than ORI does. They not only deal with Public Health Service (PHS) misconduct, they also deal with a variety of research infractions that do not come under our jurisdiction. You will hear about those today.

Institutions and the federal government both have roles for promoting research integrity. They advocate taking affirmative steps to teach, train, and set standards in the area. I will also talk a little bit about public concerns. I think the concerns of the general public, the concerns of the scientists who never get close to a misconduct allegation, and the concerns of taxpayers are reasons ORI is in existence and why we have conferences of this type.

ORI has a variety of functions. The first is handling misconduct allegations. That involves either ORI getting allegations directly and referring them to the institutions for investigation, or the institutions getting an allegation, doing an inquiry or investigation, and referring the case to ORI. We deal with institutional policies and procedures. How many of you in the audience have ever looked at your institution's policies and procedures on handling misconduct? Maybe half or so. That is really a part of the system that we have in place—for the institution to develop policies and procedures that include the PHS definition and other issues that the institution decides constitute misconduct for that institution. There is a lot of flexibility for the institution to do other things to meet their needs; hence, they establish a process. There are some common processes in the regulations, but many institutions have unique features on how to handle their particular cases and allegations. It is an important part of the system. It is a public document. It is available to everybody in the institution. Some institutions have it on their web sites. Some institutions do a desk-to-desk circulation of the document. The policies and procedures for handling misconduct are important enough for everyone to know.

Regulatory Compliance. We have individual cases of misconduct. We look at each case to see if there is a significant deviation from the regulatory framework.

Whistle Blower Protections. We have a separate requirement to establish protection for the individual who makes a complaint, or an allegation of scientific misconduct. We do not have a regulation as yet on that, but we do have a policy that institutions follow. We think the policy is working reasonably well.

Education and Promotion of Research Integrity. Instead of just going after individual cases of misconduct, ORI is trying to place more emphasis on education and promotion of research integrity. We want to work with institutions and the scientific community to make sure we have a system that is working well all the time. We also want to ensure training of upcoming scientists in ways that maximize research integrity and avoid misconduct.

Legal Proceedings. This is actually a big, albeit not the favorite, part of our workload. We have hearings on scientific misconduct when the respondent, or the accused scientist, asks for it. We have a fair amount of civil litigation. Our office does not reside within a funding agency. In other words, we do not report to the Director of the National Institutes of Health (NIH). We report to the Surgeon General, Dr. Satchell, and ultimately to the Secretary of Health and Human Services.

I want to discuss a case relevant to the hearing process and legal proceedings. How many of you have heard about the recent case at Baylor College of Medicine involving Dr. Angelinis? I know it was reported in the local press. I do not know how extensive that reporting was, but it was also reported in the national press. This case at Baylor College of Medicine involved a former Baylor scientist who had sizeable public health service grants over a period of several years. The grants amounted to several million dollars. He was found to have committed egregious scientific misconduct through a formal legal

proceeding at which he had the right to cross-examine witnesses and so forth. He has been debarred from receiving federal funding for a period of 5 years.

One of the unique features of this case is that Dr. Angelinis tried to sue his accusers and the Baylor College of Medicine for about \$25 million. As you might guess, the Baylor scientists who worked on this case also were named in the suit. This got a lot of attention from the scientific community. Scientists were concerned about their personal liability. Research institutions in general have become concerned about getting scientists to work with them on these investigations. Of course, Baylor was concerned about its own liability. The case was settled and dropped after Dr. Angelinis lost the legal proceeding. We want to commend Baylor College of Medicine for the amount of effort they put into this case. Such cases do not happen frequently, but institutions with a lot of funding-- the top 20-- have more cases. We do have some institutions unfortunate enough to get one just about every year.

The Definition of Misconduct

The ORI definition shown on the overhead is a rather long definition. The key parts of the definition are fabrication, falsification, and plagiarism for proposing, conducting, and reporting research. Fabrication, falsification, and plagiarism apply to proposing research, which occurs in grant applications; conducting research, which occurs in the laboratory or in a clinical trial; or reporting research, which occurs in publications and abstracts. Fabrication of data does not have to be published, to be considered misconduct; one could fabricate data in conducting research even if the data were not published. Institutions will find, and ORI will find, misconduct in those cases, as well. If an institution has an issue and is unsure as to whether or not it is misconduct, someone from the institution can call us and discuss it with us.

This afternoon you will hear more about authorship credit disputes, which are not considered by ORI to be scientific misconduct issues. People complain to us all the time about authorship issues: "I should have been the first author." "I was third author." "I was left off the paper," and so on. We know the scientist thinks this is very serious. We understand authorship issues affect scientific careers. However, disputes over authorship with collaborators do not constitute misconduct within the ORI definition.

Public Health Service Jurisdiction

A large number of allegations that we get every year do not fall under the ORI definition of misconduct. Institutions may find misconduct under institutional policy and may sanction the individual. When the institution refers the case to ORI, we may find that it does not meet our definition of misconduct. If you think the allegation falls within our definition, then you should report it to us. However, many allegations of misconduct that do not fall under the ORI definition will be covered under individual institutional policies, which are broader in scope. For ORI to be involved when our definition of misconduct is met, the case has to either involve a grant funded with PHS funds or a proposal for PHS funds. If scientists commit fraud in an application and try to withdraw the application after misconduct has been alleged, they will not get away with it. Submission of a proposal is considered to be under ORI jurisdiction.

Investigation and Resolution of Allegations.

The institution has primary responsibility for investigating an allegation and deciding whether or not misconduct exists. When whistle-blowers come to us directly, ORI initiates

the investigation. We will have peer review with NIH to investigate plagiarism in a grant application. NIH will report that to us. We will go back to the institution where the research was conducted, or from which the proposal came, and ask them to handle the allegation. In practice, the institution conducts 95% of the investigations and inquiries in which we are involved.

Often a situation will be unique, such as a multi-site clinical trial. Even in those cases we often work with the lead institutions. ORI does have authority to conduct its own investigations. We do that occasionally. More frequently, we do an extensive oversight of the institutional investigation. Some cases are relatively straightforward and quickly resolved. In other cases, such as the Angelinis case, we knew we had a case that would be litigated. We took many months to review all the documents and to interview the witnesses. That is not the norm. Every year we have at least one or two big cases that require a very extensive review.

The checks and balances protect the scientist to the extent that we occasionally decide not to accept an institution's findings of misconduct. Such a decision is not a reversal of the institution's findings because the institution, as the employer, has its own plenary authority that can find misconduct under its own standards and definitions. It means that we will not go forward with the PHS investigation of misconduct, nor will we penalize the scientist based on the institution's finding of misconduct. We will not publish it in the *Federal Register* and it will not, therefore, receive national publicity.

Final Case Resolution.

If we find scientific misconduct, we notify the accused scientist that we believe scientific misconduct has occurred. In 90% of the cases, we agree to a written settlement with the scientist, just like you would in other sources of litigation where the respondent would sign a document acknowledging certain actions. There may be a finding of misconduct, and sanctions may be imposed. Sometimes there is debarment from receiving federal funds, and sometimes there is a lesser sanction, such as special supervision. In 10% of the cases, we cannot do that. We will send a formal notice to the respondent. This document can sometimes be 40 to 50 pages. It lays out all the facts of the incident. The respondent has a right to a formal legal appeal. The process is similar to any civil case tried in the United States.

If ORI finds no misconduct, then we issue a report to a legal office saying that we have looked at the institution's investigation and their findings and we find that no misconduct has occurred. A copy goes to the institution. The institution is asked to notify the accused scientist and the whistle-blower, and the case is closed.

It is important to note that the confidentiality is handled differently based on the finding. If it is not a misconduct finding, the case will remain confidential. We will not publicize it. We have gone to court before and have successfully protected the confidentiality of information. If it is a misconduct finding, we publicize the case widely. We put it in the *Federal Register*, and tell the accused scientist that we are doing it. Publicity accomplishes two things: (1) It helps us implement the PHS sanctions that require the institution employing the individual to know the requirements, and (2) helps institutions avoid hiring somebody with a misconduct finding.

I am going to talk a little about the research integrity continuum. Once again, I am referring to the broad authority of the institution. The institution has responsibility for all

ethical issues, for the public accountability. The institutional definition of misconduct can be much broader than that found in the PHS. Examples of questionable research practices are authorship disputes, proper collection and storage of data, and such supervisory issues as a laboratory chief mismanaging the laboratory. The institution handles these issues, not ORI. As a part of responsible research practices, institutions need to look at their practices and training of research personnel. All of this is important. Do not think of scientific misconduct in isolation. It is part of a continuum of issues that deal with research integrity.

ORI does not consider record keeping methods to be a part of the definition of scientific misconduct. Falsification has appeared in some of our cases. In one case there was no evidence that the laboratory chief intended to falsify, and we did not find scientific misconduct. However, accurate and auditable record keeping is a practice the institution and the laboratory should ensure.

There are some positive measures the institution can take. One provision, for example, in the PHS regulations basically says that institutions should take steps to promote research integrity for all of its research. This provision is a reminder to the institution that research integrity and prevention of misconduct are their responsibilities. Many institutions have fairly elaborate policies and standards that tell their faculty, their students, and their postdoctoral candidates what to do to maintain the data, handle authorship issues, and collaborate. Some institutions even put the information on their web page to make it easily accessible.

Responsible Conduct of Research.

There is a requirement in training grants to teach the trainees--postdoctoral candidates, students, and fellows--responsible research practices. The important element is to get all the institutions to focus on this. Other institutions have gone a step or two beyond that. I was invited to Los Angeles to speak at an institution that requires all research staff to attend an annual session on research ethics. Other institutions have research training classes and programs that are open to the entire faculty.

Alternative Dispute Resolution

Many issues facing our research institutions do not qualify as scientific misconduct. Thus, many institutions have set up systems, such as an ombudsman, to try to address issues preventatively. Such a system is particularly useful for junior faculty and newcomers who may feel they do not have enough seniority to raise issues. It is very helpful to provide a means for scientists to receive assistance when they think they are being treated unfairly or when there is a dispute. We encourage establishing a climate in the institution that promotes research integrity.

We have a number of cases dealing with clinical issues. One advantage of using cases is to emphasize the issues with respect to the general public. One of our cases involved a breast cancer treatment trial in Montreal, Canada. It was a local reporting site engaged in a very extensive fabrication of research record keeping and fabrication of data in the medical chart. It involved alternative treatments, such as mastectomy versus lumpectomy. Women's groups, patients, and human subjects groups raised questions about the treatment, i.e., choices they made, doctors' recommendations, decisions people might make in the future. We announced that the data were published and there was no reason for alarm. We also advised that the findings in the clinical trials were still valid and robust. It alerted us that the public has a right to know about investigations and findings. That

particular case got a lot of publicity. One of our primary missions is to maintain the public confidence, the quality of research, and research outcomes. When you choose a new therapy or drug, you want to know that what your doctor advises and what you read in the magazines is true and accurate. These are important issues and will be discussed over the next few days.

Lastly, we in the ORI are available to handle questions. We are using the Internet to put most of our publications on our website where we are also supplying new information to supplement our newsletter. We are available, if you are interested, for workshops or conferences at your institutions; just call the Division of Policy and Education. So, if you have an allegation of misconduct and you are not sure how to handle it, or if you are having special difficulties, or if your institution just does not have a lot of experience and you need some onsite technical assistance, call the Division of Research of Investigations. On the other hand, if you have a legal issue, such as you are getting sued by the accused because you are conducting an investigation, and your general counsel is concerned about it and may not know the best way to proceed, call our legal staff. We have a lot of experience dealing with these issues. Thank you very much.

Dr. Sandra Hanneman

Thank you Chris. Our next speaker is Dr. Stan Reiser. He is the Griff T. Ross Professor of Humanities and Health Care at the University of Texas-Houston. He is going to talk to us about "Roots and Origins of Scientific Integrity."

Stanley Reiser, M.D., Ph.D.

Griff T. Ross Professor of Humanities & Technology in Health Care University of Texas-Houston Health Science Center

The word "roots" is an interesting phrase. Roots of anything. Some roots are deep; some are shallow. The "roots" of scientific integrity began relatively recently in the biological sciences. The whole ethos of the development of ethics in biological sciences was shaped by a point of view that had great currency from many centuries in science. That view was that the fundamental advancement of science would rest upon the development of quantitative techniques through which the natural world would be elaborated on and discovered.

The view of progress, thus, was embedded in the idea that the more sophisticated the instrument and theories that allowed the development of such quantitative techniques with which to examine the natural world, the greater the speed with which science would advance. This view began in the Renaissance, picked up speed in the 18th Century, and became a pretty good revving engine during the 19th Century. This is where I want to begin my discussion.

Early in the 19th Century, Pierre Louie, a Frenchman, developed a work of great significance for health care, biology, and medicine. At the time that he practiced, the early 19th Century, the theory and treatment of illness was wrapped up in the concept of blood letting. Virtually every disease had a remedy through blood letting. It was the universal panacea. Louie was skeptical about the influence of blood letting in many illnesses. He strove to find a way to test this procedure. He had long been influenced by statistical work

and had become enamored of the idea that numbers count. So he developed what was essentially the first controlled clinical trial. He separated patients with tuberculosis into two groups. One group was treated with the conventional technique, i.e, blood letting. The other was not. As he evaluated the course of the illness, he showed that patients who were treated by blood letting were no better than those who were not. He began to bring an era of over 2000 years of blood letting to an end.

In his papers and his book on the subject, he spoke about what he called a numerical method. His idea was that the only way to true knowledge in medical science was to "count." He was greatly criticized for his work. People said, "Well, how can you really divide any group of people into two groups that are fairly identical? It is impossible. Therefore, your whole method must be wrong." He countered by saying, "It is the very diversity of people that the group method overcomes and uses as its tool. Because when you have large enough groups, the diversity of each person counterbalances the other, and in the end, you have a relative homogeneity."

This idea of counting and dividing patients into counted groups was a signal advance in the biological sciences. It was an early acclamation of the idea that progress in science was fundamentally dependent on the progress in quantitative theoretical methods.

Thirty years later another Frenchman, Claude Bernard, developed a second tool that complimented the quantitative clinical tools that Pierre Louie had developed. This tool was the laboratory. In his work, "An Introduction to the Science of Experimental Medicine," Bernard effectively defined what an experiment is. He was not the first person to discuss experimentation or to do it, but he was the first person to tell us exquisitely and elaborately what the method was. He said essentially an experiment has two components. The first is hypothesis generating. The second is testing the hypothesis. But how do you do that?

There is a lovely phrase--an idea, an image--that one of his assistants, who himself was an acclaimed physiologist, said. It epitomizes the concept of the division between hypothesis generating and the testing of the hypothesis. He said: "When you walk into the laboratory, you deposit your hat and coat on the hat rack and coat rack outside and then you walk into the laboratory. When you finish your experiment, you walk out and put your hat and coat back on." The hat and coat was theory hypothesis generation that is left outside the laboratory door. Once in there, you must be freed of your hypotheses. The whole idea of the development of experimental methods in the laboratory was to develop methods to allow scientists to put at a distance, if not totally isolate, the ideas that led them to the laboratory test of those ideas.

The ability of laboratory medicine to work depended on the ability of the techniques in the laboratory to be objective enough so that the scientist could not impose his or her interest on the findings of the experiment. Thus, by the end of the 19th Century, in the two great parts of the biological sciences--the clinical and the laboratory--important works had established methods that could be used to find knowledge. In the beginning of the 20th Century, in 1900, Karl Pearson, a physicist-mathematician, wrote a wonderful book called The Grammar of Science. In the book he said that: "The scientific person was the person who could purge from his or her mind subjective judgment, and thus apply the scientific method, divorced of persona." That was the objective of Louie, Bernard, and all the great scientists of that generation--development of techniques to purge the subjective from

science so that your personality, interests, imagination, needs, and desires as a human being could be separated from the science you are creating.

Numbers were appealing because they seemed divorced from the emotions and humanity of the scientist. On the wings of these ideas, science entered the 20th Century. It has been a fabulous century for biological sciences; particularly in its first half when many of the ideas we are carrying in the second half were created. We whizzed into the end of the Second World War, which was called the Science War by many, because science essentially won the war. Radar, the A-bomb, penicillin, antimalarials, artificial rubber--all these things made the war effort successful. All these were built on the fabric of science. So we ended the post-World War II era believing that we essentially had achieved a formula through which science could advance. We further believed we were successful at using that formula.

It is at this point that a new phase of scientific creativity emerged. It is here that we encounter the first inkling that quantitative, theoretical procedures and techniques, the engines of scientific advance, were not yet enough. A significant omission threatened the integrity of this wonderful foundation that had been created over the last century and a half. The first inkling that things were not quite right came at the Nuremberg Trials. Here it was discovered that scientists in Nazi Germany had turned science on its head by inducting into the cause of science human subjects who were incapable of giving consent, and on whom horrible inhumane actions were taken in the name of science. This, of course, was an abnormal situation. And people recognized it as such.

As these events came to light, there was very serious discussion at Nuremberg to recommend that humanity abolish human experimentation. Human beings were too fragile and too defenseless to tolerate assaults of science in the laboratory. In the end they decided against such a recommendation. Instead they created a code that bound the human subject in a wall of protection and required of scientists themselves important duties and obligations. This code, the Nuremberg Code with its 10 principles, became a landmark document. It received wide currency in the late 1940s. Its foundation was the concept of requiring consent of the human subject. Indeed, the paragraph that deals with consent is about one-third of the document. It is the very first principle.

It was felt that the scientist should be made responsible for obtaining consent. Scientific consent became the inviolable principle that all human subjects could use when confronted by the scientist. These ideas started to make scientists, at least a little bit, aware that pure technique was not enough to advance science. Some other things had to be dealt with in order for science to advance.

About five years after the Nuremberg Code was introduced in the 1950s, the focus on consent and ethics in human experimentation, while not fading, certainly was eclipsed by an enthusiasm for finding yet more scientific knowledge through conventional techniques. This was accomplished, in part, with the growth and support of the National Institutes of Health, whose budget went from \$75 million in 1948 to double that every five years, virtually until the 1980s.

In the enthusiasm over the possibilities of learning so much, the ethics of human experimentation was not forgotten, although certainly not focused on. However, at least one could say that the first stage of recognizing that more was needed for scientific progress than scientific technique occurred in the period from the Nuremberg Code's

introduction in 1945 to the development of the institutional review board in 1966. The institutional review boards, or IRBs, were established because literature in the early 1960s began to show that the Nuremberg Code was being neglected. There was a frightening increase in the number of cases in the literature where human studies were conducted without the consent of the subjects. The federal government then required human studies and protocols to be evaluated first by a group of independent arbiters who included social scientists. The first stage is this focus on the ethical protection of an individual.

The second stage in the creation of a scientific ethics for biology occurred between 1965 and 1975. Here the focus was not on the individual but on society. It was generated by the great advances being undertaken in genetics. In 1970, Mayor John Belushi of Cambridge, Massachusetts, became frightened that work in Harvard laboratories in recombinant DNA might create organisms that could spread beyond the walls of the laboratory; and, being reconstituted organisms, they might create epidemics that would destroy the population of Cambridge. He banned such research within the confines of Cambridge.

This sent a message to the Cambridge community. It was part of a growing scientific concern that the public was not only worried about what scientists were doing in the laboratory, but that scientists themselves better worry. They questioned whether scientists really understood the possibilities of such contagion. Indeed, they didn't. Some close friends of mine in the scientific community who engaged in genetic research privately admitted that the geneticists were not trained in bacteriology and had no scientific history of understanding the processes of containment. They themselves were amateurs when it came to containing organisms. They, in fact, needed more help.

The Asilomar Conference in California, in the early 1970s, was the engine by which scientists began to debate how to deal with this new technology of recombinant DNA. In the end, they decided there should be a moratorium on certain kinds of experiments that had possibilities of endangering the public good. This was the first authentic moratorium on scientific research in the century. It lasted for several years. In the 1970s they began to see that they had a responsibility to society as well as to the individual.

The next phase in this growth, roughly from 1975 to 1990, involved changing and challenging the framework and procedures of experimental science. The change and challenge came from three directions--from animal rights people, from industrialists, and from the federal government. Peter Singer, in the early 1970s, wrote a very interesting book in which he discussed the ethical issues to be considered in doing experiments with animals. Animal experimentation had been challenged many times in many areas before, particularly in England in the 19th Century. But Peter Singer's work was the first major philosophical work on the subject to define it ethically. He created a dialogue about the ethics of using animals. He made the laboratory scientist think, even though they did not wish to think in this way, about what they were doing to animals.

The second major influence was financial. By the late 1970s, the growth of the NIH, while still spectacular, was not double-digit every 5 years. For the very first time, aside from drugs, industry became interested in the fundamental work of the laboratory, particularly those laboratories conducting work in genetics. Walter Gilbert, the Nobel Prize Laureate in chemistry at Harvard, stirred the scientific community when he left his post as

a tenured professor to create Biogen. This was one of the earliest, privately funded laboratories in science in genetics.

In the late 1970s and early 1980s, there was an explosion of financial interest in biotechnology. It became the darling of Wall Street. Billions of dollars were poured into untested laboratories, and the salary possibilities of laboratory scientists suddenly challenged the capabilities of clinical physicians. The money then, even today, was extraordinary. It raised questions of how science would adapt to a significant outside flow of cash where the source was more interested in profit than science. Would there be a corruption of scientific thinking for the dollar? How would a professor of science in a university relate to being a paid consultant to a private laboratory? What should be an appropriate relationship between funding and quality in science? All of a sudden, these issues became apparent. What is the ethics of this relationship?

The third major challenge came from something that had happened before in science--scientific fraud. In the early 1980s, John Darcy, a Harvard cardiologist, was found to have committed fraud in reporting his experimental work. Darcy did it numerous times in his published papers. There is nothing new about a single scientist being fraudulent. This has happened before. But in this new ethos of investigation in thinking, people asked new kinds of questions, particularly to NIH scientists Ned Netter and Walter Stuart, whose paper itself on the subject was a source of controversy because it was turned down three times.

Stuart, Netter, and others raised the question that if they were co-authors, why didn't they catch the fraud? The question was beyond the artistry of the fraud; rather, it asked whether or not co-authorship had meaning. Was group science really an integrated science? Did people who signed their names to scientific papers without a full understanding and without the knowledge have enough information to generate findings?

What Stuart and Netter wrote was that if scientists themselves could not be a dependable check on each other, which is the traditional way science advances i.e., duplicating each other's experiments to make sure error does not creep into findings, could the public depend on science for truth? The Darcy case raised fundamental issues about the responsibility of scientists to each other, particularly those who are in a relationship of co-authorship. This concern caused consternation throughout the scientific community, particularly toward those who were labeled as co-authors in John Darcy's work. So Stuart and Netter really challenged the integrity of the literature of science itself.

To add to the fuel of this particular situation, and in the context of it, a Nobel Prize winner, David Baltimore, actually had to testify to fraud before a congressional committee on the nature of his experiments. These experiments were funded by NIH. Baltimore did not physically participate in the experiment, but he was an advisor and co-author.

Margo O'Toole, a research assistant to a Tufts' professor, was fired after making public statements that the research itself was fraud. Errors were there. The Tufts' professor would not acknowledge them. This brought the spotlight on Baltimore as the most famous author in the research being conducted. It raised the question to Congress, which funds the NIH, about its activities. Can those in Congress and we the public trust the scientific institutions in this country to perform with truth and honesty the work they are paid to do?

In the context of this whole series of events, the Office of Research Integrity, which began as the Office of Scientific Integrity, was created. This office was not well received

in many quarters. It seemed to have a quasi-inquisitorial dimension. Scientists did not like to feel that their independence might be challenged by bureaucratic officials looking over their shoulders. In the end, the office was accepted as an important part of the same series of advances that the institutional review board represents. It is a public presence looking at things that are necessary to ensure the public interest. How the work was conducted had to be examined over time so that it was helpful. It represented the public's interest in making sure that good science was conducted. The scientific community also began to recognize that if they lost the faith of the public, if their work did not have integrity, then they would lose their support and thus lose science.

An example of how corrupting fraud is to the integrity of science was the fraud previously mentioned that occurred in a laboratory in Canada. The laboratory was part of many clinics doing breast cancer trials. The community of women suffering from breast cancer arose with great consternation and anger. They asked what were they to do, having been treated, if the group doing the research could not be trusted to implement the recommended protocol. It turned out that this particular laboratory's work had little effect on the overall integrity of the lumpectomy procedure being used. But, this situation showed how fragile science is in the face of challenges to its truth and honesty.

The fourth and final dimension of this evolution - - roots growing deeper - - occurred between 1989 and the present. The year 1989 was when NIH required all of its postdoctoral fellows to have experience in the ethics of science. In doing so, it required the institutions of education and training to ascertain ways of educating scientists about the ethics of the science they were doing. This emergence of ethical training in science has created much greater understanding within this institution and much greater knowledge among the scientists themselves about how to deal with the ethics of their work. Thus, the total effect of this event was to illustrate that the progress of science as being solely linked to its technical prowess was wrong. Rather, it showed that science is not merely a technologic endeavor, although technology is important, but that science, in the end, is a human endeavor. You cannot divorce the humanity and "humaneness" of a scientist from the work the scientist is doing. Karl Pearson's effort to purge science of human subjectivity was folly.

We are, and always will be, human. All that we touch reflects our humanness, thereby. Subjectivity is an inevitable dimension of all work, scientific work included. No matter how technically skillful we can be, no matter what instrument we use, if we are not honest about our work, we will corrupt it. Integrity is an effort to do our work well, to do it right, to be honest and truthful about what we do, and to approach our efforts with responsibility. These kinds of teachings are inextricable from quality and excellence. We in science must teach our students to deal with problems that arise and challenge their ethical integrity. If we do not help them to achieve understanding, technique, and a perception about these issues, their ability to be technically skillful and their other abilities will not serve them well.

I believe we have far to go. The basic message has been given to the scientific community. Some may not see why we should spend so much time debating the moral questions of science. Some may not see why it is important to give scientists techniques to evaluate moral questions. Even though they may not appreciate why there is such hub bub, they at least recognize that they cannot avoid the issue. It will take more time to make them

comfortable with the issue. That is part of your job, collectively. The fact that we have a new idea of how to make progress in which the technologic and ethical are linked is an extraordinarily important concept that our successors in the 21st century will elaborate upon.

Thank you. I want to leave some time for questions.

Question:

If the researcher in Montreal had been dispassionate about his research, if he had left his beliefs at the door, and if he had done things as he should have, would they have led to the same conclusions?

Dr. Reiser:

Yes. If the scientist I referred to in the breast cancer study in Montreal had –I don't know what you mean by "leaving it at the door." Do you mean did he leave his morals at the door?

Participant:

If he had done things as he should have...[Tape Inaudible]

Dr. Reiser:

Well, no, of course not. There would not have been a problem if he had done things that he should have. What he did not realize, probably, was that he would get himself into so much trouble by violating ethical canons. That was his problem. He did not realize what he was doing. This was not like the John Darcy case, which was blatant fraud. He was trying to help certain patients and thus changed the way in which the results were given. So this was a kind of benevolent effort to be helpful. Because he was not knowledgeable about the consequences of such behavior, he went ahead. He didn't understand the nature of what he was doing from the point of view of the ethics of what he was doing. That's how he got into trouble.

A John Darcy who deliberately changes results--putting things in that never happened--is doing things from a totally different psychology. You probably cannot do anything about that. One of the things we have to be careful about, in our zeal to prevent the John Darcys from having an effect, is not to neglect other things that are not at the level of fraud but are the essence of understanding the ethics of science.

We have to help our students to not merely avoid fraud but to help them understand fraud. A student may ask: "What are you doing?" Do you really tell him what you are doing? Do you really feel he is going to steal what you are doing? Do you lie to your colleague? How do you conduct yourself when you are working on a paper and the professor wants to put his name first when you did most of the work? How do you deal with being in science and being confronted by ethical problems every day? That is the essence of being scientifically ethical, of teaching our students to cope with all the intrigue that is part of a multibillion-dollar industry. This is what we teach in our courses through

cases, lectures, and readings. This is about a panoply of work. This is about engaging animals, about working in the laboratory in universities and businesses. It is about conflict of interest. It is about owning stock in the company for which you are doing experiments. It is a total range of issues that scientific ethics is all about. It is not just about fraud, as important as that is.

Question:

Could you address the historical roots of integrity and could you address, in the view of your course, the pursuit of integrity and why it goes wrong in science?

Dr. Reiser:

Ethics is about understanding right and wrong and making choices that will direct your action to what is right. The study of ethics will not make a bad person good. It will make someone who is inclined to use any means to get ahead think about the implications of that kind of behavior. It seems to me it is very hard, when you think about these things, to not see good reasons for being different. It becomes clear when you go through cases and think about the ethics that the core of all human relationships is trust. If you don't trust me, you don't trust my papers. That's the end of science.

If the public perceives that the scientist is more interested in making money, is more interested in position than science, willingly disregards certain points because they don't quite click on his theory, and is willing to take actions in order to advance, then the discipline is at an end. If you recognize that, not only from the point of view of professional discipline but your personal life, that your advancement depends on the views of people about your integrity, you are advancing a powerful message. I think that is really what we strive to do in teaching courses in ethics; namely, give people tools to analyze problems and help them cope with the stresses of trying to do the right thing. Virtually everyone wants to do the right thing. The question is: "How do you do the right thing?" "How do you analyze questions in a way that gives you a view of the best possible way to act?" That is what we do when we give courses in ethics. It is important not only for the student but for the faculty to make them feel that in their own work they are exemplifying what is being taught. That is essentially what we try to do. We believe there are shifts of character. Ruth Bulger is conducting a study to see if this is true.

With shifts of character, you are not only getting a better scientist, but you are getting a better person. The idea is not to simply tell the student that in their careers of science you have to be truthful, honest, and ethical. How do you become truthful, honest, and ethical? If we do not teach our students methods and ideas that allow them to become this way, it is the same as saying: "Well, You go into that laboratory and you do your experiment. Do good work. That's the end of my discussion with you. Goodbye!" We spend an enormous amount of energy teaching our science students the techniques of being scientists in the laboratory. How can we not do the same thing ethically and expect them to do it right? It is folly. You need ethics techniques just as you need scientific techniques.

Question:

I would like to ask the question: What do you do about the disjunction? People can be taught to understand the concepts of ethics just as they can be taught to understand the concepts of science and how to do it properly and yet, in their actions because of other modulating forces, perhaps be unethical or do their science improperly. It presents an interesting problem.

Dr. Reiser:

The point is that if you give students the tools of reacting to situations when they are confronted with an ethical conflict, you give them a strategy to use to make the best possible solution to that question.

Follow-up to last question:

Is it a deeper social problem? In the sense that possibly the culture has changed? And by extension ways that may interfere with science and/or ethical conduct.

Dr. Reiser:

I think the culture has tended to reinforce the idea that the public expects integrity and has reinforced the idea that, without proper schooling in how to establish that, science becomes an endangered enterprise. The public will look very unfavorably on bad conduct.

Comment from same participant:

But the public has also reinforced the notion that companies need quarterly profits rather than long-term plans, and the public influences this in many ways.

Dr. Reiser:

The best example of how this works is in medical care. As managed care organizations tried to create profits at the expense of good care, the public protested. Laws have been passed to counterbalance those profit-seeking and dangerous motives. The public can do exactly the same with science as already proved in the breast cancer study. The public has shown that it does not wish excessive profits to interfere with attention to ethical behavior when it comes to things as precious as their health. Just as managed care organizations engaged in such activities at their peril, scientific institutions also do so at their peril.

Dr. Sandra K. Hanneman

Thank you very much, Dr. Reiser. I am very pleased to see that the discussion on the topics is going well.

The original program for the conference had our next session listed as “Self-deception in Research” to be delivered by Elizabeth Heitman. Dr. Heitman had a death in her

immediate family yesterday and had to leave town. Dr. Bulger very kindly, in the last 24 hours, agreed to fill in as best she could for Dr. Heitman. Her remarks will cover some of what Dr. Heitman was going to discuss.

The title of the next presentation, as outlined in your book, is “Scientific Ethics and the Responsible Conduct of Research: An Introduction.” I presume the introduction is to connote that Dr. Bulger has had very little time to prepare this; and, secondly because this is a very large area of material, all she will have time to do is an introduction.

We are pleased to have Ruth Bulger here. She is Vice President for Research at the Uniform Services University of the Health Sciences in Bethesda, Maryland. Dr. Bulger had been in Houston some time before going to Maryland. So please welcome Dr. Bulger.

Ruth Bulger, Ph.D.
Vice President for Research
Uniform Services University of the Health Sciences
Bethesda, MD

First, I am going to broaden the topic a little more than just self-deception and gullibility, which was what Elizabeth was going to talk about. I will, in part, include that in the talk. I want to talk about scientific objectivity as well as self-deception in the discussion today.

I find that the New Yorker magazine is an excellent source for responsible conduct of research material especially because it seems to be so in tune with what the public is thinking. If you look at the cartoon on the slide, the main character says, “Oh, I think I can be principled when necessary.” And that is precisely the topic of this lecture.

What are the guiding principles of the responsible conduct of research to which scientists need to subscribe and when is it necessary to be principled? Certain concepts I believe in. The most important is full disclosure. The responsible conduct of research is valued both by investigators and by administrators. Second, the doing of science is built on trust of previous scientists’ work. We heard Stan use the word “trust” several times, and you will hear it from me as well.

During this time of a rapidly-changing environment of science, we need to notice the students who are sensitive to and have an understanding of relevant issues that are important to science as well as have the ability to recognize and analyze complex ethical situations in a morally mature way. Long ago it was well said by Louis Pasteur: “In the field of experimentation, chance favors only the prepared mind.” Hopefully the next two days will help us prepare so that when chance hits us we will be the prepared mind.

What are the goals when we teach scientific responsibility to students, who are the main people we teach, and to each other? First, I think it is very important to teach scientific responsibility. We started the course in Houston eight years before NIH required courses in research ethics. I think it is important because it opens up lines of communication. It says this is an important topic to the students and is something we think we should discuss with you. Generally, between lectures or between sessions, students will come by quite often and ask questions of the ethical nature that have been bothering them for a long time. Yet students do not really look forward to taking this course even though they know they have to take it. However, after the course, the students are surprised at how

much they enjoyed it, how much they found it interesting, and how useful it is in their lives.

The second goal is getting the institution also to think this is important. After all, it is so important that we are going to ask new students to study this material and to think about these topics. The third goal is to stimulate the students to be interested in ethical issues and to continue to read and think about them within the limits of a short course. We encourage them to read articles from the local newspaper because there are always scientific ethical issues in the paper. We want them to read. We want them to continue to be excited by this material, to continue to think, to continue to grow.

Reading about scientific ethical issues will help students learn about national, state, and institutional guidelines and policies. These policies and guidelines will continue to impact their lives throughout their careers. It is something that they need to be informed about. They cannot be expected to deal with these issues in the future without having them highlighted in their studies. Finally, what we as teachers want to do is reinforce their sense of moral responsibility, because it is moral responsibility that will help them in their career ahead.

Finally, on this issue I think it is very important to get them to recognize ethical problems and situations, or ethical components of the problems, and to get them to look at how they relate to the science they are doing. It depends on what you choose to teach the students and how you choose to teach it. You can tell them guidelines, or you can teach them ethical principles and moral reasoning skills. If you are trying to change behavior, it is moral reasoning skills that are most important because they are going to need them in gray areas of science. There are lots of gray areas. There are lots of situations where things are changing, such as authorship policy. Students need to be able to think these issues through. It should help them with the various issues that they are going to have to deal with in their careers.

Thomas Kuhn, in his classic 1962 book called The Structure of Scientific Revolution, talks about normal science. It is the kind of science most of us do most of our lives, maybe all our lives in some cases. And then Thomas Kuhn talks about a revolution in which a whole new way of thinking comes about. We look at our world differently and that does not happen often. In the doing of normal science, a gap in the present knowledge is identified. The scientist will come up with a hypothesis such that if this hypothesis is correct, the gap is filled and the world around us is better understood. So then “hypothesis” leaves his or her hat and coat at the door, walks in, and tests the hypothesis in the laboratory. The data is collected, analyzed, and finally interpreted. If the results support this hypothesis, the next step can be taken. This may be another hypothesis. Or it may be a theory.

But if the hypothesis is refuted, then we have to re-conceptualize our hypothesis and then the new hypothesis is tested in turn. In doing normal science, which is what we do, there are some questions I’d like to think about today. Do you think scientists are more honest than other people? Do you think they need to be more honest than other people? Do you think that the personal values of scientists, or personal prejudices, can influence the science that they do? How would a scientist protect against prejudice? What is the role of intuition in science? And how does that relate to creativity of our scientists? Do you think

good scientists can have different interpretations of the same results? These are things we need to think through.

Well then, if we are going to develop hypotheses, what are the characteristics that would identify a good hypothesis? First, I believe a hypothesis would have to be internally consistent with what is presently known to make it unlikely to be corrupt. It would have to have the ability to provide accurate experimental predictors. For example, if you cannot test the hypothesis, it is not very useful in science at the time. So, it has to be a testable hypothesis that is going to give you some kind of real answer. It should provide a way to unify--to fill the gap between the observations that exist. Ideally it would be very simple. We could describe the movement of the earth in a simple way or in a very complex way, depending where we called the center of the universe. It should be simple, yet broad. It should lead to further ideas to be tested. You do not want a dead end. A good hypothesis brings you forward and then leads on to the next step. So, as Jerry Garcia might say, somebody has to do it. It is just incredibly pathetic that it has to be us.

To prove our hypothesis we need to be able to test it in an objective manner. It is always objectivity that we strive for. How do we ensure this? How do scientists safeguard their objectivity? It is not enough just to be honest. You have to be objective in your observations. You also have to have good practices in data recording and analyses. These are all part of a valid scientific experiment. We need ways to prevent gullibility and to be sure the scientist is not misled. We need to be sure that the scientists do not deceive themselves or do not fall in love with their own hypotheses to such a degree that they must prove them. In these instances, such great expectation of finding an answer may lure the scientist into thinking that he or she actually sees it. So, what do we do?

First, a common way is to use blinded experiments. The scientists might not know which group of particular subjects they are observing. Or we could have a double-blinded experiment where neither the subject nor the investigator knows which experimental group that subject is in. In these cases, one would not break the code of the experiment to know the answer until after the experiment is finished. Then we would find out in which group the subject had been placed. Subjects need to be chosen in a random manner so that various differences among them are of sufficient numbers to minimize differences.

Science can also use current control experiments to ensure that it is the experimental treatment that causes the effect that is seen and not some confounding factor going on at the same time, like time. You always do a variety of control experiments. Experiments are repeated several times to ensure reproducibility. There are ethical cases we use for student discussion. For example somebody did an experiment once, got results, wrote an abstract, and then couldn't repeat it. Always repeat your data. Always repeat your experiment so that you know the data are reproducible before you go further.

A scientist, then, coming back to self-deception, needs to examine any biases that he holds that might affect what he sees. The scientist will come back to the experiment. Sometimes, a scientist is affected by what he expects. That is called self-deception. Broad and Wade wondered why scientists, who should have a skeptical frame of mind when they look at things, are prone to self-deception and to deceptions perpetrated on them. He wondered what was in the scientific method that allowed scientists to be vulnerable to this kind of self-deception. That is something we really need to think about today.

The scientist needs to make sure that he is not affected by some kind of financial or intellectual conflict of interest. An example is: If this experiment comes out positively, this company is going to give me more money to do another experiment. That would be a conflict of interest. We try to eliminate conflicts of interest. If we continue to have them, we need to disclose them so that the audience can know that X or Y or Z is taking money from this company to give this talk. We use disclosure to alert the audience that the results might be affected by a conflict of interest.

We try to have several independent observers view the data. It is quite common for several people to look at slides and initial them so that the reader knows who looked at them. People interpret various criteria differently and can arrive at different results. Finally, you need to use appropriate tests for statistical significance to show that the results are truly meaningful.

Probably the most important thing I say to students is that the scientist has to learn not to try to explain away an unexpected result, but rather profit from it. If you have all these points in a place that is different, ask why. Now is the time you can make a real achievement. You might have a paradigm shift. You might, in fact, need to put all the data together in some other way.

One thing I like to think about is the lens we have over our eyes--the colored glasses that keep us from seeing things as they really are because of who we are. The first lens I would like to try to remove is that science is objective. In spite of all these precautions we are talking about, it is very easy for investigators not to be objective. Every case is processed through a person, a human being. You may still be coloring your results. I think we need to realize that.

Bentley Grass, in 1965, argued that science in fact is not strictly objective. He believes that it is as objective as people know how to make it. But, in fact, people are the ones viewing the data; therefore, the process is inescapably subjective because the viewer is a person. Furthermore, he says that we are born blind to many realities and at best can comprehend them only by translating by means of our instruments into something we can sense with our eyes or ears. Then we can begin to reason by developing abstract mental concepts about them and make predictions on the basis of our hypotheses. We need to test our theories to see whether they really conform to our notions.

The objectivity of science depends wholly upon the ability of different observers to agree about the data in their processes of thought. In the last analysis, science is the common fund of agreement between individual interpretations of nature. What science has done is to refine an extant method of obtaining agreement. Grass said the answer to individual observation is to have more than one individual look at it

Jacob Branowski, in his book called Common Sense of Science, carries this line of thinking one step further. He believes it is a fallacy to assume that any one person can test what is really true without the aid of others. He says we must rely on others. We must be able to trust the word of others. There's that "trust" word again. It is the key word. Verification may depend on other scientists being involved with the same kind of experimental situations and confirming the observations of one individual scientist. This all rests on their integrity.

As a sidebar, it is very hard to teach some things like how to be objective. I want to tell you of one situation where I learned a lot. When I was here in Houston, I took several

ethics classes at Rice University. It just happened that the ethics classes were in the department of religious studies. During this time, I took a particular course that was called the "Gospel" treated as literature. We were supposed to be reading the "Gospel." I was trying to understand the story; trying to understand what the author was saying. Over and over again a student would make comments about what the "Gospel" said. Over and over again, our teacher would stop and say: "Where does it say that in this "Gospel?" What we really learned was that we were all bringing ourselves--our own experiences and beliefs and observations--into the text. We believed we read them there. But they were not in the text. It was an amazing shock to me to see how subjective I truly was in something where I was supposed to be objective. I learned more about objectivity in that course than anywhere else. Where do we try to teach students in science to be objective? Are students in the arts taught how to be objective more convincingly?

Take a person who steps out of the office for a little bit, comes back, and the secretary says, "The following paradigm shifts occurred while you were out." That is sort of what is happening in our world. Things are changing so fast. That is what can happen now after we are doing normal science for a particular time and our data are no longer consistent with the accepted understanding of whatever we are viewing. What happens then is the science will experience what Thomas Kuhn called a paradigm shift. This term is very commonly used as you can tell from the New Yorker view on the screen. What happens in a paradigm shift? There are several things that happen.

First, let us say newer experimental methods are used that allow you to get much more refined values. It turns out with these higher resolution instruments that what we thought was true with a lower resolution instrument is no longer true. In fact, we had a misconception and now we know more than we did. Continued research on a given topic i.e., the doing of normal science, can also reveal anomalies and discrepancies from what you predicted from your old hypothesis. As you see more and more of these anomalies, what happens is that normal science loses its power to suppress the breakthroughs. That is the stuff of creativity. That is where creativity comes in. It is the "eureka" experience. Someone recognizes that the anomalies actually fit together in a different way as a new set or a new class. That is the creative process. That is the point where there is a conceptual breakthrough, and it leads to a paradigm shift--a new understanding of our world. That's how we benefit by those points that happen not to be on the line, the ones we don't understand. We benefit by rethinking; why are they where they are and what does that mean?

Finally, Thomas Kuhn says: "The hardest part of all is the last one on our list: the conceptual assimilation." He makes a big point: "It might even take a whole lifetime because the people who believe the old theory have to die or retire, or whatever, before the new theory can be accepted." Bernard Barber agrees with Kuhn. He wrote an article called "Resistance of Scientists to Scientific Discovery" in 1961. He discussed how scientists themselves are very resistant to new theories. He identified six categories of or reasons for resistance.

The first category is methodological conception. He believes that scientists are anti-theoretical and anti-mathematical. They like to see things in terms of established models. They want direct evidence of the senses. They want experimental data. They want to see the data with their own eyes.

The second reason why scientists do not accept things deals with religious beliefs. Some scientists have resisted ideas partly due to their personal religious beliefs. I think that was certainly true in the time of Darwin and evolution. In our country we still have people who continue to believe Darwin's theory is wrong. The whole area of creationism is still in our society.

A third reason that holds scientists back from accepting new work is "authority." The sense of professional standing, i.e., what the Nobel Laureate says, or what the professor says. I have had experiences where, many years ago, we were looking at the structure in the transmission microscope of the tight junction of proximal convoluted tubules. These are very small, leaky tight junctions. We looked at them in various states of water balance. When the pathway between the cells was increased, the water was going across. We saw decreases in the number of fusion lines and sometimes no fusion lines that went along so we said tight junctions could change. About the same time, a group at Harvard looking at a similar thing said they thought these just pulled apart in the cell membrane and got broken in that area. Guess who was quoted in the literature? Not the little known assistant professor from nowhere, but the Harvard professor. It turns out that the Harvard professor was not thrilled because now leaky junctions are seen more as being able to change in structure.

A fourth reason that keeps scientists back is substantive theories of science. The fact that the old is believed more than the new--just the fact that the old has historic weight. There are also sociopolitical affiliations that affect the scientist's willingness to accept new things. You can join organizations, have positions, and buy into those ideas. They might not change quickly enough. All of these different groups clash with the idea that scientists are open-minded persons, ready to take data at face value, change their views, and accept scientific events. That would in fact substantiate what Kuhn thought many years ago.

Let us talk a little more about "creativity." How do we increase it? In our college, our school was looked at in great depth in a study done by the Mellon Foundation. All the students were interviewed at the beginning and at the end. Some of them were interviewed every six weeks throughout the whole time. What came out of this later was that the scientists were the least creative people at the university. What does that say about our science education? How are we teaching people to be creative? Are we teaching people to see, to look, to think?

Sylvania Arieti wrote a very interesting book called: Creativity: The Magic Synthesis. He listed the factors, on this screen, that enhance creativity: openness to our cultural stimuli, free access to cultural media for all citizens, relative freedom after severe oppression, exposure to different and even contesting cultural stimuli, diversity, and tolerance for interest in diverging views. It is probably not an accident that some of the great musicians lived at the same time and interacted. Another factor is promotion of incentives and awards. That does say something about what we might be doing in our institutions. How should we approach responsible conduct of research? One problem I have seen when we try to teach is that people tend to look not at basic principles but at spheres of accountable action. This afternoon I am going to lecture on data management. That is what I call one of the spheres of action.

We should look at the issue in a way different from regulations, laws, and the like. I would say probably the way we should look at it is the way the *Belmont Report* looks at

human subjects research. When we teach human subjects research, we teach three principles. We teach the principles of respect for persons, the principle of beneficence/nonmaleficence, and the principle of justice. We think of these a little differently now than we did in 1978 when the *Belmont Report* came out. We still think in terms of principles. It gives one an analytical framework to think through issues. It helps the investigator understand the underlying ethical principles of what they do.

The *Belmont Report* derived from the ethical research problems that Dr. Reiser discussed. The U.S. Congress put together a national commission that wrote 12 to 14 major reports on various aspects of human subject use. In the end, they wrote six pages that presented the basic principles that we still use in every course. We give the course to our investigators who use human subjects. It makes us ask questions about the basic principles of human use that are important in our studies.

Why have scientists not tried to articulate similar principles? We do not have a "Belmont Report" for any other areas of science besides human subject use. There are probably lots of reasons why. Science tends to be reproducible. It is self-correcting in nature. That may be one reason we have not tried to do it. Perhaps there is enough internal oversight to make sure that science is done well. In the present day, we have to ask: "Has there been enough internal oversight?" Perhaps there were wider shared values among scientists about what was important: truth and integrity. But "Have there been?" is still a question.

Perhaps the flagrant ethical lapses that we saw in human subject use have not been as open in the area of the more basic sciences. Perhaps the different scientific vocabulary restricted the public's understanding of what scientists were doing. That also has been changing recently because the public is much more interested in science. I decided that, after this conference, after we discuss topics like authorship, data and the like, I would see if we could lay down some principles. I use this kind of exercise with students. We come up with slightly different principles, which we organize in different ways. Nevertheless, we get them to say what is important. How do we then bring them down to a small number? The Belmont three is always the perfect number to deal with.

I am now going to put what I have been saying together into four principles. The first principle that I will discuss is honesty, integrity, and objectivity of the scientist. You have heard those words so many times already today that you have to realize it is the number one principle that scientists value. Secondly, I am going to describe "respect for others" and third scholarly competence. The final principle to be discussed is the stewardship of resources provided by the public, which is very important because the public provides vast sums of money for science to advance.

The first principle, the honesty of science is how we observe, record, and interpret every experiment that we do to limit self-deception. Scientists must examine their biases and limit their conflicts of interest. That is what Stan Reiser meant when he said, "When they left their coat and hat at the door and tried to come in and not be affected in the laboratory by what happened outside, or by their hypothesis outside." The scientist needs to use experimental methods to ensure this objectivity. We have gone through a list of them previously. They must honestly use and reference the work and ideas of others. This is part of integrity. They must be trustworthy. We come back to that word again and again because the entire scientific endeavor depends on trust. There is an interesting quote by

Stephen Shapen, who is an historian of science. He points out that “Honesty and the resultant trust relationship in science are constitutive of the making, maintenance, and extension of all scientific knowledge.” He points out that the very character of science would change if we had no trust. He says “Much of our modern structure of scientific knowledge would be unwound, put in reverse, and ultimately dismantled.” Instead of laboratories for the production of new knowledge, we would build great facilities for the close reinspection of what is currently taken to be knowledge. Grants would be given for checking routine findings. Published reports would look more and more like laboratory notebooks. We have to have trust.

The second principle involves noticing that we have more than humans as subjects. We have animals, tissue cultures, and other kinds of subjects. We demonstrate this principle when we follow humane care and use of laboratory animals and when we show respect, beneficence, and justice in dealing with human beings. We also need to have respect for our environment. How many things do scientists throw away, put down the drain? What are they doing to the water supply? All these issues need to be in the scientists’ minds when they are working in the laboratory. Furthermore, respect for colleagues needs to be shown as they share their knowledge with others.

Scholarly competence is the third principle. It involves doing a good literature review so you do not repeat experiments. It involves doing good technical experiments and getting adequate amounts of data –neither too much nor too little, but just enough. It is expressed in the way you treat your students to pass on knowledge to others as well.

The fourth principle is stewardship of resources. That can be expressed in many ways. Students and scientists feel differently about how important it is. I think it relates to what topics you choose and how important they are to society. It relates to rapidly publishing what you do so that somebody else does not have to do a similar experiment to take the next step forward. It relates to recognizing when results of your research bring up ethical dilemmas or quandaries. You see those quicker than other people do. This is very true in the whole area of the human genome. There are quandaries coming up from a variety of things and you need to alert others. Some scientists see themselves as adventurous and at the forefront of knowledge. That is how they get fulfillment from what they are doing. Personally, I think that science needs to be useful for society. President Clinton has stated: “We can make this age of science and technology a true age of possibility for all American people; but, we must do it wisely if we expect to get a return.”

What I would like to do is close with a slide showing a saying by Harold Shapiro. He is the President of Princeton University and is an unbelievable man. Shapiro is head of the National Ethics Advisory Board. This Board is now looking at many interesting issues such as human use, genetics, cloning, and others that are of ethical concern to us. He said “In the final analysis, it is a society that’s full of hope rather than fear, full of trust rather than alienation, full of knowledge rather than ignorance, full of honesty rather than cynicism, full of confidence rather than helplessness, that will survive and progress. It is to these issues, therefore, that the nation, the university, and life that involves science, must address themselves.” Thank you.

Question:

The book you were quoting by Broad, what is the title?

Dr. Bulger:

It is called Betrayers of the Truth: Fraud and Deceit in the Halls of Science. It is a very interesting book. In fact, both of these two writers are still writing. They were with the New York Times. They are still doing science writing.

Dr. Sandra K. Hanneman:

Thank you very much to Dr Bulger. I think she did an excellent job covering that topic, especially with such short notice.

Our next session is the only panel for today. Tomorrow will be mostly panels. We felt that the “Ethics of Authorship and Publication” fit very nicely into the professional view of research integrity; so we have a distinguished panel with us today. Dr. Ericsson will moderate the panel.

Dr. Ericsson is Professor of Medicine at the University of Texas- Houston Health Science Center Medical School and editor of the Journal of Travel Medicine. The rest of the panel includes Dr. Joseph Eichberg, Professor of Biophysical and Biochemical Sciences at the University of Houston and the Deputy Chief Editor of the Journal of Neurochemistry; Dr. Alan Price, Chief of the Investigation Branch at the Office of Research Integrity; and Dr. Karen Davis, Postdoctoral Fellow at the University of Texas- Houston Health Science Center Medical School.

Charles Ericsson, M.D.

**Professor of Medicine and Head, Clinical Infectious Disease
University of Texas-Houston Medical School
Editor-in-Chief, Journal of Travel Medicine**

When we talk about ethics, we probably have more opinions on how to proceed in certain areas than there are people on the panel. Many of these concepts are not cast in stone, but there certainly can be guidance, conceptually, for young authors who are trying to learn the ropes. I understand that our audience has some administrators who might face some of these ethical issues. We hope the discussions will be useful to you.

What I thought we would do is accept questions that are relevant to the particular topic. I will not forecast what those will be because I think we need to answer all of your questions. The panel would love to interact with you. We are pretty loose about that, although we will have a structure to follow to make sure that we make some points. So feel free to interrupt. In fact if you do not, I will feel that we are failing you for not prompting you to think about the issues. We thought we would lead you through the publication process and address certain ethical issues that evolve from that process. We will concentrate particularly on the ethical issues. At times specific social obligations that derive from the ethical issues will also emerge.

The publishing process can be taken back to the formulation of hypotheses in the research project to obtaining the various, necessary approvals of the ethics committees. The panel and I can share some of these concerns since we have served on ethics committees. The publication process involves writing up the research data. There are some issues that go into how you deal with your data. There is always some degree of editorialization of your data and codifying it into a digestible form for the reader. However, you do not want to sacrifice scientific accuracy in the process. Authorship issues will arise. We will actually go through the process of submitting articles, choosing journals, and so forth. There are perhaps fewer ethical issues involved there. Nevertheless, we will want to highlight some of these issues because ethical issues become critical once an article is submitted.

We want to examine the role of the editor in relationship to the author as well as the role of the reviewers, the confidentiality of the review process, and the selection of reviewers. There is an actual editorial process that occurs once the reviewers' results are received. Even though opportunity for capriciousness is present, those of us who administer the process try to stay as objective as we can. Finally, the publisher has a relationship with authors and editors. Copyright issues will come up, and we will discuss that if time allows. In particular, Dr. Price, who serves on a regulatory agency, has dealt with copyright issues. When he gives me a sign, there will be a nice story to tell that punctuates some of these concepts.

Karen may want to help us here because she is an investigator. Karen, what crosses your mind in terms of conducting the research, and how can you guarantee that your study is ethical as you formulate it?

Karen Davis, Ph.D.
Postdoctoral Fellow
University of Texas-Houston Medical School

When you think about a study you also think about what objective measurements you use to design your study. Oftentimes you will have multiple experiments to show the same thing so that your results can be confirmed. When you think of an hypothesis, you think in terms of what would make a well-rounded paper.

Dr. Ericsson:

Anybody want to add anything to that?

Dr. Eichberg:

Those of us who are editors are also authors, so we live on both sides of the publications fence. I think a well-conceived study with a testable hypothesis that uses proper means of analysis should result, in principle, in a manuscript that will stand the rigors of review. That is really the goal. All of the ethical considerations that go into the conception of a research project and generation of data really carry over into the publication process. I often tell my students that data sitting in notebooks is not really

meaningful data because it has not been tested in the light of day by peer reviewers. It has not been made a part of the scientific literature. There really is a continuum between doing a study, writing it up, and getting it published. There is a difference between outright fraud, which has obvious ethical consequences, and data that is not fraudulent but is sloppy or inconsistent. There really is an ethical issue on the part of an author planning to publish data as to how it is to be managed.

That brings up the issue of the proper means of data analysis. For example, what kind of statistical results are there? We are talking about a series of quantitative studies. You have to make a choice. That choice need not be what will give your data the most number of asterisks over the bars.

Dr. Ericsson:

No data dredging, please. We probably have more hoops to jump through now because the animal welfare groups want a study with a good hypothesis that will reach a conclusion. If the statistics are included up front, I can feel comfortable as an institutional review board (IRB) member that the conclusion is worth the risk to the patient or the sacrifice of the animal. If it is a negative study that is properly done, I feel it can be shared with the public. You should write up these conclusions. You should state what changed or did not change in behavior. If you do all that, and there is an opportunity to get to the IRB level for checks and balances, then, hopefully, you will carry that over into publishing.

Question:

I am John Grabowski. I think the essence is there. You plan the good experiment. You can write the article up front. You can write around the article, around the pieces. Then you get the data. At the end of the study, you get negative results. The problems of deception would seem to lead to problems of another kind. Many journals will not publish negative results despite their claims of interest in science. Yet, a well-planned study--whether or not it proves or disproves a particular hypothesis--might have an important negative finding. Yet, by not publishing negative results there is an illusion that all science has a positive end. That is a kind of self-deception. I think that produces a real dilemma because a fair amount of research does yield negative results. How do editors handle negative results, even though the study was wonderfully done?

Dr. Ericsson:

Thank you. That was one of the points we wanted to make. How does the panel deal with that? If you are an editor and get negative results, what is your response?

Dr. Eichberg:

I think you are right that there are a lot of negative results that never see the light of day. This leads to repetition of studies that need not be done again. From the editorial point of view, it depends to some extent on the importance of the negative results. That is an editorial judgment. If it is a trivial, negative result that comes to light in the journal review process, the author's responsibility is to make a case about the importance of negative results. The other recommendation I make, in terms of including negative results, is that if a study is well designed and properly executed, then a negative result can be included in the context of positive results. That is not always possible. That is more in the way, perhaps, of a piece of advice than a strictly ethical consideration. There is room, more often than imagined, for a journal of negative results specifically devoted to studies that do not work for very good reasons.

Dr. Ericsson:

I would add that as an editor of a brand new journal that just got on to Medline, I felt under terrific pressure to have enough material to meet deadlines. I find myself worrying about whether I am compromising, not the integrity of the article but the worthiness of it. The thought crosses my mind that it might have barely gotten by the reviewers and that if the journal were the New England Journal of Medicine, it might have been rejected outright. Our brand new journal is willing to accept negative results when they are meaningful. What I will invariably do is, say something like: "Look, I know how you want to have a splash or full-fledged original article, but this material can be boiled down to a research letter or a brief communication. You do not need to take a lot of space in sharing that negative result." I think as we get into the age of electronic publication, a lot of things will be more rapidly disseminated.

Follow-up Question (Dr. John Grabowski, UT-Houston Medical School):

Dr. Ericsson? Don't you think that it is as important for people to find out how those negative results were achieved as it is to find out how positive results were achieved? Wouldn't that information be eliminated in boiling it down to a letter? I do clinical trials, and we produce some pretty profound negative results. We end up having to journal shop. Fortunately, one editor of a very good journal thought negative results are important. Two others suggested that we boil it down into a letter.

Dr. Ericsson:

I did not mean to say that it would always be boiled down. Certainly, if it is a really worthy negative result that is going to have an impact and convince people never to bother to do this research again because of the definitive, negative result, then I absolutely agree with you. The reader needs to be able to critique the whole process thoroughly. But sometimes, particularly in my case, there is sort of "me too, negative results." You could really argue that it does not even need to be published. I think they can reference the

techniques and so forth, depending on the nature of study. I am willing to give it a gradation.

Question (Walter Meyer, University of Texas-Medical Branch):

Let's go back to the analysis of results. I have had editors ask our faculty members whether or not they would be willing to share raw data to make sure the analysis was done properly. But one of our faculty members would like to ask this forum the following questions. Would you know whether raw data, on which research articles are based, are available to the general public under the Freedom of Information Act (FOIA)? And, do journals in which research articles are published have anything to say about whether the raw data, upon which the articles are based, should be made available to the public? That gets around the issue of, perhaps, someone's analysis skewing the results.

Dr. Ericsson:

We are all looking at you, Dr. Price. Can you comment?

**Alan Price, Ph.D.
Chief, Investigations Branch
Office of Research Integrity**

Generically, NIH gives grants to institutions, but the institutions own the data. So, the data for your authors is owned by your institution. You have to follow whatever FOIA responsibilities you have in your institution. The government generally does not ask for data in order to release it to somebody; but, if government has data available to it, it can be released under a FOIA request.

Comment:

I think the question more likely relates to a journal article. It is not uncommon for an editor to say: "Let me see some individual raw data to back up this mean and standard deviation." I have had that happen several times. But I think this time it goes a little further when somebody in the general public can go to the journal and say: "We want to see the raw data. Can we have access to it because the article has been published?"

Dr. Ericsson:

I am not aware that there is any law that applies to that.

Dr. Price:

I do not think there is any rule. Often what happens is that an editor or reviewer requests further documentation. The author can send in the documentation. In my view, if

it does not finally appear as part of the public record, it is not, therefore, considered part of that record.

Dr. Ericsson:

Can we have some clarification here, please? For those of you who know these things, please share.

Dr. Ruth Bulger:

This afternoon when I talk about data, I will talk about the new law that exists. It is a 4,000-page appropriation bill put in by Senator Shelby at the last minute. It requires OMB to redo Circular A-110 so that the public can get data. What has happened is that it is not the best way to get data. The public needs to have ways to get data through the FOIA. I will talk about that this afternoon.

Dr. Ericsson:

The long and short of it is that if somebody wants to see my books, I have to share. I cannot just send a reprint of my paper. I do not like it. It impugns my reputation and it makes a lot of extra work. I will fight it. I think it impugns the reputation of investigators. If you are going to imply that my analysis was fraudulent, then the investigation will examine the study. Then, I dare say, our regulatory agencies will get involved. They will do their own investigation and their own analysis to make sure. We will come to that in a moment.

Comment:

They may want to publish their own raw data in a different way.

Dr. Price:

That is right. You could have different motives.

Dr. Ericsson:

It will be interesting to see this play out.

Question (Dr. Paragon, University of Texas-Houston Medical School):

I am with Orthopedics at the University of Texas. At times our department gets a lot of half-done studies from residents. Sometimes they leave without documenting their work, or we get negative results that we do not want to publish. However, we might want to do something else with the data. This certainly does not fall under hypothesis-based research where you have an hypothesis and collect the data. You get a bunch of

information kind of cobbled together. How do you handle that sort of thing within the framework of journal articles and credit?

Dr. Ericsson:

It is like what we face in clinical research where, not uncommonly, the variables are messy, and it's hard to control all of them. I have seen too many researchers collect a bunch of stuff and hope something falls out. That is not wise, but they do it all the time and they are then guilty—I use that word advisedly--of having editorialized their data. They have to decide how to throw their data together with another experience and create a report. In its demographics it could be interesting for other clinicians, but it is not hypothesis-generated science. What do we think about the ethics of editorializing your data?

I know one response already was, if you design it properly it all falls out of a hat. But the reality is that this sort of thing happens all the time, particularly in clinical medicine. I think there is much less room for it in basic science research, but it's done frequently in observational research. Comments, maybe from our investigator?

Dr. Davis:

If you think of experiments in terms of how the paper will be written, you will think about questions or problems with the study and will address them during the experiments. When you read the article, you can recognize that it was a well-designed study. That is the credit you get for it.

Dr. Ericsson:

I vividly recall reviewing a paper recently that was titled “Post-Talk Analysis.” The authors carefully pointed out that they dredged to get at this question because it was going to be very difficult to design a prospective study. They thought it was worth sharing, given the hazards of an overdrawn conclusion, and they were very straightforward about it. I thought it was a quasi-negative study, but one that had positive results. They wondered if there were enough data to design a proper study. In that sense, you learn things from dredging around in data. I think you have to be cautious about the scientific limitations of that. As an editor, I want to see heavy-duty critique, such as, was the population great enough to allow generalizable conclusions, and so on. Comments?

Dr. Eichberg:

One of the rules that I like to go by is that if you do not have something significant to say in a discussion, do not say it. As an editor you want people to make a good set of studies. Then they will write a tremendously over-interpreted discussion about it. That is where you ding them and they have to go back and cut the article down to size. That is actually a lot more preferable than having to do more experiments. You have to be very

cautious. It is more difficult when you have a committee that essentially designs the study. It tends to lose focus.

Dr. Ericsson:

What do you do if you are a junior investigator and you do not know how to design the study very well? We really should do better by our junior investigators. I think what happens is the following: they design the study and get a lot of outcome variables that they are not sure about, i.e., which outcome variable to use. So they have 5 or 6 outcome variables, all basically saying the same thing.

That is exactly what happened when we first started doing diarrhea treatment studies. We finally learned and designed our studies up front, saying this part of the analysis is for that outcome and we going to live by it. That is the way it should be done. To this day you can see in the literature published diarrhea studies that have four or five different outcome variables. One may be negative and three or four positive. I can imagine people saying, well, you know, I am going to pick the one that looks the best. That is what I am going to share. I think that happens all the time. If you find yourself in that role, what you have not done properly is design your study up front. When you design your study first, you avoid traps about what the proper outcomes will be.

What about authorship issues? You design your study, you do the experiment, and you fully anticipate publishing it. Who is going to be the author of your paper?

Dr. Davis:

At this point in my career, my supervisor will be an author on my paper because he is still my advisor.

Dr. Ericsson:

Well, is he actually going to do anything to merit co-authorship?

Dr. Davis:

Although he has not actually done the experiment, he has definitely given intellectual input. He has designed the experiment, carried out the experiment, addressed problems in the experiment, and so on.

Dr. Ericsson:

He has intellectually invested in the design, monitored the progress and the interpretation. Intellectually, he has some stock in it. What about your fellow graduate student that loaned you some gels?

Dr. Davis:

I think that within the laboratory anyone who contributed significantly to the research deserves to be a co-author. But I don't think a technician who just ran some gels, or a department chair, or a clinician who needs a publication should be co-author.

Dr. Eichberg:

From the editorial point of view, it is very difficult for any editor to evaluate who should or should not be an author. I think fundamentally this is a decision internal to the study and the people involved. I think Karen has pointed it out very well. Experimental or intellectual input should qualify one as a co-author. Strictly financial support can be an issue. Then you do not really have the basics. In addition, there can be academic or other kinds of politics that can complicate the issue.

Then there is the question of who should be acknowledged. People who make contributions to the study but whose contributions do not rise to the level of author should receive some recognition.

Dr. Ericsson:

Do you think that needs careful thought, or should we just acknowledge as many as we can?

Dr. Price:

I often have to keep everybody happy. Everybody gets mentioned somehow.

Dr. Davis:

I notice now that even for acknowledgements, people who are acknowledged need to sign off that they have given their permission to be acknowledged in the paper. I learned that recently when I submitted a paper.

Dr. Eichberg:

What you are getting at, in a way, is that once you agree to be a co-author, or to be acknowledged to a lesser extent, you are partially responsible for the content of the article. Being a co-author is not necessarily, totally, a perk.

Dr. Ericsson:

Do you require acknowledgees to sign off?

Dr. Eichberg:

No, we do not have a requirement.

Dr. Ericsson:

I do not either. I have not thought about it. I think it is not really necessary.

Dr. Price:

I want to share a story about an incident that took place three or four years ago. Someone came into the office and said she deserved to be first author on a manuscript that was in submission to a journal. I mentioned that it sounded like a dispute between her and her collaborators and that she should resolve it with them. She insisted that it was a scientific misconduct issue and wanted us to resolve it. In the end, the institution looked into the issue as a misconduct inquiry. They found that she had worked in the laboratory as a postdoctoral fellow for many years and had done a lot of work. They discovered that she had left the laboratory for a year or two and had not written up her own work for publication. The chief of the laboratory in frustration--he had a new postdoctoral fellow in the laboratory--wanted to get the experiment published and said: why don't you repeat that part and do a little more that makes it even more clinically interesting? They did and wrote a manuscript on those experiments for a short publication.

The student was asked if she wanted to be second author because she had worked on the project and developed the vaccine in question--this was in the *New York Times* a few years ago--and deserved credit. The student was asked further that if she did not want to be a co-author did she want to be in the acknowledgement section.

The student did not like either of those choices. She said "No. I should not be in the acknowledgement section because it was my work that led to this project, and I should not be second author. I should be first author and all this data should not go in. It should be my original data. So give me a chance to write it up and publish my data instead of this data. By the way, the new postdoctoral fellow probably did not have time to do this whole study, so maybe he falsified some of my data anyway."

So I looked at this very convoluted case. In the end, it really was not resolvable. The officials of the institution did not find misconduct. Our office did not find misconduct. The institution's conclusion was that the authors had to get back together and make a decision about who should be the first author. I think it is more than three years since then and it still has not been published. It probably never will be. I think that the dispute and the name calling in the press led to a diminution of the scientific community.

Dr. Ericsson:

Is there a law that guides us here? Does the original researcher own the data that was done in the laboratory or the professor who mentored the graduate student or the postdoctoral fellow and under whose tutelage the data were developed? Who owns the data?

Dr. Price:

If you look at the paper in your package that Dr. Kay Fields and I wrote, the answer is that the money at NIH in an intramural program is NIH money and NIH owns the data. If it is given to your institution as a grant, your institution owns the data. The institution's officials have to decide this. But how do you get an institution's official to force two people who now hate each other to be co-authors and decide on an appropriate publication? It has not happened and probably will not happen. It points out how "human" doing science really is.

Comment:

In our department we had that happen. It has gone both ways. I have seen a faculty member write it up and put his student as first author. And I have seen it the other way, after which the student groused a whole lot. Luckily those studies were not funded by anybody.

The other issue that I have seen happen is where a clinician will have a relationship with a company. He will have an idea for a study, get funding for the study, give the study to people in the laboratory, go off for six months, return when the study is completed, and insist on being first author. The clinician had an idea; arguably, he made a contribution. The question is where do you draw the line? What is, or is not, a major contribution?

Dr. Ericsson:

We might ask who should be first author. We typically look hard at first author papers, particularly when the author is going for professorship. If you are buried in between, it probably has less impact on the editor. Who should be first author in your mind?

Dr. Eichberg:

It would be the guy who formed the study and actually got it done. Not the guy who talked to the salesman and got a couple thousand bucks to get it done.

Dr. Ericsson:

What if I did all the research, but somebody else writes it up?

Dr. Eichberg:

In order to do the research, you would have to have summarized it sufficiently for whoever wrote it to just do the writing. I think the guy who actually did the work should have been the first author.

Dr. Price:

Two years ago, there was a case in my own laboratory that points out that sometimes there is no solution, but there may be at least a compromise. I had two graduate students. One of the students began a project and then left. A second graduate student made the work publishable. Clearly both of them were going to be on the paper. I placed my name last. We came to an issue of who was going to be first author. There was no obvious meeting of the minds about this. The way that we finally resolved it was by means of an asterisk in the final publication that stated that these two authors contributed equally to the work. It gave recognition as equitably as possible, given the fact that we cannot list the authors vertically under one another.

Dr. Ericsson:

I think we all have learned the hard way that the first author should be decided before you do the research. As an administrator, one might be able to anticipate some of the problems, especially with trainees. Before doing the research, let the investigator know that if he leaves and does not document the study, he will be the second author if someone else has to complete the work. I think the trainees should understand they are at the mercy of their mentors if they do not live up to the expectations of academic productivity and timelines. Let them know that they may suffer the consequences. If you discuss your expectations with the trainees, there will be no grounds for further complaints. I have always thought it is important to be up front with them. You may have to keep the pressure on.

The other thing that we clearly want to acknowledge is that for those on tenure tracks there is a lot of pressure to publish. Many multiple-authored articles are generated in part because of that kind of pressure. I do not know how to get around that sort of thing other than for institutions to establish guidelines about authorship. There are so many authors on journal articles, even in good journals, it seems unimaginable that everybody knows the intellectual content of the article. Everybody wants to be acknowledged. There are too many to list on the front page. Any questions or comments?

Question:

I have a nagging question that takes on a personal note. I am a relatively new investigator. Here is a scenario: You develop a project under the supervision of your last postdoctoral supervisor. It is your idea. You have permission to take it with you. When you do leave the laboratory, it is after a certain amount of personal conflict with this person, but the project is still intriguing to him or her. You take it with you, and you write it up. You want to get it published, but you reach a stone wall based on personality problems.

This person is last author because it came under his original supervision. You will be first author because it is your idea. There are a few problems that emerge. He wants everyone in the laboratory to move ahead whether or not they had anything to do with the project so he wants them to be co-authors. He is significant in stature in the field and knows an editor of a major journal in that field. If you make him or her angry you can burn

your bridges there permanently. How do you handle a situation where you want to publish because you feel the data is significant? Moreover, it has passed other collaborators' peer review.

When do you come to the point of asking him: Do you let me proceed with this and send it on to the journal editor or get off the authorship and let me publish somewhere else? How do you deal with that? Is that misconduct? Is that a personal thing that you have to deal with or do you drop the project that is the basis of your research?

Dr. Price:

I think you probably have to understand the motivation that a former advisor might have for not agreeing to publish it. It does not rise to the level of outright misconduct. It is interaction between people and different interpretations of where you are in a given study. Ultimately, I think you as an investigator would have to make a decision. You have to decide if you should go ahead and publish it without the name. There is a risk involved when you cannot get cooperation and you do not want to sacrifice it. You have to make a decision. When you submit it, you might burn your bridges. However, there are probably other journals that may be equal in stature that will publish it.

Follow-up Question:

Basically, you just have to get independent enough to say this is going to be it?

Dr. Price:

I guess in the long run that is almost the only way. You can agonize over it, but it is not really advancing your career at all.

Dr. Ericsson:

These issues seem to come up with mentors and student situations where there are opinions or personality conflicts. There is no easy answer. It sounds like the regulatory agencies say: look, it is interpersonal; you guys at the institutions have to solve it.

Dr. Price:

Yes, we say that; but it often gets foisted back on us. There was a famous case about six years ago that appeared in *Science* several times. It dealt with some important principles, like the one you raised i.e., the student's right to publish her work. This involved a graduate student who was having difficulties with her mentor and who was asked to leave the laboratory. She was asked to leave before she completed all the requirements and the work was written up. She was assigned a new committee, a new mentor basically, to help her finish her master's degree and write up the papers. She wrote it up with just her name on the paper, offered it to the mentor and collaborators, and asked if they wanted their names on her paper. They declined because they had not seen the raw

data and therefore could not verify the accuracy of the tissue records she had sequestered. They advised her that they owned the grant and, therefore, needed to see her data before they signed off on it. The student refused to turn the material back until her mentor and collaborators signed off on her paper and allowed it to be published.

In the end the vice president of the institution who was also the dean of the graduate school decided in favor of the student stating, that she had the right to publish her paper. So what happened? After it was published, the mentor said she had plagiarized the material, the ideas from his grant, did not give proper credit, mislabeled the grant number, and he did not believe the data was valid. So the validity of the study was investigated and who should be given credit for the study was questioned. They tried to foist it on us as a misconduct case. We tried to pursue it. In the end it was justly resolved. Basically we said that you have to get the student to agree to follow the rules from now on about sharing data that belongs to the grant. These disputes can get out of hand. Academic principles are important to the institution.

Dr. Ericsson:

It sounds like the supervisor did not carry through in a supervisory role as well as he could have.

Dr. Price:

If the dean of the graduate school had said we are not going to allow you to finish your degree and publish your work until you give back the records of your research, that probably would have resolved it.

Question:

When an institution asks you to sign off, isn't that essentially a transfer of property to the institution? Does that also cover commercial interest?

Dr. Price:

I have not heard of it being covered that way.

Dr. Ericsson:

When there is commercial interest involved, not just intellectual property, then the institution wants a piece of that action.

Dr. Price:

Usually it is at the level of a copyright once it goes to the journal.

Dr. Ericsson:

Even when we get grants from pharmaceutical companies, we make sure it goes to our Contracts and Grants Office. They say "White out that phrase that says you must have it reviewed by the company. We can publish what we want to publish." When push comes to shove, the institution then has the right to publish what it wants to publish. They indemnify you to help guard against that. Let us move on. But there is one other thing here, what about...

Question:

Excuse me. May I ask you a question? I was doing a systematic review with another nurse last summer with the Cochrane Collaboration. We were gathering as many randomized controlled trials on this particular topic that we could find. We found three that were really good. Actually we found about thirty, but three of them were very nice. We were reading them when we realized they all had the same authors. The authors were in a different order so we could not tell if there were three separate, different studies, or if it was the same study being published three different ways. It really made a big difference to our meta-analysis.

We called one of the authors and asked him--he got really angry and abusive on the telephone--and said no, these are three separate studies. But every time we read them, they sounded so similar. Even the subject numbers were the same -- forty-six subjects. What do you think about that? Obviously these authors were all good buddies and they were all trying to give each other credit.

Dr. Ericsson:

You have anticipated the next session i.e., submitting multiple papers to journals. Sometimes an author will revise his paper a little bit and resubmit it so that he gets three for one, for example. It seems there are two issues here. If it is obvious that it is exactly the same data that is rehashed, it might fall under misconduct and could be investigated with subsequent action taken. Maybe our regulatory person could answer.

Dr. Price:

Not for the United States government. Perhaps it would be misconduct for an institution.

Dr. Ericsson:

I would think the institution would investigate it. They would have a moral obligation to report it. If the investigator stumbled across this, would she, or he, have any ethical obligation to report that? Should the professor's institution be made aware of it and pursue it? I understand it presents a problem for research. But does the investigator have an obligation to report it--to blow the whistle on it? I understand it created a problem for your

research, but do you have an obligation to report it? To blow the whistle? Did you call the chancellor of his university and complain? Should she? It puts you in a very awkward position and not a very pleasant one at that. I do not know what I would do either.

Dr. Eichberg:

At the level of the journal, it amounts to quasi-duplication of submitted data. That is really when the peer review system is put to the test. It should be picked up there. It does relate to the review process. The review process should be competent enough and thorough enough to pick up this kind of submission and reject it. As a rule, an editor probably would not feel compunction to communicate with the institution about this. The philosophy would be that it borders on being fraudulent and if the paper is properly reviewed, it will probably die a natural death.

Dr. Ericsson:

I do not think there is an easy answer to that. But what if during the submission process, it appears that an author has taken an article and has broken it down into several articles? What are the ethics of that?

Dr. Davis:

I think in the case she mentioned where a group is publishing the same data in different journals, dividing up the data into different papers when one paper would suffice, does not do the investigator any good in the end. In fact, it harms the investigator's reputation as a scientist. Your reputation is what you build your career on. People have to trust that what you say is true.

Dr. Ericsson:

Should we agree that it is unethical? It probably is not illegal.

Dr. Davis:

In my field there was a group of investigators who published the same data. You could clearly see the same data in several different journals. You questioned all their data. Anything else they published is questionable to me because they are unethical.

Dr. Ericsson:

Are we back to the review process to try to pick that up? The fact is, though, depending on where you send the data; there is a good chance it will never get picked up. As an editor, I do not waste a lot of time looking for duplications. If it comes to my attention, it is going to be awfully hard for that person to get published in my journal. You have to make sure people are publishing good work and that it is original and not the same

paper being rehashed. If it is going to be rehashed, make it a review article. The only way to avoid this would be for the institution to review everything that is submitted for publication. I think we have better things to do with our time than that.

Question:

Would someone who does this be an unethical person?

Dr. Ericsson:

I guess it depends on how you define an unethical person. It is clearly unprofessional, but does it rise to the level of unethical? I do not know.

Dr. Price:

If you submitted a paper to more than one journal at a time, that perhaps would be unprofessional. But if you are asked to state, as a condition of submission, that you guarantee the article is only being submitted to the journal that you send it to when you are sending it to more than one journal, that would be unethical.

Dr. Ericsson:

Most journals want to know that the paper is not being submitted elsewhere. I just had a paper cross my desk, and the author's secretary had included a transmittal letter to another journal that had rejected it. The paper was rerouted to my journal. Well, I suspected what happened. So I asked them to verify that it was not being submitted to multiple journals. Actually it is a lousy study. It probably will not get published in our journal, either. Those things do happen. We have to be on the alert for them.

Should the authors have the right, the obligation, to suggest reviewers to the editor? What do you think?

Dr. Davis:

I think there will always be instances where there will be a possible conflict with groups who disagree with your theory and you disagree with their theory. There are opposing theories. I think you should be able to suggest reviewers, but it is always up to the editor. Usually you have to have a good reason to suggest a reviewer because you do not want to offend the editors.

Dr. Ericsson:

You might not know everything in that field. You may not realize there is a bona fide intellectual difference of opinion. An author may urge an editor to find a reviewer who understands his theory and can give a balanced view.

Dr. Eichberg:

Let me explain the structure of our journal that may help you understand how we do the review process. We publish about 600 papers a year. It is impossible for the chief editor, or even the deputy chiefs, to know everything about every field. Consequently, we use field editors who specialize in the area being reviewed. To some extent, we are able to evaluate reasons that authors ask or do not ask for things.

In the case of suggesting reviewers, I think it is perfectly okay to make suggestions. The motivation for those suggestions may not always be totally honorable. Some reviewers may be friends of the authors. On the other hand, an author may request a specific reviewer not be used. This happens frequently, too. That really is kind of an ethical issue because the author may not want a reviewer who may be the leading expert in the field. Or you may know that the reviewer is a competitor of that particular author. This is an ethical dilemma because the input from the reviewer might be necessary in order to get a quality review. That is one of the issues that an editor frequently faces.

Dr. Ericsson:

I know someone who is an expert in travel medicine and I like to solicit his opinion because he writes a really good review. He offers a lot of good suggestions on how to improve the study. But the guy is grouchy. He has trouble doing much more than revise and reconsider. He rejects a lot of stuff, even though his verbiage provides the wherewithal for the author to really improve things and have a nice publication. I guess the authors have to trust that I will use him. A lot of times, the authors know that he has reviewed their papers. The author has to trust the work the editor is doing. If they do not, the editor may wind up on the firing line.

Dr. Eichberg:

An advantage is that the reviews are always anonymous, so the editor really has to make a judgment call as to whether the value of a reviewer's input outweighs the feelings of the author. If the paper is only reviewed by one person, you try to dilute whatever a potential reviewer might or might not say with additional input. In the end, the editor has to come to an overall evaluation of all of the opinions.

Dr. Ericsson:

I think that is exactly how I would handle that. I normally have three reviewers, but if I have reason to anticipate conflict, I will have another person right up front so as not to delay consideration of the paper. I think the bottom line is that the editor wants the fairest assessment of that paper. No one review determines the final conclusion about acceptance or rejection of a paper. It is generally a consensus from the recommendations of all the reviewers. If I see mixed reviews, I get another reviewer. I also advise the author why there will be a delay.

Question:

Should reviewers be anonymous?

Dr. Ericsson:

You have just applied for a grant to the NIH where the expert in that field is going to review your paper. Can you see the conflict of interest if you are known to the reviewer?

Dr. Eichberg:

Often a list of reviewers who have provided service to the journal is published at the end of the year, but it is hard to pick your reviewers out from the 600 reviewers who might be on that list.

Question (Dr. Grabowski):

In the past, reviewers were not anonymous. Then we went to a system where the reviewers are anonymous. Some journals have reverted to making reviewers known. Sometimes in our search for the perfect system, we try one out like anonymous reviewers. When it does not work, we go back. Are we defending something that is indefensible? We know who the reviewers are in each group.

Dr. Eichberg:

At the risk of defending the status quo, there is no system that will work all the time. The reason for anonymity is that a reviewer will feel freer to express an opinion without fear of retaliation. It is the responsibility of the editor, however, to take the reviewer's comments and make sure the comments are transmitted to the author in a nonabrasive or gratuitous manner. On the whole, I feel that the advantages of anonymity outweigh the feeling that somebody can secretly get us.

Question:

I have a question about the status quo. Is the anonymity assumable? Would the reviewer not know the author's name? I assume that the reviewer does know who the author is.

Dr. Eichberg:

They know who the authors are.

Follow-up Question:

So if a situation arises where an author has requested that a particular reviewer not review his or her work, does the editor exercise the option of anonymity? Would you, as editors, consider allowing the author to remain anonymous to the reviewer so as to reduce possible personal animosity or personal conflict that is of concern?

Dr. Eichberg:

I think it is something that might be worth discussion.

Comment (Dr. Grabowski):

What journals actually do not do is send out papers blind. Unfortunately, because people have to cite their previous work, or tend to cite their previous work, it is not too hard to figure out who it is. But at least there is some balance in that principle.

Dr. Davis:

Practically speaking, you can usually recognize who wrote the paper. It is a small area of expertise so you can usually recognize who is doing what.

Dr. Ericsson:

I want the reviewer to know exactly what is being reviewed. I want the reviewer to feel comfortable, to be as honest as possible, without fear of retaliation. That guides me in my principle of choosing to use anonymous reviewers. I think the other features, such as removing the title page, assume lesser roles.

As an editor trying to support a new journal, I contributed articles to my own journal to make sure it could go. My previous mentor and I worked together to help make sure articles were reviewed properly. I even considered hiding my name so that I would get an honest opinion. I try to 1) get the advice of other people around me, and 2) I send it to the most critical people I can think of. I still think they pull punches when they know. There are some awkward conflicts of interest there. You try to support a journal with a good article and you hope it is good work, but will the reviewers be willing to be honest?

Question:

Do you pre-read everything?

Dr. Eichberg:

I generally read it. I do not pre-read everything. It depends on the volume of manuscripts that cross my desk. We look at the abstract and some of the highlights of the paper. Then, we choose from a list of field editors who have expertise in that area. The

editor selected in turn selects the reviewers. Different editors have different characteristics. Some are better than others in various ways. That is kind of how the system works. All papers go out for peer review unless the editor makes a decision that the paper is not appropriate for the journal. For example, an author might submit a topic not appropriate for the journal.

Dr. Ericsson:

Once in a while we get a topic that is off the wall and has nothing to do with what the journal publishes. That is relatively easy. We encourage the author to submit it to another journal. In my office, I read the abstracts and glance at the rest of it. I remind the reviewers what it is they are reviewing. Sometimes I will look at a research letter or case report if I have expertise in the area. If there is any question, I will have at least one other editor review it. We can short-circuit some of these because we can review them quickly. They do not require being sent out to reviewers. Brief reports on up to original articles, review articles--these are sent to reviewers.

What about choice of journal? That is left to the author. Ethical issues are not involved here. Everybody wants to get into high profile journals. The journal faces problems involving publishing strategies. What about the issue of sneaking in unpublished data? How do you handle that? You might see it occasionally.

Dr. Eichberg:

Again, I think it depends on whether the review article is invited but not reviewed. There is a category of review article that is actually reviewed. And in that situation, the reviewer has to be responsible for finding errors in unpublished data.

Another issue that might relate to sneaking in unpublished data is how to handle data that is already published in a refereed publication. Is it ethical to have it appear again in an uninvited article? I think it is all right if you present it in a somewhat different way or in a different context. If you are making a somewhat different point, the review will be broader than for a specific journal article. You may need that data so the reader can understand the general points that you are making.

Dr. Ericsson:

And you acknowledge the source.

Dr. Eichberg:

And, of course, you acknowledge the source, often in the legend and certainly in the references. Then I think it is acceptable.

Dr. Ericsson:

We have about 15 minutes. Let us turn to the confidentiality of the review process. Can a reviewer also be an editor of another journal that might prefer to publish the article?

Dr. Eichberg:

Well, generally not. Is it possible that the reviewer would run the article down deliberately in order to get it rejected? I think that the reviewer probably would not do that because it would diminish the quality of the article in his own journal if he were to publish it later.

Dr. Ericsson:

I think there is some integrity in the system. Most people can be trusted to work as ethically as possible within it. I do not mind reviewing in the subspecialty of traveler's diarrhea for other journals. I feel I have an obligation to do so. I know the field well and I can help them. I do not even pay attention to those kinds of issues.

Dr. Ericsson:

Can the reviewer break confidentiality to mentor the author?

Dr. Eichberg:

I would say that mentoring can be done without necessarily breaking anonymity if it is done properly.

Dr. Ericsson:

That is what the review process is, in a way.

Dr. Eichberg:

That is where the quality of the comments become critical.

Dr. Davis:

But is the reviewer required to be anonymous? He or she has the right to be anonymous. But is the reviewer required to be anonymous?

Dr. Eichberg:

I don't know. That is a good question. I have not considered that. If a reviewer asks an editor to reveal his name, would the editor do so? I don't know.

Dr. Ericsson:

I don't know. I suppose I might. Especially if it were for a worthy cause. As editor, I will certainly help an article along. As a reviewer, I am tempted to help. I write my review in such a way as to give the author exact instructions how to make the article better. Hopefully they will do it, and the editor will see to it that they do it.

How does an editor proceed when the reviewer alleges that the author appears to have plagiarized, or appears to have published some or all of the data elsewhere? What do you do next? What are your obligations?

Dr. Price:

I can give you some case studies where editors have taken on that responsibility. In one case, a reviewer saw that her own words were being copied. They were referred to us to refer to the institution. The person wanted to remain anonymous. In most plagiarism cases you can generally tell who the complainant is because he recognizes his own words. So it is pretty hard to stay anonymous.

In other cases, reviewers said these images are clearly duplications of each other. One image may be lighter than another, but they are represented as two different samples, or the images are cut and pasted from the same source as representing two different experiments. Editors have referred those to the author. In one case the author said "My undergraduate student made a mistake and here is the replacement." But the replacement was not any better than the original. The editor said "There is something seriously wrong here and if you do not inform your institution about this problem, I am going to do it myself." In fact, the editor did follow up by notifying the institution and us. As it turned out, it was a major falsification case.

In a similar case in another journal, a reviewer said: "I do not believe this statement is accurate. I know this person has a history of irreproducible results, and I question the authenticity of this data in the manuscript." Again, the journal board decided to contact the author who blamed it on his technician. "Oh, my technician admitted fabricating this data and I will take care of it. Here is the substitute data." The board itself, though, referred that to us and we followed up. The institution asked the technician who said "I have never seen this before. Somebody forged my name on the signature block for the paper and I did not do this at all."

By taking actions responsibly and following up with notification to the institution or to our office, editors have exposed falsification and fabrication of data and have handled it sensitively and confidentially.

Dr. Ericsson:

I was reading in your publication, Dr. Price, that when it comes to plagiarism, you draw a distinction between substantive crypting and lack of acknowledgement of the trivial phraseology that naturally slips into your own writing. It seems to be a gradation in your mind. It would be a whole lot nicer if you could try to not have the exact words. I have faced that myself.

I had a reviewer review a review article. It was clear that the author was not on the cutting edge of the field but was a clinician who just wanted to write a review article. It was likewise clear when you read the issue that he had been picking and choosing ideas from a bunch of things. He was changing it into his own words. And it was not directly quoted. My own response to that was to call the author and say "Gee, this has been alleged. Why don't you go back and rewrite all this to make sure there is no question about it." And he said "Well, geez, I didn't do that." He seemed contrite and I felt comfortable about it. So I agree with you. I think there could be a gradation. I did not view that as egregious crypting but as lack of quoting. Yet, the reviewer got uptight about it because there was half a phrase that was exact. I think, as authors, you have to be cautious about that, though, because plagiarism is a nasty business. You do not want to ever be accused of it.

How do we select reviewers, Joe? Why would anyone want to be a reviewer?

Dr. Eichberg:

I have not thought of all the reasons, but recently Floyd Broom wrote an editorial in *Science* in which he stressed the centrality of the peer review process in the publication of science. He asked the question "Why do reviewers review?" "Why are they willing to do this arduous task?" He suggested the following. There are some, perhaps the minority; who have a passionate commitment to the scientific process. That is one reason. Another is that they want to add this to their CV and they particularly want to review for a journal of high quality. Those are some reasons that they are willing to do it. They may be hopeful that, if they review, their papers will be favored by that journal. In my experience this is generally a vain hope in terms of the quality of submissions.

Finally, and this is not necessarily a bad thing, they like to know what is going on in the field. They want an advance look. The very fact that they are recognized as respectable reviewers does afford them an advantage. I think it is one way, in a sense, that science is kind of perpetuated by a relatively small group of people--the most distinguished. They have the greatest advantages.

Dr. Ericsson:

As a mentor of junior scientists, do you encourage them to review?

Dr. Eichberg:

Yes. I encourage them as part of the educational process, for development of critical thinking.

Dr. Ericsson:

They get better at formulating things themselves if they have to critically analyze somebody else's work. Involvement in the editorial process and the review process for good journals and, particularly when somebody has been invited to be an editor, attests to a

certain level of national recognition that might be important for tenure consideration or some kinds of promotions.

Dr. Eichberg:

Selection of reviewers is really a very important responsibility of editors. First of all, they need to be known in the field and to be respected. And secondly, you can expect them to provide a substantive review, not a three-sentence review.

Very importantly, in terms of the reputation of the journal and the satisfaction of the authors, is the need to complete the review in a timely manner. That, probably, is the greatest single difficulty an editor faces. Not because the reviewers are deliberately withholding the information, but because they have so many other responsibilities that fitting this in is very difficult.

You get to know your reviewers after a while. If you encounter a reviewer who is biased about a subject, you have to take some pains to avoid known conflicts between groups. This is where the editorial knowledge is really quite crucial.

There are a couple of other issues that pose problems. Often an author will submit a paper that will be reviewed by someone and the paper will be rejected. Then the author will submit it to another journal and the same reviewer will review the paper. It happens quite often, actually. Sometimes the editor becomes aware of this and sometimes not. Sometimes the reviewers themselves refuse to review it. It is an excellent opportunity to do a hatchet job on somebody. This is a dilemma. On the whole, it comes to knowing the reviewers. But again, the editor must factor that into the total equation that leads to a decision.

Overall, I would say that the process depends first on trust, which has been emphasized by speakers earlier this morning. By that I mean trust on the part of authors that they are going to get a fair hearing. It certainly should be the intent of the editor to be fair and objective. After all, the editor's stock in trade is to maintain the integrity of the process and the reputation of the journal.

Dr. Ericsson:

In summary the whole editorial process itself, in trying to take care of conflict as it occurs, relies heavily on the integrity and the objectivity of the editor. Any journal ought to pick a good editor who can handle it—one who has a thick skin.

Any final comments from the panelists? Any final questions from the audience? Audience, you were great. You made it come alive for us. We thank you for your participation, too. Thanks.

Dr. Sandra K. Hanneman:

Thank you to our panel and to you, the participants, for engaging in an interactive and comprehensive discussion on the issues of authorship and publication. Our next session is "Records and Data." We are pleased to have Dr. Ruth Bulger back at the podium. This is the topic that she was invited to do, and we are looking forward to hearing it.

Ruth Bulger, Ph.D.
Vice President for Research
Uniform Services University of the Health Sciences
Bethesda, MD

Thank you again. The topic I was assigned was “Records and Data.” Yet, if you look at the program write-up, it states that my talk is going to go a little further. It states that I am going to establish that fundamental ethical precepts exist in the design of all research: its conduct and representation, regardless of topic. That is broad and difficult. So, let us begin.

We are all impressed by the rapid rate of change of our world and doubly so for the advances in science. There are over five million breakthroughs so far that have come from science. Changes are happening unbelievably rapidly, especially in the age of the human genome. They are very impressive given the progress being made. These changes are no more impressive, however, than the speed with which the media moves each of these medical discoveries from the pages of the *New England Journal of Medicine* to accessible news and magazine outlets. The media get advance copies ahead of the copies mailed to all the physicians to form a 30-second snippet the next morning on electronic broadcasts, regardless of whether the work has been done in an animal model or not yet in humans. The public wants to know how scientists work to stop disease.

In addition, the world of science no longer is bounded by country borders. It is truly global. Large pharmaceutical companies can do their clinical trials and sell their products anywhere in the world. In United States domestic policy, the relationships between academia and industry are thought to be good for economic development. I think this underlies the interest of the public in disease. The interests of some of the politicians in our economic development underlie the large increases we are seeing in the NIH budget, which presumably will ultimately move technology out to the public. The NIH budget will develop technology and then move it to the public for the public’s good and for the country’s economic development. Every scientist knows that modern science is expensive and relies on public support. We as scientists rely on the funding agencies.

However, in this time of rapid change, we still have to look at the principles that underlie our conduct of science. We discussed those this morning.

When we do these talks, we are assigned topics in spheres of accountable actions. Mine is in the area of data recording and analysis. The ability to be honest and objective in observations is very important. Referring to the slide, no one wants to be like this jailed suspect here who said, “I always thought that my level of scientific misconduct was well within community standards.” As you know, and as was said this morning, the definition of scientific misconduct is fabrication, falsification, and plagiarism. Those are the three biggies--FF&P (This is the Public Health Service definition. There are several definitions. NSF has a different one). Then, there are other practices that seriously deviate from those that are commonly accepted within the scientific community. This does not include honest error.

The first--fabrication, falsification and plagiarism--are ones that ORI gets involved with. In general, the other practices that seriously deviate from those that are commonly

accepted tend not to be handled by ORI. The universities can have policies on these practices and can also take whatever actions they choose.

Of these three biggies--FF&P: fabrication, falsification and plagiarism--two of these, fabrication, the making up of data, and falsification, the changing or incomplete use of data, relate directly to the topic we are talking about today, which is records and data.

Misconduct is on the minds of various people. I subscribe to *The New Yorker* just to get cartoons for my talks because they are so pertinent. This one shows a salesperson saying, "It's the bold new fragrance from Uncle Sam, misconduct." If we are trying to stay away from misconduct, there are several ways we can teach responsible conduct of research to students. The most common--and sometimes we forget it--is that we are teaching by example. All scientists, in whatever they do at any time, are always teaching how science is done.

The question is not whether we are teaching by example, but rather to focus on the content of our teaching. I teach research ethics at three different schools. Quite often I will ask students if they have seen an animal mistreated in the laboratory. You would not want to know how many hands go up. I also ask my students how many have been encouraged to find certain results and so on. Again, you would be surprised at what you see is being taught by example. Thus, getting to our faculty is an important issue as well.

Another way of teaching is to arrange for the discussion of cases. Students love to discuss newspaper or science articles or other articles that bring up issues. This kind of teaching is done best in smaller groups where students can interact with each other. It has been shown repeatedly in the literature that using groups of students serves to increase moral reasoning skills. Students will often say, "Gosh, I didn't know other people didn't think what I thought." Maybe this afternoon in the breakout session we can look at some of these techniques. That is how we are, presumably, teaching moral reasoning skills that will have an effect on the behavior of the student. This is the result that we are interested in achieving.

We can teach by imparting some material through lectures like in this conference. This works best by teaching principles and approaches. Or we can teach what the regulations are, what the rules are, and what the thoughts in various areas are. It does not necessarily stimulate moral growth, but perhaps it is useful information for them in their work in the laboratory.

There are various steps in research. I think that this talk is on the program because in it I describe what is happening in experiments, in the recording of data, and in the analysis of the data that is crucial to science. Science is data-driven. Science is evidence-based. That speaks to the importance of how we maintain records and our data. We hope we never get into a situation similar to the one where this researcher said: "I already wrote the paper. That's why it's so hard to get the right data." How often does the expectation of what the results are color what we see? So that is why these are important topics.

If you go back to the principles I discussed earlier, data is central. Honesty and objectivity relate to how we collect data, view data, report data, and analyze data.

Scholarly competence. We need to use the correct methodology and appropriate statistical analysis. That is part of scholarly competence.

Respect for others. This principle deals with how we treat colleagues and students. Do we treat our students well by teaching example? Do we share data with other colleagues, students, and others? Respect for others is again a data issue.

Stewardship of resources. This principle deals with keeping data accurate and up-to-date. If you do not keep your data accurate and timely, then the study will probably need to be repeated, and this is a waste of resources.

Let us move into records and data. We are going to talk about why institutions should have data policies and what those policies might contain. We will talk about some ways the data is recorded and retained in the system and what might be good and bad about certain ways. We are going to talk about who owns the research data, who should have custody of the research data, who should have rights to use the data and the products of the research. We are also going to talk about what kinds of research data you have to retain. There are rules about that and what should happen to research data when a principal investigator, a graduate student, or a postdoctoral fellow leaves an institution. Some of that relates to the policy of the institution.

What we need to realize is that the principal investigator (PI) in the laboratory is the person responsible for the validity and the quality of all data and manuscripts that are generated in that laboratory regardless of the personnel involved. The PI has an overall responsibility for what goes on in the laboratory. He or she is responsible for educating personnel so that they do what is expected of them in an acceptable manner. The PI makes certain that personnel follow written procedures. The PI also is responsible for maintaining an open environment so that if somebody makes a mistake that person can come to him or her without fear of recrimination. This is most important. The PI must maintain that the only irreversible mistake anyone can make in a laboratory is to not know a mistake has been made. If somebody makes a mistake and it is not corrected, you can throw away that whole experiment. A serious problem occurs because the researcher does not know when a mistake is made.

It is also important to frequently review research notebooks. If you are the PI and you have people working under your supervision, it is very important that you go through their notebooks with them, that you know what the data is, and that you sign the notebook to indicate that you have reviewed it. This is doubly important when patents are involved.

I would like to talk a little bit about why I believe every institution should have a data management policy on how data is handled in that institution. I think first and foremost is that one needs a data management policy to keep an institution from applying a misconduct policy to a data access issue. In some schools in our city, data issues were mistaken for misconduct issues. I know that ORI does not get into this, but institutions do and they need a separate policy. It is also important to let the investigators know they are responsible for regulations that govern research. One of my major problems is how to teach my investigators what are the basic things they can and cannot do.

Any data management policy should state that the institution insists that all data must be valid and properly recorded. It should state what data has to be maintained and for how long. Universities have varying lengths of time that they require data to be maintained. Generally, it is between three and seven years with perhaps an average of five years. Data policies should state that data needs to be available for review under appropriate conditions, and that it does not apply to all conditions. For example, human subject

research can be examined by the institutional review board (IRB). In fact, the IRB audits yearly. Sometimes the IRB does a data audit every six months if the experiment is very invasive. The experiment can be audited by the FDA. In fact, we are having our FDA audit on the 22nd of March. It can be audited by more than one agency (ORI, funding agencies) for different reasons, such as misconduct. A few months ago, National Heart, Lung, and Blood Institute came out and said that we want to audit this person's data, and we had to audit the data. It took a day. So basically, data can be audited by a variety of people and must be produced in a form showing responsible conduct.

A data management policy also can define the responsibilities of various people in this process. It can advise investigators what to do when they relocate. The policy should say, if you are going to relocate, adhere to the following procedure: You will write us this; you will list it; you will do so and-so; and these are the conditions. Usually, institutions will let the principal investigators take data with them, but institutions retain certain rights to that data. For example, they might say you cannot destroy this data without our permission, or you must let us have access to it.

Furthermore, such a policy should state the university's position on how long data can be withheld from publication, specifying the length of time. For example, at our institution we do not allow any data to be held from publication for longer than sixty days. We will hear about that tomorrow. Many people hold data longer than six months, which is a real concern. This could be a useful policy when dealing with industry, i.e., when you are negotiating agreements with them.

Finally, I think that having a data management policy in place would also deter irresponsible conduct because the data is always there. It is always available for review if you have formulated a policy. I think it is very important to have a policy that protects the rights of all those involved in getting the data or the products produced under grants. Someone can adjudicate disagreements between people when issues arise over who owns the data and who has rights to it. I think schools can have different policies on these issues, but it should be clearly stated as to who makes decisions. Is it the institution, the dean, the chairman, the principal investigator?

In short, I am not sure that many institutions have data management policies, but I believe they need them. Specifically, these policies should state who is covered under the policy (i.e., students), what kind of data and products need to be maintained, who owns the data, who is responsible for maintaining the data, how and where the data is kept, who has access to the data, how the data and products will be shared, when the data can be destroyed, and how a move is to be handled. In addition, the policy should state what you are going to do and what sanctions will be applied if there is noncompliance in any of these issues.

Let us turn to the collecting and recording of data itself. I think most laboratories have two kinds of laboratory information systems or notebooks. The first I would call the methodological notebook and the second would be the experimental notebook. We will talk about storing data in computers in a minute.

The methodological notebook, or methodology notebook, was one of the most important things we ever had in our laboratory. Why? Because it has all your standard procedures in it. All the methods you are going to use to analyze things, the recipes for every solution, the references and the literature to those recipes, and the dates to which you

make any changes in the above. I think most people keep something like that. You can keep it in a bound notebook, but it is not as convenient. Data can be kept in a three-ring notebook and enclosed in sheets of clear plastic, which is necessary because people who make up solutions tend to take the paper and pour whatever the solution is on top of it during the process. Or data can be stored in a common computer. In any case, data needs to be convenient to everybody. Generally, it needs to be in the laboratory. It is indispensable in training technicians or new postdoctoral students. Everybody copies the notebook for his own use. When they leave, they take the notebook with them. It is the key to their ability to keep writing papers and continuing science. That is the first kind of data that is kept in the laboratory.

The second kind is experimental data; and, again, each laboratory will have its own system since different kinds of data exist in different laboratories. However, I will take a minute to review some of the ways people are keeping these kinds of data. Each laboratory needs to have rules about how the data are kept in that laboratory. The laboratory needs a standard procedure. I think most people still use the hardbound notebook with numbered pages. Other laboratories use three-ring notebooks and, again, some of the pages are covered in plastic. However, the three-ring binder allows them to insert pages. If you use a three-ring notebook, you should date and number entries so that there is a numbered record of all the experiments that are done in the laboratory.

One of the hardest things is to teach people never to write anything on a scrap of paper. Often, it just happens. Here it is, you know, over by the sink where there is a coffee cup sitting, and there is the scrap of paper with data on it. This is what happens when you run a laboratory, but it is just unacceptable. Finally, in the modern world there are an increasing number of laboratories that store basic data in computer files. We will talk a little bit about the problems of that and how to guard against them.

Most laboratory notebooks have a table of contents in the front. As you do the experiment, you enter them in the table so you can find the page you need when you need specifics on the experiments, such as what was done to your 6-12 animals. Again the pages should be numbered consecutively. You should enter the information immediately in ink. If you make a mistake, draw a single line through it, no more. Write the correct information below the information you have changed and date and initial the entry as to when it was changed. These are basic ways of handling data. Experiments in a bound notebook are kept in chronological order and deviations that happened during the course of that experiment are also entered. There are specific rules for entering information. For example, if you open an animal and discover it has a tumor and you have to abort the experiment, you would not take data. Instead, you would use another animal.

There can be different kinds of data books. People work at different stages in the experiment. For example, we had an animal book because every animal that we used was recorded in that book. We had books for clearance data and for negative logs, and we had different books--all hardbound, all numbered—for recording the appropriate data. You might have a different book for different kinds of experiments.

What should be included in notebooks? I have seen all sorts of notebooks. At the minimum, you date the page and write who is doing the experiment. You should write what the experiment is and state any background information that is appropriate. We enter the animal number, its weight, the amount of anesthesia, any treatments, any observations,

whatever we see as we do the experiment, tissues that are taken, and so on. The best notebooks I have seen, and I have seen some really beautiful notebooks, go much further than that. In these notebooks, the investigators put in why they were doing the experiment and what the experiment was. That is very important, especially if it will be used later in a patent application. Writing detailed information makes an investigator's reasoning clear. You can also determine when the experiment was first conceived. If you are going to use the information for patents, you need a witness to review the data, read it with you, sign it, and date it to document when it was entered and by whom. It is amazing how many scientists now think in terms of patents and applying for patents. This is an area that is relatively new to us.

In the past, I photocopied my data book monthly and kept a copy somewhere else. One of my worst nightmares was that all my data would get lost. If you lose your data book, you have lost everything because everything relates to it. An interesting footnote to this is, in our office, we had a risk assessment person analyze the laboratory recently. One of the things he checked was where data was located. One of the things he said was to make sure a copy of all data is kept in a different place. The reason is that it lowers the insurance cost for your risk policy.

Some laboratories keep data on computers. There are some advantages to this, but there are also problems with it. One of the questions people raise is how to keep detailed accounts of data in computer files. Sometimes that information is stored separately. Sometimes you do some analytical processes on it. Somehow, sometimes, you lose control. But if you need to access the data at a future time, you will get exactly what you did and did not do. Electronic records are thought to be more easily altered than those written in ink. Most people who store data on computers keep a hard copy. Some put the hard copy in a book. Again, the hard copy should be signed, witnessed, and dated. We tell our investigators to print out any material that could relate to a patent, have it witnessed, and store it elsewhere to ensure that they have proper backup for any patent filing.

Other people suggest that a third copy be kept with all the results. In that way, when you go to write a paper, you have all the data in one place. There is an association called the Collaborative Electronic Notebook Systems Association (CENSA). They are working on perfecting a system where they can close the file, digital time stamp it, and get an electronic signature on it. The system does not exist yet. When it does, you will have the data in the computer with proper backup. If you are interested in that organization and what they are doing, you can access them at: <http://www.censa.org>. The literature still describes people having problems with keeping data, particularly data on which statistical analysis was done on the computer. I suggest you look into this carefully before you choose a system that relies entirely on electronic records without the backup of a hard copy.

What kind of data needs to be stored? There are three kinds of data that are classified. One is primary, original, or raw data. Another is secondary or compiled data, which is original data that has been subjected to statistical analysis. The third is tertiary data, which is derived from secondary data. It could be a chart or whatever relates to the research.

There is general agreement that primary data has to be retained if data comes from government grants. The data should be kept under conditions that will preserve it. If you are keeping gels, for example, you have to ensure that it will be preserved.

What is this primary data? I think this may surprise some of you. Both the EPA and the FDA define it this way: "Raw data means any laboratory worksheet, record, memorandum, note, or exact copies thereof that are the results of original observations and activities of a study and are necessary for the reconstruction and evaluation of the report of that study." Raw data includes photographs, microfilm and microfiche copies, computer printouts, magnetic media, including dictated observations and recorded data from automatic instruments. The regulatory agencies also include specimens as data if they were developed in the course of that research. That is what you are supposed to keep. That is a lot of data.

Question:

Do you have any preference on how to store data?

Dr. Bulger:

There are many kinds of data. Some of my negatives are in my garage. There are so many kinds of data that every laboratory has to address for itself how it is going to store data and where the data will be stored.

Question:

Who owns the research data?

Dr. Bulger:

This is a big question. First the legal view. I refer you to an article written in 1991 by Estelle Fishfind, who is a lawyer at Johns Hopkins University. It was in *Academic Medicine* 66, pp 129-133. It is a classic article in which she says the data is owned by institutions "as a natural consequence of the conventional relationship between employer and employee as it is developed under what is referred to in the law as common law agency doctrine." This definition reflects all the data you get in the course of your employment. If a scientist works in his garage after hours and collects data there, that data is not considered to be collected in the course of his employment. If he uses that data to get a patent, for example, his employer will not assist him in filing the application, or settle any disputes that might arise, or pay any fees, because the data does not belong to the employer.

What is the institution's view of who owns the data? Most institutions and data policies I have seen remain silent on data ownership. When I wrote a data policy, I did not say who owned the data. Writers of data policies do that, not because we think the institution does not own the data, because we think the institution does, but rather because we do not want to wave a red flag in the eyes of faculty who generally think they own the data when they do not. Most data policies do not specify who owns the data, but I think the writers of these policies know who owns it.

Most policies, in fact, state that the principal investigator or head of the laboratory has the right to and the responsibility for the custody and maintenance of the research data. That is reassuring because that is exactly what principal investigators want. They want custody of the data to maintain it for their own use in writing papers. That is the standard that is set. As I have said before, institutions generally let the principal investigator take the data with him or her, but the institution retains certain rights, such as rights to access, rights to specify data retention periods, and rights to demand that the investigator preserve the data, and so on. In our data policy, the principal investigator signs a paper stating that he or she will do certain things and then the data is allowed to be moved.

What is the government's position on who owns data? There are several positions. One position is from the Office of Research Integrity (ORI). In September 1994, in the little newspaper that they put out, ORI said: "research data generated under PHS funding generally is owned by the grantee from the institution, not [by] the principal investigator or the researcher producing the data. The institution is the grantee and assumes legal and financial accountability for the award of funds." NIH guide Vol. 24, No. 33, September 1995, says: "under the grant mechanism, recipient institutions have custody of, and primary rights to data developed subject to the government's right to access."

If one is generating data under a contract instead of a grant--those are grant-related activities--one uses different legislation, and that is called the FAR. It involves whether someone has rights or not to have copies of the data or to use the data in their work.

What is the industry position? In this case, ownership of data is negotiated with industrial sponsors. It is very helpful if you have a university policy that states how long industry can hold data. Ours states 60 days and no more. Then you can say, "I'm sorry you can't have the data longer, because our policy is such and such." In some relationships between industry and science, a school may abrogate its right to data and let the industry have it. I wonder, in those cases, then, why they are doing the research. That again is an institutional decision and your institution needs to have a stated position.

Another kind of data that is dealt with is the case report form. All people doing clinical trials fill out case report forms. Usually the pharmaceutical company involved wants the original forms. The investigator should keep a copy for two years past the marketing approval of the FDA. Medical records are always the property of the institution. No matter who owns the data, the principal investigator has the responsibility to maintain it. There is usually a university policy on data retention, which is generally five years.

Let me quickly run through some of the exceptions. The FDA requires that data from clinical trials should be kept two years after the marketing application is approved. If you are working with clinical trial data and if the drugs are in the marketing phase, you must keep the data for two years after that. In some cases you could end up keeping the data for up to 20 years. It may take 12 to 14 years just to get through this process, including the two years after the shipment and delivery of the drug, investigational use has been discontinued, and the FDA has been notified. That is the rule for clinical trials.

Data related to patents is kept for the life of the patent, which is 20 years, in order to guard against interference or infringement of your patent. That data remains at the institution even if you move. Data should stay with the institution that has the patent. Data from federal funds is generally kept three years after the last expenditure report. The expenditure report is usually due 90 days after the grant closes.

Patient records are owned by the clinical care agency. They are not research records. Incidentally, if you use clinical records, check to see if you have the proper human subject approvals for use of those records. They are to be maintained indefinitely. If data is contested or if ORI has an interest in your data for some reason, you are to keep that data until all litigation claims, audit findings, and misconduct charges are resolved.

Who controls the data? Again, institutional policy is needed; it is up to the institution to state that the PI has the right and obligation to keep and to be able to produce all supporting data for manuscripts and grant applications. That, of course, is what the PI wants as well.

There are a variety of disagreements as to who can use the data for papers and who cannot. The institution should have a policy stating whether the PI or the university has the right to make that decision. In this situation, I prefer the university over the PI, because the university can balance rights among various people more equitably. And it is important to know that will occur as a matter of course.

When an investigator moves away, the policy should state what will be done with the data. Will the PI promise to preserve it? Will he or she make it available? What is going to happen to others working on the project? This question brings us back to data access principles that your institution has laid out. If your institution does not lay them out, you may have a problem.

We had a graduate student taking one of the ethics courses. He said that a student had just gotten a Ph.D. and was leaving. He said the student could not take any copies of the data. So the graduate student asked what he should do because he was going to be in that same laboratory. The questions are: "What is the policy?" "What is your institutional policy?" "What kind of graduate program do you have?" "Is the graduate student a technician working on the grant or an investigator who is working in an independent area of research?" The question of who has the right to take the data is an institutional policy issue. In our institution I asked our lawyer, and he advised me that we own it but he would let the chairperson decide. This answer raises another question, "Should the graduate student ask the chairperson?" You need your sponsor to be your supporter. I suggested to the student that he discuss it with his sponsor. If his sponsor says he cannot take the data, he may choose to stay in the laboratory or not.

One last thing I want to talk about is the issue of the Freedom of Information Act (FOIA) impact on research data. Senator Richard Shelby placed an amendment in the 4,000-page 1999 appropriations bill, without any hearings, without any discussion by anybody, that directs OMB to revise Circular A-110 . Circular A-110 controls how you run your grant in an institution. It is sort of the bible of what you can and cannot do. Senator Shelby put in the following words "To ensure that all research results and data are made available to the public through the Freedom of Information Act." It further says, "This would allow the American people to review data for themselves to ensure that the conclusions are solid."

As you can imagine, this could be a problem. There are exemptions to the FOIA. There are nine exemptions by law. Any information that is identified as national security information can be kept confidential. There are many problems with the law. In the first place, data has not been defined. What constitutes data? Are videotapes data? Are recordings data? Are gels data? What does data mean? Is Senator Shelby using the same

definition of "data" that we use for data retention? What if you have a tape of an interview with a human subject who can be seen on the tape? Is that subject to FOIA? Do you have to make a copy of it? How do you safeguard privacy?

Another question that arises is whether data could be requested and used before it is published? Could it be requested in the middle of a clinical trial? Do you have to break a clinical trial and send the data to this private citizen or that company at their request? Would it invalidate the informed consents for an ongoing study? If all that information has to be given, would you have to go back and get new consents from all of your past patients? Is it retroactive? Is it proactive? Who knows? Who pays the cost? That's completely unclear.

What will happen to industry? Will it share its information with non-industry scientists with whom it is partners on projects? If industry knows that it is subject to FOIA the minute that its information gets into the hands of anyone supported by government funding, does that conflict with the purpose of the Byah/Dole Act, which is trying to pull industry together for the good of getting technology and transferring it. How does this relate to the Byah/Dole Act? It is completely unknown.

We are a government agency so all our information is subject to FOIA. Some interesting things are happening. We have had to copy every one of our animal protocols, all minutes of our animal committees, all minutes. Can you imagine copying that amount of data? We had to hire people to do it. The requesting party presumably is supposed to pay. However, if they pay the government, the money goes into the Treasury. So we still have to bear the entire expense on our own. Also, we receive FOIA requests because we work with a foundation. Other foundations look at what our agreements are with that foundation. There is a lot of mischief that can go on in this area.

The OMB circular is open for comment. I think it is important that scientists comment. Someone said at lunch that there are 171 comments. Two-thirds of them are for the act. So scientists need to comment. There may not be any fixes for this law. Remember it is a law. OMB has come out with some very tight language regarding the release of information. The language states what can be done after publication, that the release is through the agency that was involved (NIH for example), and that information given out can only be information that underlies policy decisions.

After we go through this process of comment, putting it out, and re-commenting, the question still arises: Will this stand up to legal challenge when the language is so broad? The person from Senator Shelby's staff said that basically she did not think so. One answer that might emerge is the result of George Brown thinking of putting in a bill to repeal this. That action would probably be the best way. Then we have to ask: When does the public have a right to the information and how should they get it? There probably are some good reasons for the public having access to this kind of information, particularly about the underlying government regulations, to see if it is valid.

We need to have some way to ensure that the data to be distributed is distributed at an appropriate time. One such way is to have a National Academy of Science/Institute of Medicine study. Another way is to have government agencies work with investigators to develop a plan so that we can do this with a scalpel and not with a meat axe. People should register their comments about what should happen and perhaps write Brown, who is very important. I would say that we have come back to "chance favors only the prepared mind."

It is better to be safe than sorry when you are talking about data. Remember, for the outcome that you want, it is necessary to be educated, prepared, and alert. Thank you.

Dr. Sandra K Hanneman:

Thank you Dr. Bulger. I'm sure the issues you raised will provide for heated debate in the breakout session.

Our next speakers will address the topic "Ethics of Randomized Clinical Trials." First, we have Dr. Harold Vanderpool who is Professor of Preventive Medicine and Community Health at the University of Texas Medical Branch at Galveston. The second speaker is Dr. Dorothy Macfarlane, who is Acting Director of the Division of Research Investigations at the Office of Research Integrity.

**Harold Vanderpool, Ph.D., Th.M.
Professor, Preventive Medicine & Community Health
Member, Institute for Medical Humanities
University of Texas Medical Branch at Galveston**

This is a great conference. May I express my genuine appreciation to all of you who have put on this impressive symposium. Dr. Sandra Hanneman, Ria Griffin, Elizabeth Heitman, Joseph Jones, Paula Knudson, and many others. The title of this address is: "The Values and Functions of Ethics in Research Involving Human Subjects." I will talk a good bit about institutional review boards (IRB). When I mention IRB, I include nurses, members of research teams, the researchers who are primary investigators themselves, and certainly also IRB members.

What do I mean by the values and functions of ethics in research involving human subjects? The title of this talk coincides with certain recent developments in the United States. I will begin with and then refer several times to the work of the advisory committee on human radiation experiments (Advisory Committee), whose final, somewhat lengthy 900-page report was released in 1995. This committee was a forerunner of the present National Bioethics Advisory Committee. Its function was to review various types of radiation experiments that had been done on Americans before and after the Second World War in order to make recommendations.

The Advisory Committee report has been influential in publicizing their message that "efforts must be undertaken on a national scale to ensure the centrality of ethics and the conduct of scientists whose research involves human subjects." The existing national commission then said that there was a need to determine whether establishing competency in research ethics should be a condition for receipt of federal research grants, both for institutions and individual investigators.

Within months, the President of the United States created the National Bioethics Advisory Committee with the immediate charge of putting the recommendations of the advisory committee on radiation research on the table for deliberation. These recent enactments invest ethics with enormous value and visibility. But how do IRBs presently value the ethics of research? Should they, or should they not, invest ethics with greater value and visibility? I suggest that there are fuller possible responses to these questions.

Each response represents a different understanding of the nature and function of ethics in our deliberations regarding human subject research.

I will use the term ethics and research ethics to refer to the modes of reasoning and the moral imperatives within the extensive literature on the ethics of clinical research. My description and comparison of these four points of view are designed to enable and challenge each of us to identify what we think about the values and roles of ethics in our work and deliberations and to assess the strengths and weaknesses of our position. You might ask yourself right now: What do I assume the role of ethics to be?

The first response to the questions asked is that ethics is considered only marginally. That is, ethics is marginal to the overarching concern of abiding by the United States federal regulations and the regulations of one's university. This notion is deeply ingrained in our current system of regulatory control. The federal regulations say, for example, that the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.

Ethics is not included in this itemized list of what we need to employ in order to determine whether research protocols are acceptable. To compound this problem, within the list is the directive that standards of professional conduct (namely, codes of ethics from nurses, professionals, psychologists, and physicians) are essential criteria for ascertaining the acceptability of research. Unfortunately, the notion that codes of professional conduct can determine the acceptability of research conflicts with the warning of the advisory committee on radiation research that the ethics of research must be distinguished from, not confused with, the ethics of clinical practice. The Advisory Committee particularly has in mind a distinction between the degree to which the ethics of clinical practice involves relationships to patients where the patients are not understood and recognized as self-choosing agents and the degrees to which they must be in research.

This and other factors in the federal regulations contribute to the common assumption that the IRB, researchers, and others do not need to accent the significance of ethical reasoning in their review and approval of research. This is in part because it is assumed that the regulations rest on ethical principles. Instead of learning about ethics, many of the IRB members assume that they must instead be thoroughly familiar with federal regulations and rely on local IRB traditions, personal beliefs, and common sense to reach decisions. Studies have shown that IRBs spend most of their time applying the rules within the regulations, especially the rules involving informed consent and informed consent forms.

This bureaucratic way of proceeding appears, according to studies, to be widely utilized in IRBs, even as it marginalizes ethics. Studies have shown that IRBs rarely study the *Belmont Report* and pay little attention to the literature on research ethics. Studies have also shown that most IRBs offer little or no training in ethics or in the dynamics of group process to their new members. Some IRBs are changing this. At the University of Texas Medical Branch we now have short courses on research ethics, but often IRB members do not attend.

Based on his own experience and study, Leonard Glantz argues that IRBs "think ethically only when they deal with areas of research that are not governed by the regulations." Once federal regulations are enacted, they generally are not inclined to adopt

stricter guidelines than what the federal regulations require. Glantz says that “if the question is whether the informed consent is adequate, one looks at section 44.116 to see what is required. Can there be a waiver to informed consent? By looking at sections 46.111 and 46.116 one can determine whether the standards for waiver of informed consent have been met.”

While personal biases may enter into this discussion, Glantz says the decisions are generally shaped by external rules. Examples of the uncritical following of, and adherence to, the regulations are found in the final report of the Advisory Committee on Radiation Research. I refer to that because the members of this committee did two very extensive studies of different kinds on what is going on with protocol review. The committee discovered that many consent forms use “boilerplate language drawn from the regulation to cover critically important ethical issues, including alternatives to participation, confidentiality, potential benefits, and the voluntarism of participation.”

Most, if not all of us, myself included, who have served on IRBs and have worked with research protocols are familiar with this boilerplate language. Here is an example. “Taking part in this study is entirely voluntary. You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled.” I do not think I have seen an IRB form that did not have those words in it. The boilerplate language that, for example, asserts to the prospective subject that participation is voluntary, sweeps the truly important ethical issues pertaining to the voluntarism of the research subject under the rug.

Whether research participation is, in fact, voluntary, whether prospective subjects are being respected as self-choosing agents, depends not only on just telling them that participation is voluntary but also upon who solicits their consent, under what conditions, and by means of which discussions, which documents and procedures. I would argue that research protocols that use the right terminology, voluntarism, without grasping what the term connotes and requires ethically are vacuous. Beyond emptiness, using ethical language without heeding what it logically requires can easily mask wrongs and harms with the appearance of virtue.

Consider how ethics is further marginalized. The federal regulations assume that the diversity of IRB membership strongly contributes to the protection of human subjects. I think we would all agree that it contributes more to the protection of human subjects than a uniformly non-diverse committee would. But if we look closely at this issue, there are a variety of reasons why diversity itself will not work as a bureaucratic measure. More is needed. I argue that more involves becoming more ethically aware and sensitive. Even though diversity exists within the committee, there may be people who have not really thought about the ethical issues in a more in-depth sense.

The IRB may not feel it has much public accountability. We have just seen how public accountability is an issue on the floor of the government at the present time. IRB meetings, even though they are open to the public, are essentially conducted in secret except for one outside member who, by the way, is easily co-opted. I don’t mean this in a devious sense; I mean only that they all co-opted as a friend or acquaintance of those already on the committee. Of course, the influence of institutions and personal economic self-interest easily depends on the IRB deliberations in spite of its manifest diversity. Regardless of the underlying reasons for marginalizing ethics, it persists. Why worry over utilizing,

recovering, and thinking about ethics when the federal regulations package ethical principles as mandated courses of actions and when most IRBs are trying to make sure that the research protocols conform to these regulations?

In contrast to these views, the current system minimizes ethics, the second, third, and fourth points of view--that I will sketch-- embrace the need to utilize, if not recover, the centrality of ethics to employ that phrase of the radiation committee for our deliberations. My discussion of these viewpoints will indicate why the just-sketched features of the current system fail to protect adequately the rights and well-being of research subjects and how attention to research ethics offers greater protection.

The second point of view concerns the value that functions of ethics manifest loyalty to the *Belmont Report* which was published in 1979 and which set forth the ethical principles and guidelines for research and their applications. This loyalty is exemplified by the Office for the Protection from Research Risks, which in its most recent guidebook called the *Belmont Report* has a seminal policy statement that contains the “three quintessential requirements for the ethical conduct of research involving human subjects.” Of course, you know these to be beneficence, respect of person, and justice. This view values the thinking of the national commission that oversaw the crafting of the *Belmont Report*. And, by the way, a group of us are going to meet within a couple of months to review and possibly revise that report.

The *Belmont Report* calls upon us to distinguish the ethics of research from the regulations of research. Belmont itself says that the regulation's rules often are inadequate to cover complex situations. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized, and interpreted. IRBs and researchers who uphold this view regarding regulations will regard the regulations themselves as establishing minimal standards for the review of research. This push for the incorporation of broader ethical principles fosters various levels of interaction between IRB members and investigators and causes thorough discussions of protocols with recognizable ethical problems that cannot be handled with mere boilerplate language.

To illustrate the inner play between ethical reasoning and regulatory rules, consider how the “no more than minimal risk” rule in the federal regulations should be applied to research involving children. The federal regulations define minimal risk as the possibility and magnitude of harm or discomfort that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine, physical, or psychological examinations or tests.

In practice, the phrase “performance of routine, physical, or psychological tests,” which fits the minimal risk definition, is taken to mean everything from gently scraping the inside of a child’s mouth with a wooden spatula to remove surface cells (the buccal smear) to taking fluid from a child’s middle ear via a needle passed through the eardrum. The latter is allowable under the given definition of minimal risk because it is regularly done in clinical practice. While none will quarrel with the buccal smear, the ethical permissibility of the second depends on what? Obviously it depends on whose perspective is being used to determine what is ordinary or what is risky and not risky. Should minimal risk be determined by the researcher, by IRB members and the researcher, by parents, and/or by the children? The subjective dimensions of minimal risk determinations are not addressed

in the federal guidelines. And, rightfully I should say, they are now the subject of rather intense debate.

Ethical reasoning over the permissibility of minimal risk protocols involving children requires not just an assertion of the federal regulations in some straight fashion. But rather a critical scrutiny of what this key regulatory concept needs. Only then can a proper decision about whether its application will or will not protect child subjects from harm be made.

As a second illustration, consider how those who are loyal to Belmont can, and will, use these principles to revise the United States federal regulations. When the *Belmont Report* discusses the voluntarism of research subjects, it does not just say we should tell every research subject your participation is voluntary. The Report says that the issue of voluntarism expressly deals with coercion, undue influence, and unjustifiable pressures in ways that, if heeded, would protect research subjects from several of the disturbing unethical practices that were discovered by the studies conducted by the radiation advisory committee. These accents in the *Belmont Report* are all but lost in the regulations. Upon listing the basic elements of informed consent, the regulations collect the complex issues surrounding voluntarism into the phrase: "A statement that participation is voluntary should be provided to every subject." These points illustrate why ethical reasoning needs to be discovered as a central concern by every researcher, member of a research team, and IRB that might not otherwise critically follow the regulations. Ethics can be put in straight forward ordinary terms. We do it all the time. The question is: "Can we become aware of our assumptions and our patterns of reasoning?"

The third view of the roles of research ethics is what I would call the virtues of character view. This is in addition to the Belmont view point. This third perspective on the value and roles of ethics in IRB and researcher deliberations can be called the virtues of character view because it assumes that all who conduct and review research proposals should discover how our virtues of character foster ethical knowledge and competency. IRB members and researchers who adopt this perspective will not lapse into the mold and moods of housekeeping bureaucrats.

There are more parallels between conductors and reviewers of research and practicing nurses and physicians than we might otherwise imagine. The physician-anthropologist writing about doctors, author Dr. Arthur Klineman, illustrates how doctors with different virtues and outlooks experience medical practices in exceedingly different ways. Some are absorbed in what they are doing. Some do what they were trained to do but have lost the initial levels of commitment, excitement, and enthusiasm. Others feel constantly hassled by modern medicine and its bureaucratic and legal constraints. They all practice medicine but have very different attitudes and task orientations. Klineman's vignettes of physicians in practice reveal that those who remain deeply committed to their patients view themselves as curious. That is one of the virtues they maintain. They view themselves as students of nature and human nature. In that state of mind, they go to the hospital with a new set of possible stories and discoveries about the human dimensions of the care they give. And they go as doctors who think in views about the many facets of human life through their day-to-day experiences.

William Carlos Williams, one of the greatest of modern poets, says in his autobiography, "My poetry formed my medical practice. But my medical practice was

essential for my poetry.” Now there is someone who maintains an interest in medical practice! Were he a researcher, he would maintain his interest in research. In that way the commitments of nurses and physicians and others are maintained by their temperaments and their virtues of character by the way they look at the world and by what virtues they seek to cultivate. These parallels point to a tradition in philosophical ethics that focuses on cultivating moral virtues, a tradition from Aristotle to the present. It does not focus merely on intellectually comprehending and applying ethical principles.

This view is upheld by Henry K. Beecher and has been consistently advanced by Dr. Edmund Pellegrino, who holds that “intelligence is not enough, because human morality calls for a comprehensive and complimentary blending of principle-based and virtue-cultivating ethics.” Persons who simply follow the rules may be morally relaxed and even unreliable. They may fail to act according to ethical principles, not because they do not know what these are, but because they may empathize, have a sense of fairness, a sense of commitment to the public responsibilities they are assuming as trustworthy protectors of the rights and well-being of others. Notice those virtue words: empathy, fairness, trustworthy. Virtues of character compliment learning about and acting in accordance with the principles of research ethics. Accents on the moral virtues of those who conduct and review research are found in the radiation advisory committee’s final report, though they do not point these out. “We call for more than professional education in research ethics,” the committee asserted. “We ask that the biomedical research community, together with the government, cause a transformation and commitment to the ethics of human subject research.”

The fourth and final view that I will discuss is the *Belmont Report* revisionist’s perspective. Revisionists view the *Belmont Report* as advancing a moral reformation that must ever be revised and reapplied to the ethics of research. They say that Belmont is not enough. Keep thinking. Keep moving. Keep imagining. In effect the revisionists subscribe to the motto of the western world’s first great reformation, the Protestant Reformation. *Reformata sed semper reformanda*. Reform, but always to be reformed.

The late Benjamin Freedman exemplifies a typical revisionist. He held that the *Belmont Report* applies its principles in too limited a fashion. Consider, Freedman argues, what persons who are asked to enroll in Phase I cancer research trials should know. They should understand that these are toxicity studies designed to establish and maximize tolerated doses with little possibility of therapeutic benefit. They should also be told the cohort of the Phase I trial for which they are being recruited. They should be told whether they are being asked to enroll in the first cohort where the toxicity is at a minimal level or in the later cohort where the toxicity is greater and where any chance of therapeutic response is also greater. They need to know that and not just be enrolled in a Phase I clinical trial. Freedman goes beyond Belmont by asking: “Where shall we apply these issues?” He also asks if the rights and welfare of patient subjects in these and other cancer trials ought to require that the opinions of desperately sick patients should influence the design of these trials. Researchers and reviewers cannot presume they can predict patient preferences about maximum tolerated dose levels without securing patient participation. The patients may want more. They may want to endure more. Ask them.

I can tell some stories about what has happened at the national level concerning the ethics of animal-to-human organ transplants. I have brought patients into studies. They

have made an incredible difference in the deliberation of the Institute of Medicine, a part of the National Academy of Sciences, and other groups that I have been involved with. This is only one of the issues that leads Freedman to conclude: "No aspect of a trial is immune from ethical interest." He reaches this conclusion by thinking creatively and critically about the logical import of the ethical principles articulated in the *Belmont Report* rather than being bound by the ways that Belmont applies its principles. Belmont applies its principles in very good ways. Benjamin Freedman says we have to go beyond that. We should constantly think about why we should, and whether we should, on the basis commissioned by its own principles.

Jay Cates represents a Belmont revisionist in a second sense. He faults those who are loyal to Belmont for failing to rank or prioritize Belmont's ethical principles in ways that would more fully protect the rights and welfare of human subjects. Cates displays utmost loyalty to the Nuremberg Code and to American law both of which he believes do not allow researchers and IRB members to balance or trade-off compromises between subjects' rights and researchers' interests in their own work or for the benefits of society. He holds that the ethical principles are easily betrayed by the dynamics of physician-patient and nurse-patient relationships within clinical trials. Cates thinks autonomy, the first principle of Nuremberg, has to be prioritized and everything else is secondary. I am not saying that I fully agree with Cates. I can find examples where I would not agree with him. But, by and large, I do accept the revisionist point of view. As a member of the radiation advisory committee, Cates said that he "expected to discover [in the studies they did] ethical problems in the committee's study of contemporary IRBs and research protocols," but that he "was stunned by the extent of these problems." He said, for example, you know when I read all these protocols, I can see how the regulations encourage, perhaps even mandate, overwhelming patient subjects with information on every conceivable risk and benefit to the point that its "numbing detail obscures rather than clarifies what participation entails." This criticism poses a question as to the way the regulations' basic elements of informed consent have given rise to consent forms that demand extensive attention by IRBs and researchers. The forms are not only designed to respect the subject's right to choose but also to protect researchers and their institutions from legal liability.

Cates contends that this and other problems exhibit the flawed nature of our current regulations, which appear to rely so heavily on informed consent but which in practice bypass truly informed consent. For Cates, these serious deficiencies can only be remedied if we who are involved in human subject research and its oversight "have a more thoroughgoing appreciation of the moral issues at stake whenever we ask human beings to serve as a means for the ends of others." Cates' views were sufficiently cheered by other members of the radiation committee that they said that on a national scale we must ensure the centrality of ethics and the conduct of science when research involves human subjects. Taken together, these revisionists are telling us that the *Belmont Report* is a vital milestone--but not the capstone--of the ever-challenging enterprise of protecting the rights and well-being of human subjects.

In conclusion, the last three views that I have explored underscore the imperative of discovering and/or recovering the ethics of IRB decision making. Those who hold to the second loyalty of the Belmont point of view are acutely aware of the degree to which

ethical principles must be used to interpret, apply, and reform the federal regulations. Those who hold to the fourth Belmont revisionist perspective believe that ethical reasoning must continually reform what we take to be the rights and well-being of human subjects in research. And those who hold to the third, the virtues of character approach to their ethical armamentarium, will strive to be committed and trustworthy protectors of research subjects and the entire research enterprise. All three of these views undercut the logic and the approach of the first view that regards ethics as marginal and that rests on the comfortable time and energy-saving assumption that faithfully following what the regulations require will take care of all of our moral responsibilities.

The silence, or virtual silence, of United States federal regulations on the value and roles of ethics is worrisome. The regulations incorporate codes and rules pertaining to research in its directives; yet, they leave out crucially important rules. The regulations do not expressly mention how its rules must be interpreted and applied against the background of moral principles. This silence accentuates the seriousness of taking ethics seriously. Thank you very much.

Dorothy Macfarlane, M.D.
Acting Director of Division of Research Investigations
Office of Research Integrity
Public Health Service

I am going to address a totally different aspect of research integrity as it relates to clinical trials. What I would like to address today is the integrity of research data in clinical trials and look at it from the perspective of what we have learned through our scientific misconduct cases that involve clinical research. These are cases that we have looked at within the Office of Research Integrity (ORI) over the last few years.

First of all I would like to talk about the kind of climate that seems to allow this sort of thing to happen. This climate includes the kind of people who commit scientific misconduct or falsification or fabrication of clinical research data. I will talk about why they do it and strategies that might prevent it in the future.

I would like to talk about physician-investigators. I looked at 21 cases of scientific misconduct in which we found misconduct since 1992. Only four of those cases involved a physician who either falsified or fabricated data, or who directed others to do so. Dr. Crosson, in Montreal, falsified data on breast cancer studies. He hired high school help as data managers and instructed them to falsify case report forms that were sent in. He told them it was the best way to get patients into the studies so they went along with him and accepted this falsification. He is the only one we found that directly falsified information in a multisite clinical trial.

Two others are physicians who falsified information in very small single-institution studies. In these cases, it seemed to be a matter of taking shortcuts to get something published. One of them fabricated medical records by writing patient visits into the medical records when he had not actually seen the patients. The fourth physician was actually a resident who was acting more as a data collector, or secondary person, than as physician-investigator. He was not the principal investigator for the study.

We rarely see direct falsification or fabrication by physician-investigators. In the other 17 of 21 cases, we found a common theme, which is physician negligence in overseeing data collection. In fact, most of the principal investigators at the site disclaimed any responsibility for the data.

We looked at one large NIH-sponsored trial that had a manual of about 300 pages stating the responsibilities of everyone involved in the trial. The responsibility of the principal investigator according to this manual was (1) to examine patients and (2) to represent the institution at the annual meeting. That is pretty sad. It leaves the clinic coordinator, data managers, research nurses, and clinical research associates with too much responsibility for the trial and too little supervision. We found instances where the data managers were responsible for just about everything in the study: recruitment, determination of eligibility, randomization, obtaining informed consent, scheduling follow-ups, and reporting all the data. However, they had absolutely no communication with the physicians except to look at their records. This is not adequate quality control.

The other condition that seems to foster data falsification and fabrication is too much work. Many times one person can easily handle the beginning of the trial where you are recruiting patients and determining eligibility. Over time, however, the workload builds up. In addition to recruiting, you have patients under active treatment and patients with long-term follow-up. No one has gone back to reassess what the workload is, how many people are involved, and what sort of manpower you need to do the work at the different points of the trial. This is critical. The principal investigator should monitor this situation to make sure that project staff are not overworked. These examples illustrate the climate in which people cut corners and decide that it is easier to just invent a follow-up call to a patient than call the patient.

Then there is too little training. Instances of misconduct occur with large trials that reach into the community and that affect physicians in practice who are not really research-oriented and who may never have done research before. One of the cases we had last year involved a physician-principal investigator in group practice who delegated responsibility for the clinical trial to his financial officer. The financial officer then delegated the responsibility to the lowest medical assistant who had no training in research, no professional training, and was not a registered nurse. This person was expected to do everything from recruitment to dispensing drugs and completing forms. Furthermore, the financial officer decided to give the medical assistants a \$25 bonus every time they got a round of forms completed and turned in. The combination of all these things was just the right set-up for fabrication to occur, and it did.

People who are brought into clinical trials without proper training have too little appreciation for the importance of what they are doing. As Dr. Vanderpool was speaking, I was thinking that the result of scientific misconduct is the ultimate betrayal of the patient who has volunteered to be in a clinical research study. Why? Because these patient/volunteers think that the data that will be generated by their participation will be meaningful. Thank you.

Dr. Sandra K. Hanneman

Good morning. Welcome back to the second day of this conference on research integrity. Today's focus is the ethical and social contract with society: the public view. Most of the presentations today are structured around a panel format with open microphone time. This is the audience participation day, and we encourage you to address questions by coming up to the microphones in the two aisles. It would be helpful for all involved if you would state your name and your institutional affiliation before you make your comment or ask your question. If you are addressing your question to a specific panelist, it would be useful to state that as well.

At this time, I would like to introduce Dr. Joseph Jones who is the Dean of the Graduate School and Professor of Biology at Texas Southern University.

Joseph Jones, Ph.D.

Dean of the Graduate School and Research and Professor of Biology Texas Southern University

Good morning. It is my pleasure today to bring greetings from the administration, faculty, and students at Texas Southern University on the occasion of this conference dealing with research integrity: a professional, ethical, and social obligation. In many ways, this conference has a special meaning to the sponsoring institutions: the University of Texas-Houston Health Science Center, The University of Houston, The University of Texas M. D. Anderson Cancer Center, Texas Woman's University-Houston Center, Texas Southern University, Prairie View A&M University, and the Office of Research Integrity of the Public Health Service. A special meaning is resident in the cooperation between the six academic institutions and the Public Health Service because it may be a signal to us that we can pursue other cooperative projects together.

Recently I was asked to get information on the various cooperative programs within institutions throughout the United States. I was amazed at the number of cooperative programs that exist in Houston, in other parts of the United States, and in the world. This conference suggests that research integrity is a central core of these cooperative programs. It suggests that we feel there will be honesty in dealings and that there will be an honest attempt to achieve the goals of the projects based on integrity.

Because of the times in which we live, partnering is the direction that research and grantsmanship must take to be viable entities in the community of scholars. Certainly Texas Southern University is open to expansion in cooperative research and training programs. Cooperative research efforts require a common knowledge and understanding of the importance and operative guidelines for maintaining professional integrity in the pursuit of research, in publishing research findings, in dealings between researchers and in dealings between institutions. In every effort, integrity is extremely important, especially in a society that tends toward pecuniary interests more than interests that are germane to the project.

This conference is especially timely for all of our institutions because institutional boundaries are evaporating as research becomes more cooperative and team-oriented. I wish to express my thanks to you for coming to the conference because it suggests you feel this is an extremely important topic. I wish to thank all of the partners in the conference

who worked together. And I especially want to thank Dr. Hanneman and her staff member, Ria Griffin, who rendered humane service in the operational aspects of the conference and put together a meaningful conference so that we can all benefit from it. I also wish to thank the Office of Research Integrity of the Public Health Service for its support of the conference and to those of you who advocate integrity in research matters and in cooperative programs. Again, I welcome you and extend to you my best wishes and the wishes of our university for your success in this very important conference. Thank you so much.

Dr. Sandra K. Hanneman

Our first panel for the day is the Public View of Biomedical Research. I invite the panel to come up to the table. Dr. Arthur Vailas will moderate today's panel and introduce the speakers. Dr. Vailas is Vice Chancellor of Research and Intellectual Property Management at the University of Houston System and Vice President of Research at the University of Houston.

**Arthur Vailas, Ph.D.
Vice Chancellor of Research and Intellectual Property Management
Vice President of Research
University of Houston**

Thank you, Sandy. I would also like to thank everyone who was involved for organizing this conference and for the opportunity to address an important topic in the domain of research integrity. As you know, research is constantly being challenged in a variety of ways. Today we have speakers that will give us unique perspectives of research, its alignment, its value, and its importance to the public.

I would like to invite Dr. Leonard Zwelling to come up to the podium. He is the Associate Vice President for Research Administration at the University of Texas M. D. Anderson Cancer Center.

**Leonard Zwelling, M.D.
Associate Vice President of Research Administration
University of Texas M. D. Anderson Cancer Center**

What I thought I would talk a little bit about is the relationship between the media and science. A news story on TV that runs for two to three minutes, reporting a great breakthrough in science is a common occurrence. The story gets patients' hopes up, and then ends with something like: "This will not be clinically useful or available to patients for five or ten years," which deflates the entire last three to five seconds of the story. The question of course is: "Why does that occur?"

A story that caught people's attention was the story in *The New York Times* one Sunday morning in May. The story appeared over the fold on the front page. It reported research on some new drugs, angiostatin and endostatin, that were used to treat cancer in mice. My question is: "Was it the substance of the science in the story or the fact that it

appeared on the front page that interested people?" I was on the Stairmaster when I read that story, and I knew I would have to wear a blue shirt the next day because television reporters would be all around M. D. Anderson asking us questions. That is exactly what happened. Yet, data about the research had already appeared in *The New York Times* in November. Clearly the public perception of what is going on in science has changed dramatically. I think Dr. Cox will speak more about that in a few minutes.

A lot goes on between the chemistry in the laboratory, the biochemistry in the cells, what happens in mice, and what eventually gets to people. I want to talk briefly about that. An initial discovery might be a new way to treat cancer in mice that may or may not have effects on people. There is a long process of translating the research into something that is applicable to human beings-- that is what all research is about. Part of the process is clinical research. I loosely define clinical research as research that involves simultaneously caring for patients and doing research. It is probably the hardest kind of research to do because the clinical investigator has to be mindful of two things: what is good for the study and what is good for the patient. These two things may not be the same things, but they need to be. There are federal laws and regulations designed to protect patients. Institutional review boards oversee the protocols--the descriptions of the research conducted on patients--and guarantee that the patient's rights will be protected. The FDA also affords some protection to patients who are undergoing new therapies. The institution forwards its protocol to the FDA for review and approval. The FDA makes sure that the drugs go out to people as fast as possible to do good. I think I will stop here and let you ask questions.

Dr. Arthur Vailas

Thank you, Dr. Zwelling. Our next speaker, Dr. Geoffrey Cox, is Chairman of Aronex Pharmaceuticals, Inc.

Geoffrey Cox, Ph.D. Chairman and CEO Aronex Pharmaceuticals, Inc.

Good morning. Thank you for the opportunity to participate in the discussion this morning. From the introduction, you recognize that I am responsible for a company that is a representative of the biotechnology industry in this country. I will probably give a different perspective from that which came through in the handouts that were prepared for this discussion. I am far more upbeat about what is happening and how research actually gets out into the marketplace than perhaps what is indicated there.

In this country, about 1500 companies are involved in biotechnology. Of these, 350 are public and the market capitalization of those companies is about \$80 billion. Aronex Pharmaceuticals is one of those companies, and it exists in The Woodlands, Texas. It is developing products that come from MD Anderson Cancer Center and Baylor College of Medicine. We have programs that are now being filed with the FDA.

What has happened in this country over the last 30 years is an absolute explosion in biotechnology. Remember, this industry did not even exist 30 years ago. Nobody had thought of it. Today we have an enormous industry that generates products. These are the

products emanating from academic and medical research institutions throughout this country and throughout the world. I believe this is an enormously positive story. The other message it sends is there is a very healthy academic and medical research environment generating ideas that are translated into the commercial arena. This industry was created through the ability of organizations to do research and transfer it out of these institutions and to finance it through venture capital and the stock market. I think what you see now is a range of products that are truly changing the way in which medicine is carried out. We will continue to grow because we are really in the very early stages of this process.

Today people with diseases, genetic disorders, and specialized types of diseases are receiving treatments where none existed before biotechnology. Large pharmaceutical companies did not address these marketplaces; they are unable to address the needs of small populations. The biotechnology industry has fulfilled a very special need by helping the transition between research and the commercial arena and also by addressing medical needs.

Dr. Zwelling discussed media interest in scientific breakthroughs. I might add that there is 5 to 10 years, probably nearer to 10 years, before a product reaches the marketplace. Probably something in the order of \$200 to \$300 million is what it takes to finance bringing one product to the marketplace. A big pharmaceutical company will probably say it is closer to \$400 to \$500 million. About 1 in 100 of the products in preclinical testing actually makes it out as a product. As Dr. Zwelling pointed out, they have to go through various tests and regulated procedures before they can be taken to the FDA for review and approval. About 1 in 10 at the early stage of the clinical program actually makes it out. Even in Phase 3 programs, the last stage, there is probably only a 50-50 chance your product will be marketed. This process and timeline is what drives so many of the costs.

The public perceives the new product as enabling them to have healthier lives, longer lives, more disease-free lives. I think that is something we would all endorse and feel is a very valuable and excellent story. There is another side to this. People become extremely fearful of technology. Think what has happened in this lifetime. I was 10 years old before Watson & Crick actually defined the structure of DNA. Since that time we have seen the whole development of the biotechnology industry. In 1970, the first recombinant genetic engineering took place. In 1990, the first example of gene therapy took place. In 1997, Dolly was cloned.

People read about these scientific achievements in the press, and the press scares the living daylights out of them. Everyone knows that science can be used in good and bad ways. Society determines which way science will be used. The dialogue between society and science will go on for a long time. There is a fear factor when people think about genetic testing. Genetic testing reveals what somebody's genetic make up is, what you or I may die of, or what we may become sick with in later years of our lives, what the problems of an unborn child are. These are tremendous challenges for society to deal with. Genetics technology is absolutely exploding in an exponential fashion, and it will continue to do so. Because of genetic testing, you may not be able to get health insurance. If you cannot get health insurance, you may not be employable. If you take a 20 year-old who has a genetic test that proves he may die of heart disease or may develop heart disease when he is 45 to 50 years of age, he may be unemployable. Everyone will want to have a voice in that.

These are the challenges that need to be discussed in a political arena, and they are the challenges we need to get our arms around.

Gene technology is going to affect our lives absolutely and fundamentally over the coming years. We can regard it as a very positive challenge that gives us the opportunity to have healthier and better lives. We can also regard it in a very negative fashion because it presents problems that we do not know how to handle. The danger is from a political point of view. Politicians, because they are elected officials, need to address the issues of the society they represent. Sometimes they take short-term positions that do not bring benefit in the long-term. These are the issues that we should discuss this morning. Thank you.

Dr. Arthur Vailas

Thank you, Dr. Cox. As was mentioned previously, at some point United States Congressman Ken Bentsen will join us and will give us the government's point of view. Until then we can discuss how we can best address the issues of research alignment and its obligation to the public. I would like to seed this for thought. As you know, research is expensive. There are a lot of demands placed on research. There are people who have an economic interest on research. Their research is a tool that is also used to develop human resources to continue the process of innovation and teaching. There are great expectations for research, and therefore, a lot of political pressure is placed on research as well as on information gleaned from research to produce positive results. I would like to entertain any questions or comments from the panel and from the audience as to how research can have a greater partnership with the public. What do we need to address in order that this partnership is fully understood?

Dr. Leonard Zwelling:

Marketing patient care is one thing and that is usually what constitutes MD Anderson's marketing efforts for the most part; it is concerned with patient care. It is a different issue from research. How anything that happens at M. D. Anderson gets into the media is often through a press release after it has gone through peer review or is about to be published. We have an obligation to have a press release for the press to get it into lay language.

MD Anderson is certainly unique. Our mission is really research-driven patient care. That is what differentiates our patient care from patient care given in other places. We really cannot neglect one or the other. It is part of what we do. In any conversation we have, I think we try to present ourselves as objectively as possible. There is a dual role between the press and the collective "us" - - biotechnology and the pharmaceutical industry. In biotechnology, if it is not a publicly held company, they go into the venture capital markets. I think there are different pressures on people and some of them are financial. On the academic side, it is not money all the time. It is really the idea of getting our name out there as a place where people want to come.

Dr. Geoffrey Cox:

Biotechnology started off by claiming that they were going to be much more successful than big pharmaceutical companies with their success rates. I think it is too early to say that is true. Some of the initial targets that were genetically-engineered products maybe had a higher success rate. But as we go forward I think the success rate of biotechnology will be quite similar to that of the pharmaceutical industry. Biotechnology does suffer, as you quite rightly say, from the fact that it does not have the deep pockets large pharmaceuticals have, so they very often do not do extensive Phase 2 trials, which are very expensive.

You should not underestimate, though, what biotechnology is for. This industry addresses many diseases, many disease areas, many conditions that big pharmaceuticals will never deal with. These days, unless they have a product that is going to generate sales of \$400 to \$500 million, the pharmaceuticals won't touch it. Many of these products have excellent markets of \$50 to \$100 million, but the products may address genetic diseases where there may be only 20,000 to 25,000 people. I was involved with Genzyme Corporation, which developed a product for Goshay's disease, which is a terminal disease. There are about 25,000 people in the world with that disease and perhaps about 5,000 who absolutely need treatment. There was nothing out there for them. Genzyme took the risk of developing a drug and today those people have an opportunity to live a healthy life. The large pharmaceuticals would not have developed that drug in a million years. There are dozens of examples where biotechnology brings that type of perspective to the industry. I think it is really in the interest of everyone that the biotechnology industry does survive.

The other thing is that we live in a capitalist society. I think it is terrific that there is an industry that raises money to support the development of these products. A lot of the research, of course, has been initiated at the National Institutes of Health, the National Cancer Institute, or places like M. D. Anderson Cancer Center, for example. But the distance between what is a great idea and a great piece of research and creating a drug is a tremendous step and a tremendous amount of investment. The FDA establishes exactly the same standards for drugs coming out of small companies as it does for drugs coming out of very large companies. There is a regulated process, a clear set of conditions that everyone has to meet. Biotechnology is doing better at understanding the rigors of the regulatory process now than it has in the past. It is making sure that even when it has a good drug it designs good clinical trials. There is some evidence that good drugs have failed to get through the process because they have not had well-designed clinical trials.

The last point you raised was the conflict in the media about breakthroughs. There is no question someone will try to get something published in newspapers in order to push the price of the stock up. It does not necessarily come from the company. People who have investments in companies may choose to either promote that stock or take a short position on it and publish something negative. We have to deal with the consequences of those types of public relations issues and it is quite disturbing. Moreover, people can make anonymous comments on the Internet about companies and about their products. They do so without any requirement to be responsible for the nature of those remarks. I am always advised not to respond to message boards. We have a Security Exchange Commission that really needs to take some action on that.

Dr. Arthur Vailas:

Before we go on to the next question, I would like to introduce the Honorable Ken Bentsen. I invite him to the podium to give his overview.

The Honorable Ken Bentsen Congressman United States House of Representatives

Good morning and thank you for having me. I apologize for being late. We were held in session last night to work on a bill that deals a little bit with Securities and Exchange Commission and were debating whether or not we should commit United States ground troops to the Kosovo region in the Balkans. Unfortunately, by the time we finished with that, all the flights to Houston had left, so I had to catch a flight this morning. I want to thank you for having me and I want to thank the University of Texas-Houston and the other sponsors for putting this event on today.

I just want to spend a second or two talking about my end of this issue and the federal government's role in biomedical research. As it has probably been stated, it is now clear that the American people believe that a federal investment in biomedical research should be a strong priority. Polls have consistently shown that more than 60% of the American public believe that the federal government should be spending more, not less, on biomedical research projects that we believe lead to new treatments and cures for such diseases as cancer, heart disease, diabetes, Alzheimer's, and AIDS. I want to assure you that I agree with the American people on this, and I think a majority of the Congress does as well.

As you know, last year Congress provided a little more than \$15½ billion for the National Institutes of Health, which is one of the main federal agencies responsible for funding biomedical research. This amount represented an increase of more than about 15%. It was only part of a goal that a number of us in Congress had to try and double the NIH budget, at least nominally, over a five-year period. I would say this also shows a correction, or a reversal, on the part of the Congress. It had been proposed that we cut the NIH budget by 5% in real terms. In 1995, as it would relate to the fiscal year 1996 budget, that was rejected and then we had some real increases in the range of about 5% to 6% one year and about 2% to 3% the next year. This last year, for the fiscal year 1999 budget, we finally got a significant increase. I think this is important.

From all the evidence I have seen, America's biomedical research is the envy of the world. I think that it is hampered by the fact that only as little as one-third of meritorious peer-reviewed grants are funded by the NIH. I believe that funding more meritorious grants will help, not just by finding new cures and treatments but also by allowing the United States to retain the competitive advantage it has in this area. I am the new co-chair of the biomedical caucus along with my colleague, George Geekus, who is the Republican member from the State of Pennsylvania. We are sponsoring legislation that should increase NIH's budget by at least \$2 billion more for fiscal year 2000. In addition, Representative Connie Morella has joined us in organizing an effort to actually have about a \$2.3 billion

increase in funding. We feel pretty confident that we will be able to get back to the level of last year, when we had about 200 members of the House supporting this effort.

Finally, as a senior member of the House Budget Committee on the Democratic side, I will once again, as I did last year, offer an amendment in the budget resolution to double NIH funding or set the path for doubling NIH funding over a five-year period. Unfortunately, last year we were not able to get that adopted by the budget committee. However, we were still able to get the Appropriations Committee to move in that direction. This year we believe we will have a budget resolution. We think it is imperative that we at least try and get this type of language in the budget resolution, which may be drafted next week by the House Budget Committee. The budget resolution sets the framework and dollar limits with which each appropriations subcommittee can fund programs, including the NIH.

Let me talk about some of the harsh realities that we face in this effort and why it is important for everyone here, as well as your colleagues across the country, to express their support for this effort to their individual representatives in the House and Senate. While it is true that we are running a surplus in the budget this year, and we are projecting a significant surplus over 15 years, we also are living under very tight spending caps over discretionary spending. That is one of the reasons why we have gotten into this fiscal situation that we are in today. The surplus, at least for fiscal year 2000 and 2001, is attributed completely to the Social Security Trust Fund. For political reasons, if nothing else, this fund is pretty much off limits.

There is also a desire on the part of the administration as well as the congressional leadership that we should significantly increase the defense side of the budget and increase the funding of education that the federal government provides. In doing so we remain under the spending caps that were part of the 1997 Balanced Budget Agreement. We increased the defense side of the ledger and parts of the nondefense discretionary side of the ledger. The fact that the firewalls, which were established between defense and nondefense, are gone in fiscal year 2000 puts tremendous pressure on other federal discretionary programs, including the NIH, National Science Foundation (NSF), and the National Aeronautics and Space Administration. You can pretty much use elementary mathematics to figure out the predicament that we are in. We will not have the money to do it all.

I would encourage you, if you agree with me on where we ought to be going with NIH money, and NSF funding for that matter, to contact your representatives and explain to them why this is important. I think it is important for the country, not just in a micro sense, as it affects the treatment of patients, but also it is an important economic issue for the country. We should maintain our leadership role in this area. I will work very hard to do that. I am hopeful that at the end of the year, when we finally get down to a budget that we can go ahead and follow-up on what we did last year.

Again, I appreciate you having me here and would be happy to answer any questions.

Question (Tim Harrigan, Orthopedics, The University of Texas-Houston Medical School):

The issue I have is the connection between research results and stock prices, which I think Dr. Cox discussed briefly, along with message boards are something that we really cannot do much about. We all have to some extent industry-funded research. So the pipeline of medical results to the media and to stock prices is one that I think needs some careful attention. I think M. D. Anderson's policy of not announcing new therapies until the work is peer-reviewed is good.

What else do you see as a way to control that? I know, for instance, in the breakthrough with angiostatin, there was a company involved that made the device. Where do you see places that we can possibly put in systems that will keep some of this from polluting the whole research environment?

Dr. Zwelling:

There is a conflict of interest policy in most academic centers that precludes an investigator from participating as a principal investigator in research if he has an interest in a company sponsoring the research. The first thing you have to do is put a firewall between the person doing the research and the outcome of that research, particularly as it affects the value of that person's portfolio. And that is what we have done. I suspect most other academic institutions have done that as well.

Dr. Cox:

I would also make the comment, though, that companies have another problem, which is the matter of public disclosure. If I stand up at a conference, or put out a press release saying that we are investing in a particular program, then when the results of that program become available, I am required to make a public disclosure of it. If not, I will be sued for not having disclosed it to investors and for not making sure it is available in the public domain. So it is not quite as simple as you make out.

There are sets of rules and guidelines and we have to live by them. I would say in defense of the company in the example that Dr. Zwelling raised that the situation was not instigated by the company. They certainly were the source of some of the information, but they were hugely embarrassed by the outcome of that whole exercise. They were embarrassed that there is a company whose stock price went from a few dollars to \$80, and then back down to \$25. Now they have investors who bought the stock at all sorts of prices, and they know they have to go through an extraordinary, lengthy, and arduous clinical program with all the normal issues associated with that. I am quite sure that they do not want that type of media attention. Companies cannot control the media. They are not necessarily going to do what a company wants. That is what a free press is about. You take the good and the bad that goes with it.

Follow-up Question: (Tim Harrigan, The University of Texas-Houston Medical School)

The other issue that I have seen is fads and research. Scientists follow fads just like the general public. For example, in engineering you can almost date a paper by whether they mention fuzzy logic or wavelets or other things like that. The skill an investigator has in doing that is a separate and completely different issue than the skill that an investigator has in doing good science. I wonder if you could comment on how you have seen that operate in your institutions and in your companies?

Dr. Zwelling:

Most of the people at MD Anderson do good science and want to do good science. They would rather avoid the television cameras. Most scientists I know, whether they are basic scientists or clinical scientists, are willing to explain what they have done at the appropriate moment, after it has been peer-reviewed and is about to hit the scientific press. The best scientists I have known are people who have followed a problem through regardless of the fad. I am not sure that the best science is influenced by fads as your question might suggest.

Dr. Cox:

Can I just add to that? I think that good scientists who do good research are entitled to publish that research. That is part of their professional advancement and professional recognition. I do not see anything wrong with that. From a company's point of view, I strenuously try to avoid making what is called "forward looking statements." Forward-looking statements have risks associated with them. Any time I think about making those statements I go through a legal process to make sure that I can actually back them up with facts.

Some of the things you mention are things that biotechnology got in trouble with in the early years. They were trying to raise finances and were trying to do those things. I think there has been a tremendous learning curve. I think the industry is much better organized and much better prepared in terms of the way in which they address those things. I'm not saying it is faultless, but, at the end of the day, I think they do genuinely try to keep their investors appropriately informed.

Question: (Chris Pascal, Office of Research Integrity)

This discussion is very interesting to ORI because we consider part of our core mission is to maintain public confidence in the integrity of research and in the honesty of research. I have a question to ask the panel, but I want to give a little background from the discussion yesterday. Our office investigates alleged fraud, falsification, and fabrication of data involving Public Health Service funded research. One of the cases we had several years ago involved clinical trials in Montreal. The trial was funded with Public Health Service funds. Substantial fabricated data were found in the clinical trials. When that

became public, there was great concern expressed by the patient community, by the women's groups, and by the medical community about whether or not treatment decisions made on these clinical trials was somehow affected. It turned out they were not. The data were re-analyzed and published at a later date. There was great concern about whether or not treatment decisions were based on fraudulent research.

I think the discussion today raises, for me at least, a similar issue, although it does not necessarily involve fraudulent research. It does not involve cases under ORI's jurisdiction. I am concerned about public confidence in research outcomes involving new drugs, new therapies, even when the underlying data is sound and when the underlying research is reported to the FDA. I think our society has become very dependent on scientific advances for spurring improvements in health care. I think, frankly, people are psychologically dependent on that as well. The expectations in some cases are too high and are unrealistic. I am concerned that it really skews the debate in this country about policies and what is good in health care.

We have seen examples of drugs that were initially proven to be quite efficacious but after they got on the market there were concerns raised about whether or not they had dangerous side effects. One such drug is FenPhen, the diet drug that got a lot of publicity some time ago. More recently, we have Viagra, which, as far as I can tell from news reports, is efficacious. However, concerns are being raised after approval and a successful worldwide marketing campaign about dangerous side effects. Maybe individuals were being encouraged to try it when it was not really suitable for them. Specifically, though, I am interested in (1) is this sort of practice an issue? and (2) what can be done about it? I really see a gap in communication. It is not just the research now. I am not picking on the bench scientist or the clinical scientist who is doing the research. I am talking about the way the system is set up. Sometimes I see new therapies and new drugs oversold to the public; and in the end, these therapies and drugs can be harmful. Overselling can erode the confidence the public has in the science base.

Dr. Vailas:

There are a couple of observations I can make. One that has been mentioned is how the press reports things. Obviously they will have to take some responsibility in how they deal with this. In terms of outright fraud, we have mechanisms to deal with that whether it is on the criminal side or on the civil side. We have laws with respect to fraud for marketing purposes and other laws that guard the system and the consumers.

If there is a societal perception that within a short period of time things are going to be better, the public's just going to have to figure that out for themselves. One of the things we can do in clinical trials, at least from our end, is to expand our ability to conduct clinical trials by bringing Medicare, Medicaid, and private plans into our investigations to increase the sample size more quickly. Hopefully this will give a determination more quickly.

Dr. Cox:

I have to say I would not know how one could develop a fraudulent case in a clinical trial with a double-blinded study. The FDA rules are rigorous about these trials. They are also rigorous about the reviews they do to make sure that the data are collected in a blinded fashion, that the data are analyzed in a blinded fashion, and that the data are interpreted with no unreasonable bias. I believe that everyone can feel very relaxed about it. There have been one or two examples when in the early stages of the clinical development, or preclinical development, an individual worker skewed results. Those usually have been appropriately dealt with. By and large, I think the FDA does an excellent job in ensuring that drugs that come through its agency have gone through the appropriate trials.

Question:

This question is directed to Representative Bentsen. I am concerned about Senator Shelby's quiet insertion of language into the 1999 appropriations bill that would allow all data that comes from research funded by federal money to be made available to the general public under the Freedom of Information Act. I was wondering how you would advise us to try and change that. We are sending out letters. But how would you advise us? There are many in the research industry and in the university sector against that for numerous reasons. The reasons range from privacy factors for health care components to the premature release of data that may be incorrect and not validated or that would jeopardize commercial interest or the institution's proprietary material. An adversary might try to get data that you have been working on and see what type of research route you are taking. What can we do? What are you going to do?

Mr. Bentsen:

I am not very familiar with that. Some things I know; some I do not. But I am happy to take a look at it. There is generally strong public support for what is called "right to know." I generally support that concept. When you release information, you not only raise specific concerns about whether or not the data is accurate or inaccurate, but also about what implications, such as liability risk, may arise. In the research and health fields, there are applicable privacy issues that are perhaps bigger issues than managed care. Genetic privacy is one of those issues. We have to protect the public's right to know. However, the question is how to determine what the public should or should not know. What is good and what is bad data. We have to look at that.

Follow-up Comment:

Just for your information, I believe it is OMB Circular A-110 .

Mr. Bentsen:

Oh, it is a regulation.

Question (Dr. John Grabowski, UT-Houston Medical School):

Is there any way of stopping Senator Shelby?

Mr. Bentsen:

It is Bradley who actually works on my staff and who is much smarter than I am. He will look into that and let me know. We will get back to you on that.

Comment (Dr. Ruth Bulger):

I think the issue is not whether the public has a right to know certain things, like data that underlie regulations, because they do have a right to know. That was partly why it got inserted. It was getting data under EPA regulations. The way it was put in is broad and undefined. Furthermore, it is on a short track because OMB is looking at how to change Circular A-110 so that all data is available for public evaluation. I think it is using, as somebody said, a meat axe when you should use a scalpel. There is a right to know but it needs to be defined better.

Mr. Bentsen:

That analogy is used often in our line of work. Sometimes we are wrong and sometimes we have to go back and make corrections on it. I am more than happy to look at it.

Dr. Sandra Hanneman:

Please join me in thanking our panel members. After a short coffee break, we will show a brief videotape featuring Senator John Glenn speaking about his return to space. Then we will convene our next panel to discuss the topic of "Science vs. Mass Appeal: John Glenn's Re-entry into Space."

[From the videotape provided through the courtesy of NASA]

"There gloom the dark broad seas. Come my friends. 'Tis not too late to seek a newer world. Push off, and, sitting well in order, smite the sounding furrow."

Senator John Glenn:

"I'm very proud to have been part of the beginnings of America's space program. And, needless to say I'm excited to be back. I'm honored, but more than that, I'm privileged to have the opportunity to participate in taking us in some new directions. We know the whats of aging. But I want to try to contribute more to learning about the whys of aging."

Narrator:

I am a part of all that I have met. Yet, all experience is an arch through which gleams that untraveled world whose margin fades forever and forever when I move.

Senator Glenn:

“I think it comes down to America’s sense of curiosity. The willingness to go out on discovery. The willingness to look at the unknown. We have been a curious and questing people throughout all of our history. And out of that came this surge that we know as our great economy that we have here today where our standard of living exceeds anything known around the world. It is that kind of research and that kind of interest in research and this kind of quest for the future that I think is the job that NASA does best. Their job is to push back the frontiers of the unknown, and let us know in our own times these things that can benefit all Americans.”

Narrator:

Old age hath yet his honor and his toil and something ‘ere the end, some work of noble note may yet be done not unbecoming men that stroll with God.

Senator Glenn:

“The success of America’s space program has opened up not only the sky but also our country and the world by producing immeasurable scientific benefits. We have gone in that short period of time, and in those few decades from what we called a capsule with one person in it up to where we’ll now put up, in just a few months, the first part of an international space station. And we’ve gone to the other extreme of the cold war to where our former adversaries are now going to be cooperating with us on this international space station.”

Dr. Sandra Hanneman:

At this time, I would like to bring the panel up to the stage and introduce the moderator, Dr. David Low, who is the President of the University of Texas-Houston Health Science Center.

M. David Low, M.D., Ph.D.
President
The University of Texas-Houston Health Science Center

I wore my American space program tie this morning just to let you know whose side I am on. I was drafted into this task, and I must say that if I had been given a chance to determine the title, I would not have chosen the title we were given, but I will deal with it.

"Science versus Mass Appeal." What does that mean? It sort of implies that they are different. There is some comparing and contrasting that one might do. It implies that somehow mass appeal and science have different objectives; or, if something is appealing to the masses then maybe it is not scientific. We are given an example and while the topic focuses specifically on the metaphor of John Glenn returning to space, it is really a metaphor of other things where mass appeal is engaged to justify, promote, or explain science.

For example, instead of John Glenn's return to space, I might have chosen Michael DeBakey, who is older than John Glenn by 20 years. Dr. DeBakey is regarded as an icon by some people. His face, figure, and accomplishments are used as a metaphor by the American Medical Association to justify whatever it is they want to justify. Recently, he was used to promote the interest of American medicine, and, presumably, also the interest of the American people who may be patients of American doctors. You see several other examples of this kind of promotion--the child with the crutch, the child with AIDs, the poster child for the March of Dimes. These people, who want to raise money for crippled children, want you to feel sorry for those crippled children. They want you to feel that if you give your dimes then the child will be able to throw away her crutch and walk. That is not exactly what they are saying to you, but that is the appeal.

When I give talks about society and health, I sometimes say that folks on the other side of the street, the Methodist Hospital, St. Luke's Hospital, Texas Children's Hospital, Baylor Medical School, UT-Houston Medical School, in effect, would like you to believe that they are just one medical miracle away from eternal life. The implication is that if you just give them another million dollars to do their basic research, they will deliver on whatever the fuzzy promise is. Everywhere you look in science, especially in medical science, you are going to see this same medical mass appeal used to justify something. And that is the phenomenon we are here to talk about this morning. Is this a good thing? Is this a bad thing? Is it a neutral thing? Does it get us to where we feel society should be going?

We have two experts, at least on the space side of things, to lead the discussion. I should say, by the way, that the space program could hardly be a more spectacular example of what we in America find appealing. The two individuals who are here to help us examine the question are John Charles, who holds a Ph.D. and is a scientist in his own right, and Mark Carreau, reporter for the Houston Chronicle. Dr. Charles is the project scientist for human life sciences for STS107 that is planned for January 2001, a prophetic number I guess, at the Johnson Space Center. This is the man who is responsible for integrating and implementing all human life science investigations that are sponsored by NASA. He is also responsible for the other medical intramural investigations and activities at NASA. In addition, he was the discipline scientist in human life sciences, again for

NASA. In that capacity he was responsible for all 12 of the human life sciences investigations that were flown by NASA or investigated by NASA in collaboration with the National Institute on Aging in a Baltimore longitudinal study on aging. He is an expert on the topic at hand.

I am going to ask the panelists to speak for as long as they like. We think that will be on the order of 15 minutes each. They will be allowed to present their cases. Dr. Charles will speak first. Then I will introduce Mark Carreau. He will speak as a representative of the media.

Dr. Charles:

Thank you, Dr. Low. It is my pleasure to be here today to talk about the topic. I have been looking forward to this. I began my career as a cardiovascular physiologist doing my own cardiovascular research for NASA in 1983. Gradually I transitioned to the facilitator's role that I have now. In this capacity I am responsible for helping other folks get their investigations onto different missions; such as, space stations and shuttles. I also worked with the Russian program, the Mir, for a while.

I remember, in 1962 when I was seven years old, pretending that I was John Glenn on the playground at my elementary school. When he flew, I was, in my mind, on the launch pad with him; but, of course, in reality I was lying flat on the dirt playground with my legs over some stump pretending I was in the capsule. It was and continues to be a great privilege and a real pleasure to have been associated with John Glenn. Perhaps one of the biggest thrills is that he knows me by name and calls me by name whenever he sees me.

I want to take a few minutes to describe the payload that we had on STS95, the experiments that were selected for Senator Glenn to perform, and then talk to you about what we did with that information.

This slide shows the following crew members: Senator Glenn, Dr. Scott Paracyzinski, Chiko Muoki, a Japanese astronaut on her second space flight, Pedro Duque, from Spain, on his first flight, Kurt Brown, the commander, Steve Lindsay, the pilot on his second flight, and Steve Robinson, who was responsible for making sure the payload got implemented and for the other 80 something experiments they had on this mission. Kurt Brown made sure to remind me that there was much more to this flight than John Glenn's return to space.

It was a prescheduled, routinely manifest shuttle mission with a half-module used as a laboratory module in the payload bay of the shuttle. Part of the mission was designed for a commercial enterprise and part was for NASA, because NASA provided the space shuttle that got them into space. Speaking of the noncommercial part, there was a small portion of the experiments dedicated to the medical aspects of the mission. Some were added specifically for the Senator and some predated the Senator's presence.

The next slide describes the life science investigations on board. On this list is the clinical trial of melatonin as a hypnotic and the protein turnover study. Both of these are what we call payloads, which simply means they have some degree of priority in NASA's hierarchy. These studies were going to be on the mission no matter what. Charles Czeisler of Harvard Medical School is the principal investigator for the melatonin study, which is really a study of sleep in space. This is the second flight for the melatonin study. I chose to

call it melatonin to make it sound more interesting; but it is really a study of circadian rhythms and sleep quality in space flight.

The second investigation is protein turnover during space flight. The principal investigator for the study is Arnie Fernando from the University of Texas Medical Branch in Galveston. That was the first flight for the protein turnover study. This study was designed to investigate the buildup and breakdown of proteins in the body to determine what causes muscular atrophy in astronauts during space flights. The rest of the investigations were added specifically to take advantage of Senator Glenn being on board.

The magnetic resonance imaging (MRI) by Adrian LeBlanc at Baylor and the bone mineral loss and recovery by Linda Shackelford at NASA's Johnson Space Center were both added to document the change in soft and hard tissue in the Senator's and the other crew members' bodies in conjunction with the protein turnover study. They provided additional information for Arnie Fernando's investigation of changes in protein balance in the body. Another investigation was to quantify the postural instability of astronauts after their space flight. Everybody knows astronauts are wobbly and unsteady on their feet after space flight. Dr. Paloski is one of the leading investigators in the world to understand the physiological mechanisms for that. It ties into the aging aspects of this mission because the elderly are more likely to lose their balance. When they do, they tend to fracture bones in ways that are relevant to the other investigations--the protein turnover, the MRI, and the bone mass density measurements.

The next three investigations on the list are cardiovascular. The elderly are more prone to have cardiovascular problems as they age; and astronauts do have cardiovascular effects in space flight and after their missions. Janice Yeld from the Johnson Space Center had three investigations on board. One was a preflight and postflight study to assess essentially orthostatic tolerance, i.e., the ability to stand still for a period of time without getting lightheaded and fainting. Another of her investigations was in-flight Holter monitoring to record 24 hours worth of electrocardiograms in space flight. The purpose of this investigation was to determine if just being in space flight changes the heart's electrical activity by comparing it to preflight records.

The orthostatic function during entry, landing, and egress studies blood pressure and heart rate responses to the return to gravity during the actual landing of the shuttle. This is a set of hardware that records blood pressure and heart rate during the first exposure to gravity after the experience of weightlessness. These are all relevant, not only to astronauts, but also to the elderly because of the changes that occur in both groups as they age, or as they fly in space.

The next is the study of the body's immune function. This study is conducted on many missions. The beauty of this study is that they use leftover blood from the medical operation's blood draw taken during the preflight and postflight physicals. These investigators use the leftover blood samples to understand the body's immune system. It was a very timely tie-in because of the increased risk of immune dysfunction in the elderly that could be compared with previous and current studies of astronauts in space.

Finally, we had an investigation in which the Senator was not a participant because he was not from Japan. This was an investigation sponsored by the Japanese Space Agency to document the effect of space flight on their astronauts. Glenn participated in the other

investigations and a large number of the crew were participants in one of the other investigations in order to provide comparison data.

I want to give you a quick travelogue through the mission to show you some of the experimental activities done in space. Here is John Glenn preparing for sleep recording on one of the nights. He is heavily bedecked with monitoring instrumentation that allow researchers, when they get the data after the flight, to understand quantitatively how he slept. Behind Steve Lindsay's foot is the sleep compartment. This is one of three closed bunk spaces that provide the sleeper some degree of privacy and isolation. The electrodes on Glenn's head monitor his brain waves. The electrodes on his face monitor facial muscle tension--another indicator of state of sleep. The thermistor under his nose monitors respiration along with the vest that is labeled ALFI, which is a pulmonary function test. On his finger is a pulse oximeter for measuring oxygen saturation, and on his wrist is an actigraph for measuring his activity at all times. Chiko Mukai was outfitted similarly to the Senator. On certain days after sleep monitoring, she and Senator Glenn would do a 30-minute set of questionnaires on a laptop computer to assess their higher intellectual functions. This was done to determine if changes in intellectual function can be correlated with the quality of the sleep the night before. Chiko Mukai did take melatonin on two of the four nights of sleep monitoring. The study compared her data with and without melatonin. As you may recall from the media reports, Senator Glenn did not take the melatonin. We have four nights of just sleep monitoring. About 95% of the experiment consisted of monitoring sleep and circadian rhythms.

The other investigation is the protein turnover study. Pedro Duque and Senator Glenn are the subjects in this investigation. This is the first of several flights on which this investigation will be done in order to understand the physiology of muscle wasting and protein turnover in space. The Senator was involved not only as a subject but also as the operator in several aspects of the mission, especially in things related to his data collection. For example, he and Scott Paracyzinski spun down blood for preservation in a laboratory centrifuge and did an acute clinical check of some of the blood by using a small clinical device. On his right wrist is an actigraph, which monitors his body motion and lets sleep investigators know when he moves around and when he is not moving around. Astronauts exercise routinely even on short shuttle flights for the protective effects it gives and for recreation as well as for positive increase in mood and well-being. On longer shuttle flights and on Mir missions, exercise is an important part of the astronauts' maintenance of health. The Senator was religious about exercising every chance that he had open in his timeline.

I mentioned that there was a Holter recording study. The Senator was outfitted with the electrodes for the clinical Holter recorder. It is another device that was essentially bought off the shelf, modified for space flight, and then used during multiple missions in space. This is the first flight in which the device was used. The Holter recorder will be used routinely in future flights.

Astronauts have to prepare for landing. On Glenn's right thigh is the set of hardware that records blood pressure and heart rate during reentry and landing. That set of hardware ran continuously during the flight. He followed, as all astronauts do, the routine fluid loading protocol in order to partially re-hydrate himself in preparation for the return to Earth's surface gravity. This offsets the effects of the deconditioning that occurs in space

flight that leaves astronauts slightly woozy or lightheaded, as a result of fluid loss in space flight through normal means.

We also had some investigations that were done preflight and postflight without any in-flight components. This is an illustration of the stand test, the cardiovascular study of Danielle showing the array of instrumentation that is used to make measurements of blood pressure and heart rate. Ultrasound is also done to document changes in cardiac function and blood flow during rest and while exposed to the effects of gravity when tilted. All these investigations are done before and after flight to determine effects of the flight on that particular organ system.

The bone mineral loss and recovery study used a DEXA scanner-- dual energy x-ray absorptiometry scanner – not only to make detailed measurements of overall body calcium bone density but also to make regional estimates of soft tissue. I believe this is the Senator's own personal scan. An upcoming issue of *National Geographic* magazine will show these kinds of data.

Next is the body scan. Each section of the body can be scanned individually for detailed assessments of changes in bone density. The MRI device makes measurements of soft tissues, especially in the vertebra, the inter-vertebral disks, the muscles along the back that maintain upright posture, and the muscles of the calf and extremities that are used for locomotion on the ground.

We brought the mission, which lasted about 10 days, to a conclusion on November 7. We give the investigators approximately one year after the flight to collect all their data, analyze it, and prepare it for publication before we ask them to turn the data over to us. I cannot tell you what the results are in any formal sense because some of the investigators are still analyzing the data. The investigators have one year after their last data set is received to present the data to us. If the last data set is not acquired in any particular flight, then the one-year clock does not start. In the case of the sleep study, we should have results one year after the mission. In the case of the protein turnover study, we will not have results this year because that was the investigator's first flight. He is scheduled for other missions, including STS107 in 2001, and it would not be fair to him or to the research community to expect him to publish results that may be changed when more data are acquired.

I want to say a few more things. This mission and the presence of Senator Glenn seemed to spring onto the public scene abruptly, but there was actually at least a decade's worth of work leading up to it. The Senator had talked about flying again in space for a long, long time. In 1972 *Newsweek* and *Time* reported he would like to fly again; and, if NASA decided to do a geriatrics study, he would certainly volunteer. In 1989, a conference on the correlation of aging and space effects on biosystems was held by the National Institute on Aging (NIA). I understand the Senator did have some role in motivating this conference. It was jointly sponsored by NASA and NIA, and it generated a large document discussing what the similarities were between space flight and aging. It addressed the issue of combining studies in those two areas in order to learn more about the effects. In the 1990s, work continued behind the scenes. In 1996 and 1997, there were subsequent meetings to try to determine the role of collaborative studies of aging and space flight.

I hope you will all agree when the results come out that the mission was worth the attention and the effort we put into it. Although we had experiments specifically for the

Senator to perform and to specifically measure changes in the Senator's body, none of those experiments were made up just for the Senator's flight. They were investigations that we had used and will continue to use on other astronauts. We had used them on shorter flights. As we acquired a data set that we were comfortable with, we discontinued some of those investigations, but we continue to make many, if not most, of these same investigations on astronauts during long duration flights. We will continue to try to understand the effects of space flight on the human body. And with that, Dr. Low, I am going to sit down and let Mr. Carreau talk.

Dr. Low:

Thank you very much, Dr. Charles. Our next speaker is Mark Carreau. Mark, I guess, must have come from Kansas because that is where he got his degrees. Mark has been with the *Houston Chronicle* since 1986. He is a specialist on their national reporting staff on space flight and has worked in that area now for 15 years.

**Mark Carreau
Reporter, National Desk
Houston Chronicle**

Thank you, Dr. Low, for that introduction. The world was certainly inundated with John Glenn during his flight in late October and early November. The demand for information was constant. My favorite story about John Glenn was a letter from a 72-year old woman to our newspaper. We published the letter November 25. I think this letter and her comments illustrate that whatever happens, science or not, it probably had a lot to do with something that was not science at all. This lady lived in a second-story apartment building. For eight years she said her view from the front window was blocked out by grime and dirt. She had thought about what to do about this. She could not get anyone to do anything about it and felt it was too risky for her to do anything. After Glenn's flight she went outside one day and noticed a maintenance crew painting her apartment. She borrowed their ladder, went up the ladder with a rag, washed her own windows, came back down, went into her apartment and looked out at a world that was a little clearer for the first time in a long time.

I do not know what to make of that, but it is probably an example of how you really cannot predict how a story like this will go when it gets loose. I think John Glenn's flight got loose, beyond maybe even what NASA thought would come of it.

It might be instructive to talk about, at least from my perspective in the news media, how this story came to the fore. Like Dr. Charles, I had read and heard little pieces of information that Glenn was eager to fly again. He freely admitted that he wanted to fly after his 1962 flight, but he was not able to do it. Glenn never really understood why this happened. However, he believed it had something to do with a directive from President Kennedy that Glenn was too much the hero to make another flight for Mercury or Gemini, or one of the moon missions. He also had age going against him because he was the oldest of the original astronauts. He probably wisely figured out that he needed to make a career change, which he did successfully. But he never did lose interest in flying again.

The point where I began to feel this was going to happen was in July of 1997. You might remember when the probe landed on the surface of Mars and everybody was excited about it. The flight control center was at the Jet Propulsion Laboratory. Dan Golden was the NASA administrator there and he was to answer questions about the future of NASA's Mars policy. Golden was asked if John Glenn was going to fly again. Mr. Golden said that Glenn was determined to fly. He said he did not know how it was going to come out, but that they were taking it seriously. In fact, he said he had never met someone so determined to undertake this venture. Finally, in January 1998, the rumor that this would happen was confirmed.

We are at the point where it is just personality. Is there any science here? From the standpoint of those who cover NASA day to day, week to week, and mission to mission there was a great deal of skepticism that this would be all science, or half science, or one-third science. Our test for a news story is probably a lot less than yours. We had an American hero, a Mercury astronaut, a United States Senator who is going to fly at 77, which is at least 25% older than anyone else flying. We had plenty of justification to make this a news story. And we did.

For this talk, I went back and reviewed my own transcript of the first press conference, as well as, the second, third, and last interviews before Glenn flew. I was struck by something I had not really grasped. It was always Glenn who talked about the science. It really was not the NASA administrator and the other people. They would present the experiments and the mission activities and emphasize the science; but, when it came to questions about the justification for the flight, it was always Senator Glenn who said it was science. NASA really never said that. They talked about Glenn's inspiration to older Americans and the inspiration his flight might give to children. The news media responded in record numbers; in fact, at Glenn's shuttle launch, there were 3700 members of the news media gathered at Cape Canaveral. Some of the networks had 60 to 70 people; and, you wondered, what are these people doing? It was a zoo. There are several reasons for that. It was a compelling story because of Glenn's age and his hero status. There were two foreign astronauts, and they had press corps who were interested in their countrymen flying with an American hero. There was an unusually large response and number of people covering at least the start of this mission.

I remember during the months before the flight there was a constant number of people battling whether to observe the shuttle crew as they trained or to interview John Glenn. If you got 5 or 10 minutes to interview somebody, you were lucky. There was that much interest in interviewing somebody who had something to do with John Glenn's mission.

I mentioned something to Dr. Charles about an event that happened this week within NASA. I was contrasting it with the whole experience of the John Glenn mission. The event involved a decision under consideration for several weeks to make an emergency flight, or an unscheduled flight, this fall to repair the Hubble space telescope. The Hubble space telescope is an amazing feat of engineering and is being used to benefit science. Yet, that story did not crack the front page anywhere. It was not a very long story wherever it played. I do not know if someone like John Glenn would have been suitable for this kind of mission; probably not. It does show that you cannot draw this line and say this is science and it is going to get treated one way, and this is something else and it is going to be treated another way.

It is very difficult to put a boundary around something like John Glenn's flight and say it should not be treated as science. If you took the upcoming Hubble mission and tried to give it the same treatment Glenn's flight got, you probably could not do it unless something really unexpected happened. At the *Chronicle* we discussed Glen's mission for weeks and assigned more people to report on various facets of it than we will for the Hubble repair mission. The bottom line came down to this--we figured there was not too much we could do. The astronaut's core is here in Houston, the mission would be run from Houston, and some of the investigators are from Houston. We decided that we ought to do everything we could so that nobody did more than we did, at least in our judgment. We decided to be prepared to do anything we could to compete with any story on this particular flight.

Dr. Low:

Thank you very much, Mark. We are going to ask the panelists to stay at the table and now we are going to bring the audience into the question. You have heard from the scientific director of the flight on which Senator Glenn flew and you have heard the summary. The question is: Did the mass appeal have anything at all to do with science? Was that a good thing, or was that a bad thing? Or, was it neither? There are microphones on two sides of the room and I am told, John, that you are always the first up to ask the questions, so you get the honors again. You have lived up to your reputation.

Question (Dr. Grabowski, UT-Houston Medical School):

I imagine everyone was very appreciative of both. I guess the question I would have for NASA is: "Would there have been an interest in, say, putting Dr. Low up there?"

Would there have been an interest in aging of that magnitude had it not been inspired by Senator Glenn's persistence? Would that flight have occurred now or ten years from now, or for that matter when people go to Mars and grow old in the process? I think the Hubble issue is important, despite some of the early foibles with the ground lens. It might be good to get Senator Glenn to make a comment on the importance of that science. Maybe that is a way he can pay off a debt for going on the second trip. Was there an interest in aging beyond the issue of motor capability?

Dr. Charles:

There has been a long-standing interest in collaborating between the aging and the space flight research communities.

Dr. Charles (responding to inaudible question):

Well, that is not a bad thing. It is nice to have an advocate. I think we can all agree there are probably lots of good ideas, lots of areas for research, that just have not found the right advocate yet. I personally think it was a good thing to do, if only to dramatize the relevance of the aging population in our society and the fact that they continue to contribute. I thought the story that Mark told about the woman cleaning her windows was indicative of the inspiration Glenn's re-entry into space evoked.

To perhaps forestall some additional questions: yes, it was a study with a sample size of one, and it is very hard to do statistics on samples of one. Although at NASA we have an abundance of small N samples. We work the "bejeebers" out of them statistically if we can. I hasten to add that every investigation on the ground or in space begins with a sample of one. Sometimes it is the pilot data that shows you whether you are on the right track or need to go back and rethink an idea.

There are currently no plans to fly any more elderly citizens in space, at least in the foreseeable future. I do not think that it is inappropriate. If we want to stick with that approach, I think we need to see what we have learned from this and decide whether we want to proceed.

I am hopeful that the role for more mature populations will increase in our space program. I am hopeful that astronauts, as they age, will continue in space flight. There may be a role for more mature individuals on longer missions. Trips to Mars might be best undertaken by more mature individuals who have different life goals and different life expectancies than younger people. Young people may expect to come back and have families and vigorous careers when, in fact, the effects of space flight, like radiation and extended weightlessness, might predispose them against that.

Mr. Carreau:

John Glenn, in the first press conference, was asked what good would it do to have one data point. He said: "Well, the first time I flew, you know, I was the first one to do it and the only one to do it. And all it proved was that we could do it. By that I mean, it proved that the U.S. could put a human in space and have him pilot and make decisions. Previous space travelers who orbited had all been Soviets and their missions were secret. For the most part, the data was not available and NASA chose to be very open about it."

Glenn openly demonstrated that a human being could do something. It was a good political comment. Something that I thought was ironic was that at the time Glenn and the first seven astronauts were chosen, they were carefully screened from a lot of people, and selected to do the missions. If NASA had been really authentic about doing an aging study, they probably would have screened a whole lot of people and picked a small subset to do an experiment like this. NASA felt that Glenn's qualifications were unique and that a lot of people would be eliminated as a result of the training aspects, health requirements, and endurance tests. Glenn was just the natural person to do it. I think, in the end, it was accepted that this was a demonstration, and that there was much more about this mission than just science.

Question (Malcolm Duker, Professor of Pathology, Temple University):

I was a teenager at the time of the first Sputnik, and I remember vividly the great interest in outer space adventures between Sputnik and the first landing on the moon and the precipitous and enduring decline in public interest since the first step on the moon was taken. There have only been episodes of public interest, like the Challenger failure or Apollo 13, or the Glenn mission, but no sustained interest.

The basic question is how to interest the public in both the scientific utility of the space program and the overarching goal that is the expansion of Homo sapiens from this home planet to other places in the universe, which, of course, is the ultimate goal of this type of project.

Dr. Low:

Does one of you want to respond to that?

Dr. Charles:

I think that is a very good set of points, both about the interest of the public and about going to Mars. When I get old enough, I want to go to Mars, too. I did more explaining about the science that we do on every mission in the context of John Glenn's flight than I have done for all the other missions that I have worked on in the last decade and a half. That includes my experience in the Russian Mir program. I have tried to explain periodically what it was we were doing that justified putting people on the Mir station. There is value in this kind of undertaking if it brings public attention to the ongoing work that is done on every mission, which is to try to answer the basic physiological and biological questions about adaptation to space flight.

Mr. Carreau:

There is a huge public interest in science. We are talking here about space science, but I think there is also a great interest in medical science and engineering science. The popular press puts more and more attention into these areas than it ever has. There is a huge amount of information on the Internet, if not on the printed page, about what is going on with all the NASA programs. A lot of it is generated by NASA because they have public affairs machinery and a clause in their initial charter in 1958 to educate the public about what they are doing.

There are magazines, trade press, popular press, web sites at the launch site in Florida, and we certainly have one in Houston. We get a lot of people looking at us, checking us out on our web sites. Science magazines also get a lot of public interest over the Internet. I think there is an educational process involved in getting people who cover the stories up to speed, on the cutting edge. We probably do not have enough reporters that are grounded in things like that to cover stories as intelligently as we should.

There is a huge issue of privacy with medical data, and it makes it impossible for the news media, let alone the public, to find out how, for instance, John Glenn himself personally fared on his space flight. His data points are going to stand out because of his

age, if the data points are somehow identified. As I understand it, the astronauts volunteer for the experiments. They cannot be compelled to participate in them. And they are also reluctant to disclose personal medical data as any of us would be. That is one area where it is difficult to put the personality and the result together to get the sort of impact on the story that maybe you would like to see.

Question (Dr. Sandra Hanneman, UT-Houston School of Nursing):

In spite of all the explaining that John Glenn did regarding the science associated with that particular flight, of the billions of words that were printed in the media across this country and shown in the visual media, a relatively tiny miniscule proportion of those address the science. I have read huge sections in the *Chronicle*--I mean whole sections--on this flight and found hardly any information on the science, with respect to aging.

The question I have is: given the public's insatiable appetite for sound bites and fast breakthroughs, how can any of us - - media and scientist working together - - (a) transform the majority of society from a sound-bite, superficial, glitzy, shallow level of understanding to a deeper level of scientific literacy, and (b) Is that even an appropriate and realistic goal?

Mr. Carreau:

It is probably unrealistic. Life is rushing by all of us every day. I am amazed at how many people I work with who do not even read the newspaper we publish every day. I am never surprised when people say: well, I didn't see what I wanted to see or what I expected to see in the newspaper. I think in our case, and not to be too defensive here, we try to give people as much as we thought they could take. We listen to everything that everybody can say, and we filter it out.

I remember when the whole issue of whether Glenn was going to take melatonin came up. It turned out that the *New York Times* broke the story on this. Within a few days either *Time* or *Newsweek* disclosed in an article that Glenn was not going to participate in that facet of the study. Even people who should have known about these developments had missed this kind of crucial point some weeks earlier. NASA could have been a little clearer when it briefed reporters.

Dr. Charles:

Following up with that, I think Mark already mentioned one way we can get more information to more people; and that is with the Internet, with the worldwide web. Certainly NASA puts a lot of information out there. I know we try to put as much as our access to the web will permit. It is pretty much incumbent on the individual reader to go follow the links and get to it. But I think it is an excellent way to get the detailed information out there. There is usually a point of contact attached to that.

Dr. Low:

It suggests that somehow this society is scientifically illiterate, which I do not think is true. I think there is a range of scientific literacy in America, just as there is a range of literacy. Some people are profoundly and sadly illiterate, no matter what the topic happens to be, and some are wonderfully intelligent and well read. From my own personal experience over a fair number of years, my assessment is that the literacy quotient in America is rising; at least the scientific literacy quotient is rising.

I will give you an anecdote, and I am quite aware that this is, again, one of those samples of one. We have a Nobel prize winner in our institution. He was giving a talk that we sponsored at the Museum of Natural Science. This was a public talk, at least public in front of an audience that we had invited. He agreed to take questions at the end of his discussion. His Nobel prize was for discovering the utility of nitric oxide, especially in relation to the use of nitroglycerin in treating angina. He discovered, in fact, that it was nitric oxide that was the mediator that caused the smooth muscle relaxation in the arterial walls of the coronary arteries. Well, at the end of his talk, he spoke a lot about nitrogen--how prevalent it was in the atmosphere and how nitric oxide has been viewed as a toxic gas. At the end of the session, a lot of people asked him questions, including my daughter who is 13 years old. She said: "Well, Dr. Murad, I'm interested in nitrogen fixating in nitrogen-converting plants, and I'd like you to tell me how those things work and particularly what relevance that has to the nitrogen in the atmosphere, especially in relation to your talk." He gave her a plausible answer and she kept her peace. Then on the drive home, she said: "You know, Dad, Dr. Murad is very nice but he's wrong. That isn't how they work at all." So, not all of us are scientifically illiterate.

Question (Amy, University of Houston):

I was hoping to shift the conversation to the ethical dilemma of using mass appeal to promote science, which is often useful, especially with public health problems. What are the ethical responsibilities in using such a strategy to appeal to the masses?

Dr. Low:

That is a very good question. Where is the ethical boundary in all of this? I think all of us understand the practical utility of using a hero like John Glenn to highlight the efforts of NASA in space exploration. No question, it is useful. It gets our attention like almost nothing else, and it clearly has benefits. But is there a downside?

Mr. Carreau:

I will take a quick stab at that. I think NASA spent some capital and it probably cannot do that every year. It probably cannot do that every three years. They need to pick their opportunities, and they did a good job this time. If they attempt something similar to this again, I do not know how it would turn out. My guess would be that it would not be the same experience. There was something about Glenn. He was definitely an American hero and that made a lot of difference in the way this played out. Nobody could really get

in his face and say that he did not have honor and that was a big factor in all this. As a backdrop, he had the events going on in Washington with the Clinton administration last year. It helped make this story even more compelling to people. I do not know whether you could make this happen again or not. I sort of doubt it, but who knows.

Dr. Charles:

If I am not missing the point, the Senator was probably going to fly in STS95 whether we had a dozen experiments or two dozen experiments or zero dozen experiments. That was pretty much a predestined thing once a decision was made at NASA headquarters to fly him. I think this was an opportunity for us to explain the ongoing science that we did. Every chance we get to explain science is a good thing. I suspect we will jump at every opportunity to explain good science to people who want to hear about it. I agree with Mark that you have to choose your opportunities wisely and not take the same horse to the well too often. Generally it was the right thing to do at that time and then subsequent opportunities will have to be judged on their own merits.

Dr. Low:

My own take on this question is the following: Within the range of all the possibilities of human behavior and behavioral choices, there is an infinite gradation from black to white. There are things that are absolutely wrong and evil and there are things that are absolutely good and positive. But in between there is a really infinite gradation of shades of gray. The issue is how honest we are; how honest was NASA with us about why they were doing this and what it really means. NASA never tried to justify this on the basis of science. It was John Glenn who felt that he was going to contribute to science. One can understand that once he got himself on the flight he felt responsible for helping NASA justify putting him on the crew. I think I understand that in human terms.

If NASA had said that it is going to cost \$10 million more to put Senator Glenn on this flight than it normally would have cost, and that it is justified because of what we are going to learn about aging in space flight, then I would be concerned about it. They did not do that. In this particular case, I believe one could justify John Glenn being there for reasons other than scientific ones. If NASA had really, seriously tried to justify it from a scientific point of view, I would be a lot more skeptical.

Question (Ralph Metzger, UTMB at Galveston):

My take on this discussion and some of the ethical questions that have just been raised is that this is not something that NASA set out to do. This is not a question of could they pull it off again. Had they sought out an old guy, or John Glenn in this case, because he would represent a charismatic icon to bring attention to the program, then perhaps the discussion could be along the lines of –well, is it appropriate to do, should a government agency be looking for things that would fall into the realm of stuntsmanship. I do not get that this was stuntsmanship.

I would like to revisit the question that Dr. Hanneman raised. What do you believe is the popular press's role, or the newspaper's role, in education with respect to science?

Mr. Carreau:

I guess there would be my answer and then there would be the answer for the enterprise – a newspaper or a TV channel that delivers news, such as Channel 13 or Channel 11. At some level it is a business and we have a market that we serve in order to do the business successfully. In Houston, the *Houston Chronicle* is the only newspaper, so we do not have to compete with another newspaper to make that goal. This gives us the opportunity to look out at our audience and our potential audience and say: what can we do to make our product more valuable to the people who live and work here? Certainly, with the Texas Medical Center and the Johnson Space Center, you have two of the most prestigious science organizations in the world, so you need to tell people what role these organizations play in your community.

That is what we do at the *Houston Chronicle*. But, personally, I wish we had more people doing it. Believe it or not, covering the space program is a full-time job. A lot of people do not realize that, but it could probably be more than one full-time job. I would certainly think that covering the activities at the Texas Medical Center would justify a few more people than we have doing it. I do think people have a thirst for information, and I think the introduction of the internet is a great opportunity to archive material that people can get to long after a story has come and gone. That is the kind of thing I see that a news organization like mine needs to do: think in terms of what you are producing, give it news and context value so that it has a shelf life that is longer than one day or one week.

Dr. Low:

I would applaud Mark's interest in this. I think that the science pages of the *New York Times*, for example, are wonderful. I think these are very educational and very valuable and very consciousness raising. I see some members of the media playing an extremely valuable and responsible role in getting an answer to Sandy's question: what do we do about science literacy.

I think the schools are doing better as well. We see that. The people we bring into first year medical school now, or first year dental school, or first year of nursing, for example, are far more scientifically literate than I was when I went into medical school. It is pretty obvious. Their level of sophistication and understanding in science is much deeper.

Dr. Sandra K. Hanneman:

Thank you very much to the panel. The next session is "Setting the Biomedical Research Agenda." We expressly invited somebody from the National Institutes of Health to address this topic. I am very pleased to introduce Dr. Mary Groesch who is Senior Health Policy Analyst in the Office of Science Policy at the National Institutes of Health.

Mary Groesch, Ph.D.
Senior Health Science Policy Analyst
Office of Science Policy
National Institutes of Health

Thank you. I am very pleased to be here today. I assume there is quite a mix of people in the audience in terms of how familiar you are with the National Institutes of Health (NIH). So I will give the 30-second version of NIH 101 so that you will have some idea as to how it is organized.

Our mission is simple. It is to discover new knowledge through research that leads to better health for everyone. NIH is the world's leading biomedical research institution. We support more than 50,000 scientists. They are located in more than 1700 research universities, academic medical centers, and institutions throughout the country. NIH is part of the Public Health Service, which is part of the Department of Health and Human Services. NIH itself can be thought of as a federation. It consists of 25 distinct institutes and centers. The whole group is headquartered in Bethesda, although some laboratories and actually one of the institutes are located in North Carolina. The institutes and centers were each created by Congress and each has a unique mission. One of the handouts in your packet lists all the different NIH institutes and centers and their mission statements. The various mission statements might focus on a particular disease, a particular organ, a stage of development, or sometimes it is even cross-cutting research like research resources or sequencing of the human genome.

More than 81% of our budget goes to extramural research, and this is distributed through a variety of different funding mechanisms. It might be research project grants or center grants, research and development contracts, training, career development, construction, various categories like that. The intramural research accounts for about 12% or 13% of our budget. Most of that is conducted on the NIH campus in Bethesda, Maryland. The intramural research program includes the NIH Clinical Center, which is a 350-bed research hospital. This accounts for nearly half of the clinical research beds that are used in the country.

My presentation is on the complexities of setting a national biomedical research agenda, and not surprisingly that is very closely tied to funding issues. As you know from Congressman Bentsen's remarks, our fiscal year 1999 budget was \$15.652 billion. This is a very significant budget increase over the previous fiscal year. It is an increase of 15%. This very generous increase has understandably prompted questions and concerns about how effectively NIH will be able to spend the money in the space of just a year. As you might expect, our answer is that we will have no problem wisely managing not only this increase but also equally generous increases in the future. I would like to tell you how we invest this money as well as a little bit about the process by which we arrive at decisions and how we work to strengthen our priorities.

A good question is what does an additional \$2 billion mean for the research community as a whole? One might ask: "Well, since our mission is to generate new knowledge through research, why don't we just put the whole \$2 billion into new research projects?" Our answer is that would not be a fiscally sound move. We are going to invest

quite a bit of that. But there are some other important considerations. I am going to spend a little bit of time describing those considerations.

With the increase, we will be able to fund more than 9,000 research project grants this year, including about 1700 new competing grants. This also accounts for how the new funding for research projects will be spent. The handout you have shows the breakdown of where the funding goes. The handout also shows specific examples of projects and gives some detail. A small, but significant part of the funding will continue to support our previous commitments. This funding has to include inflationary increases, so we are actually talking about a lot of money.

We use some of the new money to increase the average size of awards. You may wish to take this slide seriously: "Due to a tightening of the budget, we are forced to curtail overtime and weekend schedules. We request that all major breakthroughs be achieved as early in the week as possible." What has been happening for a while now is that because of limited research dollars, we have been under-funding programs, or providing less money than what was recommended or requested. This is what we refer to as downward negotiation. As you can imagine, this sort of action causes a problem, because research is a cumulative process. You cannot sit back and say: "All right, I want you to achieve all you said you would do with less money," because it is a stepwise fashion and you need to be able to go from one step to the other. So what has happened is that researchers write more grants to get funding supplements. This takes time away from their research. It turns into a vicious circle. The investigators use a lot of valuable research time to try and get the additional funds. And workload goes up because we are processing more grants. With the FY99 increase, we will be able to fund research projects closer to the recommended level.

Another thing that we can do is to begin to fund more critical high-cost proposals. Some research projects are more expensive than others. For example, if you are trying to develop animal models, some types of clinical research are very expensive, especially ones that involve large patient populations, or ones that have to be conducted over a long period of time. Research that requires very advanced technology and instrumentation is also expensive. When we have had very limited resources, we had to weigh the very important but high-cost proposals against the equally important but lower cost projects. It has been going in favor of lower-cost, more research projects. Now we will be able to increase funding of the critical, high-cost proposals.

We also will be able to increase funding to research centers. Research centers bring together a lot of multidisciplinary expertise that is applied to one problem. Often, the research centers are focused on clinical research. Some of our funding goes to support a network of about 75 general Clinical Research Centers (CRCs). These are located throughout the country, and they provide very critical clinical infrastructure for much of the research activities that go on. We will be able to broaden the scope of the general CRCs. New areas will be added, such as surgical, obstetrical, and intensive critical care. With increased funding, CRCs also will be able to develop new core curricula for training clinical researchers.

A significant amount of research training is supported by research grants. Any time that we expand the number of research grants that we are funding, we also increase our training capacity. The primary goal in the training area is not to significantly increase the number of trainees but to ensure that they are better trained and can survive and flourish in

a research atmosphere. One of the things that we do is increase training stipends. It has been difficult in the last few years to attract the best and brightest minds to research. It is not a very attractive proposition when students find out what their salaries are going to be for the next five, six, or seven years of training. NIH training stipends have been very low relative to other agencies. We will raise the stipends and that will help us maintain a steady supply of well-trained investigators.

We also realize that in order to train young people we need to ensure that they have trainers. What we want to do is support mentors for the trainees. We have developed three new extramural grant programs. These awards are known in shorthand as the K23, K24, and K30 awards. The K23 award is the Mentored Patient-Oriented Research Career Development Award. What this will do is attract junior health care professionals to clinical research. It will provide didactic training for them with mentors. The program is going to be directed toward physicians, chiropractors, nurses, and PhDs who have been certified to perform clinical duties. It will allow them to commit at least 75% of their time to actual clinical research training.

The K24 award is the Mid-Career Investigator in Patient-Oriented Research Award. What this will do is provide protected research time and mentoring opportunities for mid-career clinical investigators. It will be a means of relieving them of some of their patient care duties so that they have more time to act as mentors. These awards will target highly skilled investigators who are in mid-career or who have been practicing in their specialty for 15 years or more.

The K30 award is the Clinical Research Curriculum Award. It is an institutional award. It goes to institutions to help them either strengthen or establish multidisciplinary, didactic training in clinical research. This is another way to strengthen clinical research training.

One of our goals in the area of training is to increase the diversity of the investigator pool. We do this in two ways. One is to improve minority participation in medical research, which is a very high priority for the NIH. We are expanding programs that will boost minority recruitment and retention in the basic sciences. Another way of achieving diversity is to encourage trained investigators from other disciplines to participate in biomedical research. The other disciplines we are talking about are physics, engineering, chemistry, and computer sciences. Increasingly, many of our advances depend on these types of expertise, and so we are trying to encourage these people to use their talents in biomedical research. Some of the ways we encourage this is through program announcements that specifically invite people with this expertise to apply for funding. We are creating a bioengineering consortium, and we are investing in instrumentation development.

I have shared with you some highlights of where we will invest the new funds. What I want to talk about next is priority setting. In light of the tremendous increase we had this fiscal year, there has been a great deal of interest in how NIH makes its decisions. This interest comes from both advocacy groups and Congress. Congress wants to feel confident that we have some systematic way of arriving at decisions.

In fiscal year 1998 appropriations for the Department of Health and Human Services, the Secretary was required to contract with the Institute of Medicine to have them do a comprehensive study of the policies and processes that NIH has in place for setting

priorities. The resulting report was released in July of last year. It contains 12 recommendations. NIH has been working to respond to these. Some of the things we are doing were already ongoing activities, but we are strengthening them.

First, I think it would be important to talk about some of the considerations or criteria that influence how we set priorities and how we allocate the research dollars. One of the major criteria by which we build our budget involves evaluating current scientific opportunities. When we request increased funding, those requests are based on proposals that have come in to exploit new biomedical discoveries. The proposals may be for isolation of new genes for human diseases or to encourage studies that we can do only now because of recent findings. We are always trying to build on the most recent findings. Sometimes it is to strengthen technology that will open up pathways for more research in a lot of different fields. This could be computer science imaging or gene mapping technologies. But whatever it is, the NIH uses a very stringent review for scientific quality on every research proposal that comes to us. We do this because this is the way we feel we can get the maximum return on the public investment.

We also have an obligation to respond to public health needs. Public health needs can be judged by the incidence, severity, and cost of treating and managing specific disorders. It is really very difficult to try to calculate public health needs. There is not always a clear correlation between expense and results. One thing that we have learned--if you consider us as administrators of science--is that many significant advances occur when new findings open up new realms of research and that not all problems are equally approachable, no matter how serious they are. Sometimes when research is done on a very rare disease that does not affect many people directly, the researcher discovers benefits that apply to more commonly occurring diseases. In contrast, to pour money into a disease just because a lot of people have it, when there are no scientific opportunities to capitalize on, is wasteful.

We do think it is important to maintain a very large and diverse research portfolio. It is impossible to predict where the next advances are going to be. It is impossible to predict what connections will be made between findings in seemingly disparate fields. What we found is that very often it pays to support research across a wide array of topics because it happens that, at other times, you can capitalize on findings in some other research area.

NIH has to support the human capital and the material assets of science. We support a great deal of research training and acquisition of equipment and instruments, especially programs where the equipment and instruments can be shared among a lot of different researchers. We do support some limited construction projects, and we do put funding into institutions to enable their research programs. We have to make a lot of different kinds of decisions when we distribute our money. The decision might be based on what portion goes to basic versus clinical research, or what portion goes to grants or contracts or centers, or what portion goes to responding to emerging diseases or new patient advocacy. We have to do this portioning on an almost daily basis. It requires constant evaluation of what we are funding, what the needs are, and where we think the best investment will be.

There are a variety of different ways to assess health needs. Many facets need to be considered when we talk about scientific opportunities. We are not able to allocate funds to do research on this disease versus doing research on that disease by using any set formula. There are a lot of different ways of measuring the health needs of the nation, a lot of different ways of cutting the pie to distribute those funds and each of them has its own

advantages and disadvantages. For example, if we were to use health needs alone to gauge priorities, the research funds might be distributed based on number of people with the disease, number of deaths caused by the disease, degree of disability caused by the disease, or degree to which a disease cuts short a productive life. The distribution of funds could be based on the economic and social cost of the disease or on how important it is to act rapidly to control the spread of a disease.

The problem is that using any one of these criteria alone to make a funding decision would produce a very different result. For example, if we were to allocate funding by basing our decision according to the number of individuals affected by the disease, then we are going to emphasize the more common diseases. But this might have a very limited overall effect on health and survival. We might end up funding a lot of research on the common cold and allergies but very little on childhood cancers.

If we were to allocate funding according to the number of deaths, then this could neglect chronic diseases. Chronic diseases produce long-term disability and very high costs to society. We might end up neglecting diseases like mental illness and arthritis. If we were to allocate our funding according to disability or economic cost, then questions would arise very quickly about how we quantify these kinds of costs. Should the direct cost of medical care be included? Should indirect cost, like lost productivity, be taken into account? Funding according to the economic cost of an illness is going to under-fund diseases that result in a very short illness and a rapid death. We might have a lot of funding of Alzheimer's disease and muscular dystrophy but very little for sudden infant death syndrome or certain kinds of cancer.

By the same token, funding based on immediate dangers to the public's health could divert research from much broader, long-term impact types of research. We might have a great deal of research done on AIDS and TB, but very little on Parkinson's. All of these criteria for weighing health needs are quite justifiable. If we apply any one of them, exclusively, we will neglect some other, very important classes of research. These criteria, if used exclusively, would tend to under-fund research on rare diseases. As a science-funding agency, we have a responsibility to base research funding on all aspects of disease, regardless of the number of people it affects. There have been many benefits to common diseases that have arisen from research on rare diseases. It is not easy to determine how we will allocate funds according to the impact or the burden of various diseases.

There are many conceptual problems here. There is a real dearth of good data in this area. We are going to explore these issues. We are going to convene a small group of economists and other experts, ask them to identify data sources, review models that use the burden or cost of disease for priority setting, and look at how these data might be used to show how research leads to improvements in health.

The allocation problem is even more complex than this. While NIH focuses much of its research on combating specific diseases, a lot of the research that it supports is of no obvious relevance to a particular disease. I am talking about basic research, but not all basic research. I'm talking about untargeted basic research. There can be basic research that you can easily link to a disease. NIH has found that it is really very important to maintain a balance between disease-specific research and untargeted research. By maintaining a balance between the research types, we can balance long-term and short-

term benefits that arise from research. This is the best way to maintain a steady supply of health advances or scientific knowledge that can lead to health advances.

We do not have a single formula that can incorporate all of these different factors; we do not use any one of these measures exclusively. We try to take them all, or at least a subset of the measures, into account. The subset that we use varies from disease to disease depending on its characteristics. We need a lot of expertise in making assessments. This requires a breadth of vision across many disciplines and the judgment to determine the likely yield from making investments in these particular areas. That is where the expertise in all of the different institutes and centers of NIH comes into play.

Another factor that we have to take into account in allocating research funds is the importance we place on investigator-initiated research. A great deal of our funding depends on what ideas come in as proposals from the extramural community. The NIH Director plays a very important role in our priority-setting process. He shapes the agency's activities and outlook. Although each individual institute and center decides on its own how it will deploy its talent and funds, the Director has an important role in shaping the plan. Our director right now is Dr. Varmus. He has developed several guidelines for growth. These will be used to guide NIH programs into the new millennium. These guidelines are reflected in projects that you saw on the handout stating how we will spend the extra \$2 billion from Congress.

The first I have already talked about--making full use of our existing research capacity. This guideline both reminds us that in the past very meritorious projects have gone un-funded because of limited resources and allows us to redress that practice. There is no doubt that we have been under-funding or participating in downward negotiation. I have already talked about engaging new disciplines in medical research and exploiting advances from the biologic revolution. If we are going to be able to capitalize on new findings, it is going to take more than the kind of conventional research infrastructure that we have. We are going to have to acquire very advanced technology and instrumentation and a lot of new animal models for testing these new ideas. That is very expensive research.

Another guideline promotes harnessing science to the service of public health and health care. We are saying that we place a very high priority on translational research, research that is going to take basic findings and turn them into applications for human disease. Within this category, we are trying to strengthen clinical research and to make sure that we have the computer-based systems in place so that we can harness all the data that is being generated, data like that from the human genome project. We can categorize it, collate it, and have it accessible to researchers around the world.

The final guideline suggests initiating innovations in the organization and review of science. This initiative includes not only some of the new types of funding mechanisms, such as awards, but also includes new ideas, such as the consortia that will encourage large-scale collaborative, interdisciplinary research. It is going to take both today's science and tomorrow's science. It is going to take input from a lot of different fields. One example of this kind of consortia approach is the brain molecular anatomy project. This project is an initiative to map the genes that are expressed in different parts of the brain during development, during adulthood, and during aging. Projects like this are going to

require the combined talents of many different kinds of investigators. For genetic research, we are going to need computers, epidemiologists, and a variety of other expertise.

Another example of how the NIH Director provides the overarching guidance for priority setting is in areas of research emphasis. About four or five years ago, Dr. Varmus identified what he called the areas of research emphasis. These are fields or areas of research that he deemed to be very right for progress, areas where we could expect a lot of progress in the future if additional money was available to explore them. Initially he identified the biology of brain disorders, new approaches to pathogenesis, preventive strategies against disease, genetic medicine, bioengineering computers, and advanced instrumentation. Two years ago he added new avenues for the development of therapeutics. Just this year the final category of health disparities was added. Each year, Dr. Varmus goes out into the institutes and centers with requests for them to turn in proposals for research that would fit these categories. He makes his selection and has a particular pot of money that can be applied to encourage research in these areas. This money is used for one year of funding only. After that the institutes are required to provide support.

In studying the research priorities, the Director also works very closely with all of the institute and center directors. They engage in discussions not only among themselves but also with scientists in the extramural programs and with intramural investigators, groups of patients and their families that are interested in particular diseases, and with professional and scientific groups, along with members of Congress and general members of the public. They ask for advice on many different topics, such as the potential impact of particular research areas on human health and what these different groups think are the most critical scientific opportunities. They ask for advice on the gaps in knowledge that warrant additional research. Finally, they explore economic issues and what should be the best balance between intramural and extramural funding, and among clinical, basic, and epidemiologic research. Thank you.

Dr. Sandra K. Hanneman:

The next and last panel session is entitled: "Industry Sponsorship: Why Does the Pied Piper Pipe"? I would like to invite the panel to come up while I introduce the moderator, Dr. Jack Crawford, Professor in Ophthalmology at The University of Texas-Houston Medical School.

Morris L. J. Crawford, Ph.D.
Professor Ophthalmology
University of Texas-Houston Medical School

Thank you, Sandra. I would like to introduce the session participants. George Phillips is Professor in the Department of Biochemistry and Cell Biology at Rice University in Houston. He uses x-ray and crystallography and electron microscopy to study the molecular mechanisms in the regulation of muscle contraction. Next is Dr. Grant Ko, who is a clinical project director at Schering Plough Research Institute in New Jersey. Dr. Ko is board-certified in psychiatry and neurology. He is a member of the American Psychiatric Association as well as the Society for Neuroscience. Next is Chris Pascal, who is presently

the Acting Director of the Office of Research Integrity of the Department of Health and Human Services and a member of the North Carolina State bar and the bar of the United States Supreme Court. He is admitted to practice before the 11th Circuit Court, Court of Appeals. I am Jack Crawford, Professor in the Department of Ophthalmology and Vision Research at the University of Texas-Medical School. I do research on the development of the brain and vision.

The metaphor for this session comes from the old German folk tale concerning the Pied Piper of the prosperous town of Hamelin. The Pied Piper had a contract with the mayor and council to rid the town of a plague of rats. The Pied Piper piped. The rats followed him into the river and drowned. However, the mayor reneged on the contract. So the Piper sought revenge by playing a different tune. This time he led the town's children out of the town to a dark mountain where they were swallowed up and lost forever. The lesson to be drawn from this tale might be that breaking a business contract could have dire consequences, or it might be that corporate greed gets what it deserves.

We raise the question about the expectations of the principals involved in the contract. The Pied Piper piped in expectation of 50,000 deutsche marks for his prodigious skills and effective services, whereas the mayor and the council of Hamelin expected to get relief from the plague of rats. It is the expectation of contracting parties, the expectation of corporate sponsors and researchers who carry out the research that is the topic of this session. What are the expectations of corporate sponsors of biomedical research? What are the risks for the integrity of the research, especially the integrity of the investigator? What are the ramifications for biomedical research, and what should the public expect from the research alliance between corporate sponsors and their university faculty?

First and foremost, there should be the expectation of an honest application of the sound principles of science. One aspect of the research liaison between corporations and universities, that is, the giving of gifts by the corporate sponsor to the principal investigator, was investigated and reported last year in a *JAMA* paper entitled "Looking a Gift Horse in the Mouth" by Campbell, Lewis, and Bloomingthal. The aim of the study was to investigate the frequency, the importance, and the potential implications of research-related gifts from companies to academic life scientists. Using a well-designed survey format, the authors collected data from over 2,000 life science researchers from the 50 universities receiving the most NIH-sponsored support. They tabulated the percentage of faculty who had received a research-related gift from a company in the last three years and analyzed the investigator's perceived importance of the gifts for his research. What, if anything, did the investigators think the donor expected in return for the gifts?

The results showed almost half of the investigators had received research contract gifts from their industry sponsor during the three-year period. Most often these gifts took the form of biomaterials with discretionary funds, equipment, and support for students - - the latter falling in line with smaller percentages. The faculty recipients in basic science and clinical departments did not differ in the frequency of the gifts. Senior male faculty received more gifts than did female and junior colleagues. The faculty who received the gifts had a longer and more productive research history and teaching history with more publications and more student contact hours. Researchers who received gifts of paid trips to professional meetings were more likely to have products under review--almost a quarter of them--than were those who received other sorts of gifts.

What did the researchers think that the gift donors expected in return for these gifts? Two-thirds thought that an acknowledgement in any publication was expected. One-third thought that the donor expected prepublication review, and 20% thought that the donors expected a future consulting relationship. Two-thirds reported that the gifts were important to the success of their research, suggesting that gifts have a large effect on the professional lives of life scientists. This finding may answer the initial question as to why the Pied Piper pipes. One reason could be that he pipes his research to keep the research funds coming, and gifts sustain the scientific melody. The report suggested that gifts to research faculty outside the institutional contracting process might have a corrupting influence on the quality of the research product, namely, the search for truth and new knowledge. The obvious conclusion is that taking a research-related gift that bypasses the institutional administrative structures deserves more study and discussion among the academic community.

We would like to turn now to members of the panel to give a brief opening statement and to comment on the questions that were raised in the *JAMA* article. After brief comments, we will open the floor to discussion. I would like to start by asking Dr. Phillips if he would begin the program.

George Phillips. Ph.D.
Professor, Biochemistry & Cell Biology
Rice University

The metaphor of the Pied Piper is rich with possibilities. Certainly the stakes were high and children's lives were lost or at stake. Who is the Pied Piper? You would need a few minutes to determine who is luring whom away. Who is the corporation luring away? This is an interesting starting point. So let me first try to summarize why industry is so interested in these relationships.

They would like to have early and easy access to ideas. Why should scientists and researchers sit around, be creative, and come up with ideas if others do not appreciate them? Many industries like access to expensive facilities. If you are not a giant company, you may not have the millions of dollars to deal with these high-tech facilities. Getting access to the facilities could be an important part of an arrangement. It gets a little scary when a company wants their products endorsed. A big-name professor selling a new product carries weight. This is one of the areas where there may be a conflict of interest issue.

Why would researchers be interested? There is always the possibility of personal financial gain. Who would not want to have a wonderful invention, get rich, and retire as a result of developing a useful product? Financial support for research activity was mentioned as a primary reason for researchers getting involved with companies. Money is not always easy to get. In the old days when scientists lived in castles, they did their research and paid for it from their own wealth. Most of us have to count on money from others to carry out our research.

Researchers are also interested because they desire to participate in the real world of discovery. Not every research-physician likes to stay in an ivory tower. Some people like to get out and make a difference in the world by helping people live better. What better

way is there to do that than to partner with a corporation in developing a product that is marketable? But what are some of the dangers?

One of the main focuses of this session is the potential danger of bias that might result from these mutually contradictory or mutually beneficial interests. The lack of fair interpretation of results is a very serious problem. It guides the development of institutional policies outlining what kinds of relationships individuals can have with corporations. A second potential danger is direct conflicts of interest or conflicts of commitment. Does the professor work for the company because he did much of the research? Does he work for the university but ignores his teaching and focuses instead on his research? A third potential danger is creeping commercialism in science. If science becomes more concerned with short-term gain, or some sort of cynical exercise, an erosion of trust may occur. Everyone in the scientific enterprise should be concerned about this. We want the public to believe in what we do. We want to serve society and earn their trust by behaving responsibly.

Just what are most universities interested in? Lots of them want their faculty to go outside the traditional ivory tower and participate with industry. To not have any connection with companies is morally wrong. Here are some typical statements received from universities in this survey. They talk about the good things that we have. "These services could provide a mechanism for enriching the professional experience of the faculty and broadening their background for construction of research activity." "How can you teach students what industry is like if you know nothing about it?" "Why would this not lead to a better teaching experience, if you had a broader experience?"

The university also expresses concern about these kinds of relationships and what detrimental effects they might have. External activities must not interfere with certain activities such as conducting research, publishing scholarly work, teaching, and the like. Nowhere is there any discussion about potential bias, self-illusion, or other things that could be a consequence of the human desire to succeed, to do well, or to make money. But it is implied in conducting research. It also acknowledges that there can be conflicts. We need to have a free flow of ideas. This is sometimes detrimental to the interest of a private enterprise. It can result in a potential conflict between the researcher, the university, and the industry sponsors. We admit such conflicts are unavoidable. They need to be managed. We can manage conflicts in an ethical way rather than pretend that they do not exist. We can develop ways to deal with them.

What should be the general roles of the different partners in such a situation? Universities should have institutional leadership, written policies for the faculty, patent support so information can be revealed, and review action mechanisms to deal with specific cases. The survey you described said most faculty expect some sort of review of manuscript. Most universities have changed that to a loose expectation of written verbiage, such as the following: the company may review publications for 60 to 90 days and after such time the professor will be able to publish work without restriction. More and more we find policies written down to protect scholarly interest of students. Universities articulate more carefully now than in the past.

What are the responsibilities of researchers? To develop sound moral principles and to apply them in the conduct of science teaching and publishing practices. Researchers also have an obligation to relate their scientific knowledge. Scientists should take this

responsibility seriously. Government should exercise leadership in policy development and require institutional compliance with the policy.

What is the responsibility of profit corporations? They should understand that they affect public interest and should refrain from harboring expectations of personal profit and from making inappropriate requests such as asking a professor for exclusive patent rights when it is more than likely that the university will develop other ideas. They should not have expectations that undercut the mutual beneficial aspects of their arrangements. The public has a responsibility to maintain this as well. The public should insist on accountability, because they support universities and buy products from companies, pay taxes, and so on. They should try to understand the issues of research and participate in sorting them out.

What are some issues that propose a threat to the integrity of science? John Baylor, formerly of McGill University and a former general editor, wrote an article in which he stated that a researcher who was serving several masters could fail to mention weak spots in data analysis. He or she could selectively report some percentages of populations. This could be broad, or it could be some sort of self-deception or irrational data. The researcher could ignore samples of populations because the outcome of the experiment is not what was expected.

Another threat to the integrity of science is ignoring sample size, or incomplete and inaccurate reporting of prior work. For example, in your test, you may find that something works; but you know that there is a body of knowledge that says it does not work. It is unethical to ignore previous bodies of work. There is another threat, namely, the tendency to ignore how one's work fits into the larger picture. Am I doing something that will help in the treatment of diseases and will have a broader impact? Is this realistic economically? Looking at the general picture is part of the practice of science. The bottom line is that sins of omission may be easy to hide, but they undermine the scientific enterprise. This is where training for the next generation of scientists needs to be bolstered, and good examples need to be set.

Most everyone agrees that falsified data is absolutely unacceptable. But there are some people who believe the following, which is from Joshua Lindbergh and was published in *The Scientist* a few years ago. "My own experience over the past 50 years has been that the loss of efficiency in science is a hundred fold graver if it reaches sloppiness in the experimental design, self-delusion, and confused reporting than it is from intentional fraud." Most of the thinking about ethics in science could easily gravitate toward fraud issues. These are very serious considerations that need to be kept in mind. Good scientists like to believe that, in the end, everything comes out all right. If the data is not right, someone else will repeat it and in the process the right answers will be obtained. However, sloppiness can sure slow down the process. When the stakes are high, as in health care and people's health, you do not want to spend an extra 10 years correcting sloppy research.

Let me just close with some ways that minimize bias in university and industry partnerships. More and more universities and institutions are using them. There is a lot of kicking and screaming among researchers when they are told that they cannot take corporate money anymore or when they are told that they have to resign from the university. We need the university administration to manage cases where there appears to be abuse and to draw the line. Many institutions have not yet developed the backbone to

draw these lines and to have an ongoing dialogue with researchers. Many students and faculty do not talk to each other about these things; consequently, there is no clear understanding as to what is socially acceptable behavior. Conferences like this are very good for getting people to talk about these concerns and to begin to develop a collective sense of right and wrong. Many times neither the corporation nor the faculty member has any prior experience. It is very important to train your student scientists to exercise proper ethical treatment of data. We cannot let down on that without risking more opportunities for sloppy or bad science. We have to teach new bioscientists more about reasoning and ethics in their essential roles in the scientific enterprise. I am proud to say that the University of Texas-School of Public Health has courses on ethics for students in biomedical sciences. More institutions need to be in that league. In addition to being mandated by NIH training grants, it is also the right thing to do.

Grant N. Ko, M.D.
Clinical Project Director
Schering-Plough Research Institute
Associate Clinical Professor of Psychiatry
New York University Medical Center

George laid the groundwork for some thoughtful issues that we should consider about how we conduct ourselves in either academic or industry research. I would like to take a path that focuses on the bread and butter of what industries in the process of developing medicines do, while talking a little bit about the drug development process.

Safety evaluation of the compound is one of the first things attended to when bringing a drug to market. That entails animal testing. We cannot test a drug on humans and not know what the possible risks are without first testing the compound on animals. Half of the compounds fail to make it past the safety evaluation. When we know how the drug reacts in an animal, we can go to Phase 1. Phase 1 involves normal volunteers who tend to be young, healthy individuals. These volunteers often times are from specialty units at university medical centers and typically are undergraduate or graduate students. They can also be people from the community who do this type of volunteering for a living.

Two-thirds of the volunteers advance to Phase 2 testing. In this phase, the scientist tries to determine if there is an early efficacy read on what the compound is doing in the diseased population. After months of testing in the patient population, many compounds prove not to have any advantage and they fall by the wayside. If they show efficacy in early clinical trials, they are tested in more extensive, double-blinded, placebo-controlled trials. These trials are required by the FDA for registration of the compound. Approximately 80% of the compounds that make it to the next phase, Phase 3, will receive product registration. You may want to think about the ethical dilemmas this poses and think about the questions George raised, and how they might affect your thinking when you are in a position to develop compounds in your clinical population or are collaborating with other researchers.

It takes several phases and several years to move a compound from its inception to its registration as a medication. The preclinical testing may take 3-1/2 years. Then the compound has to be tested in Phases 1, 2, and 3. It then goes to the FDA for review and

approval of a dossier, which can take another three years. If it takes 12 years to complete the process and the patent life of a compound is 17 years, the company will have only five years to market the drug. When a product is used on humans, there is an IND filed. The IND states why we think the medicine will be useful or beneficial.

Why does research and development cost so much in a pharmaceutical company? Reasons include expanded discovery research, extensive clinical trials, clinical cost per patient, chronic degenerative diseases that require long studies, and quality of life studies that document the advantages of a new compound for survival and economic outcomes. The drug development process is risky, lengthy, and costly. This is some of the reality that goes on as to what it takes to take a chemical compound and make it into a medicine, to bring that compound from the discovery process in the laboratory and in animal studies to where it is authorized to be sold as a medicine to the public.

Chris Pascal, JD
Acting Director
Office of Research Integrity
Public Health Service

I just want to give a little background before I launch into some studies that I think are relevant to the topic. It has been mentioned in the last two days that there are conflict of interest policies governing the research sponsored by the Public Health Service (PHS) and the National Science Foundation (NSF). The policies require the institution receiving PHS or NSF funding to establish procedures for resolving financial conflicts when the investigator has an equity interest or other financial interest in the research. The topic today, Industry Sponsorship, is broader than that. I think it covers all types of sponsorship, even when there is no PHS or NSF funding involved.

ORI does not have responsibility in the public council for financial conflicts of interest. That is an issue that is handled by the NIH in the Office of the Director. I believe they coordinate the program for the entire Public Health Service. However, we do get asked questions from time to time. Do our scientific misconduct cases involve financial conflict of interest? It is not unusual for us to get press calls. The press thinks that because we handle misconduct cases we must be responsible for conflict of interest issues. We tell them that we do not usually get those situations. We do not review potential financial conflicts of interest. It is possible, in some cases, that there may be financial conflicts that the institution did not know about. There may be financial motivations involved in committing scientific misconduct, such as interest in receiving a grant award, getting tenure and/or promotion. That is not the normal thing that we talk about when we talk about a financial conflict of interest; that is just background information. Otherwise, interest in this subject exists only as it relates to the research integrity issue. This issue is not dissimilar to issues of scientific misconduct, which is honesty in reporting research and conducting research, and the public confidence in the research that results. In this area there is also an interest in and concern about industry sponsorship that involves bias.

There are two studies I want to mention. One is from the University of California, San Francisco. It was reported in *JAMA* a few years ago and received publicity. In this case, a UCSF investigator received industry sponsorship to study a type of drug or compound. My

recollection is that he looked at the brand name drug of the sponsoring company that held the rights to it versus three competitors to see whether or not they were bioequivalent, that is, if the efficacy was equivalent. At the time of funding, this particular researcher had done prior studies that suggested the company's drug was the better product. The expectation was that this was going to be favorable to the company. When the study was completed, the principal investigator's interpretation of the data was that there was no difference between the drugs. The paper was submitted to *JAMA*. The investigator either forgot or ignored a provision in the contract that stated the company had veto power over publication.

Most industry contracts provide for review by the company. They also allow for delay, if there is a need to file patent applications or things of that sort. But the agreements do not provide for veto power on the part of the company. In fact, UCSF has a policy against that. But the University had not reviewed this particular agreement. Litigation was actually threatened. In the end, perhaps because of adverse publicity and also because of meetings between the different parties, the company withdrew its veto of the publication, although it continued to disagree with the results. In the *JAMA* issue, the company published a criticism of the findings. The editor who published this was Drummond Eddy. Mr. Eddy has been very active in the research integrity area. He drew some lessons that he thought were important; for example, academic institutions need to have policies in this area and publication is paramount. Industry agreements cannot unduly restrict publication, and faculty in institutions need to stand up for academic freedom. I do not know that this is a very common outcome. This is the one that received publicity. When a sponsoring company is suspected of suppressing adverse results that can damage its reputation, the reputations of all involved can be damaged. Commercial institutions may have an incentive to handle these issues, but they need to practice good research integrity.

The second study that I want to mention was published in the *New England Journal of Medicine*. I think it was January of 1998. It dealt with potential financial conflict of interest concerning the author's paper, which dealt with a type of drug. There was a study of approximately 70 articles on the safety of calcium channel antagonists that were used in the treatment of hypertension. Apparently, there was some controversy about this drug. The next study compared the financial support of the authors by calcium channel manufacturers with the outcome of the article. In other words, the outcome of the article would either be favorable toward the use of the calcium channel antagonist, or neutral, or critical. The findings showed a significant difference in whether or not there was support for the author by companies involved with this drug. That is to say, 96% of the authors whose studies supported use of the drug received financial support versus only 36% of the critical authors. This is not proof of causation. It is just an association, because it is also possible that the companies went after the authors that were already published in the area, or who had already demonstrated their interest in the area and generally were favorable to use of the compound. However, it raises issues of potential bias and maybe even an unconscious bias. In most cases the investigators would probably say that they were still being objective. The issues here are whether or not these associations raise a possibility of skewing the scientific method with the interpretation of results.

Dr. Crawford:

Let us open up to questions for the panel. If you have a question, step up to the microphone or ask it in a loud voice, please.

Question (Dr. John Grabowski, UT-Houston Medical School):

I have a whole series of questions. I think it is pretty clear that the ratio of compounds looked at to those that go anywhere is pretty trivial. Who knows what the real number is? It is clearly a costly process. Knowing that you have spent all that money up front, how does that influence the corporation? Related to the issue that was raised, Dr. Ko, how do you select investigators for clinical trials?

Dr. Ko:

Generally, we look at the literature and find people who have published in the area. We think about whether the clinical population can be delivered within the time frame that is necessary to move forward in an expeditious way. We pick several investigators that have good reputations. Some are affiliated with a university; some are not. But the point is that they are good clinical investigators. They take care of their patients and are not going to get themselves or the pharmaceutical company thrown into jail. These are the considerations that we think about. These are issues we should all think about with regard to our patient care, anyway. Occasionally you do make mistakes in choosing an investigator.

Follow-up Question (Dr. Grabowski):

We can say this knowing that Dr. Ko works for Schering-Plough now, but has worked for some other companies. What is your experience in terms of clinical trials where you pay a number of sites to do the work? And what you see at any given site? And what is the frequency rate of sloppiness, of improper implementation? The issue was raised with respect to the breast cancer trials where a fellow in Montreal was clearly unethical in his activities. It can include individuals who are not really doing what they claim to do for the company. There is a whole range of possible misconduct. Is it your impression during the years that you have been involved in implementing clinical trials that these things are common?

Dr. Ko:

A lot of what goes on is not fraud so much as it is just not very good attention to detail. Oftentimes we find the copious amounts of paperwork required for a FDA study are way beyond what the investigator writes down in his green notebook as he moves along from week to week. There are safeguards that the FDA has instituted to make sure that investigators and pharmaceutical companies are accountable for showing the data when the auditors come. In a general way you find people who need to be admonished as a result of an audit. We send people out on a regular basis to clinical sites to address issues such as

not having consent forms signed, or having paperwork that looks like it has not been filled out at the visit time. After doing pharmaceutical-industry sponsored trials, investigators get a whole new level of attention to data-keeping details.

Question (Tim Harrigan, University of Texas-Houston):

I come from the world of medical devices, which is actually a lot messier and more crassly commercial than pharmaceuticals. One of the issues we have dealt with is postmarket studies. In this type of study, you have local product champions who may be busy hip surgeons, and the surgeons write the follow-up papers. They are flown all over the country and all over the world to give talks. I think this is an area that needs exploration, because it is an area where lucre really creeps into the science.

The other issue that we deal with is that when you get a research contract you get ongoing contact with the company during the study. We are in the middle of one study that is a terrible headache for our department because the local manager for the company is not very competent. He insists on changes in the study and changes in the control group. He changes the timelines. When you get into those relationships with a company, there is not an awful lot of guidance. You can say "Go away," but then he will go away with most of your money. Or you can say "We will not do the study." It just seems like you are locked into something and then everything becomes fishy. Contracts do not always stay the way they are supposed to. Can you comment on any kind of experience with those two issues?

Dr. Phillips:

Things do evolve with time. That is why contracts should be severable with notice by each side. Then you can start again if you have to. In any case you should avoid a contract in perpetuity when you know that things change fast. Every case is going to be different. If you think there is a possibility that you will have different ideas about things, have some termination clause so you can get out gracefully. That would be my way of attempting to deal with that. Whether that would work in every case is obviously suspect.

Dr. Ko:

You are pointing to an issue that probably is more pervasive in Phase 4 postmarketing research than it is in Phases 1, 2, and 3 prior to FDA approval of a device or a compound. It is partly the responsibility of the investigator who is the big name to pull away from those situations where he cannot stand behind it in good conscience. I do not deny that there are some companies out there that will take advantage of people's reputations to help their company's product that way.

Follow-up Question (Dr. Harrigan):

Does your marketing arm have specific policies about product champions?

Dr. Ko:

There are rules and companies get admonished by the regulatory agencies. There used to be a practice of setting up trips for doctors who would do a lot of scriptwriting for particular products. That practice has ceased within the last four or five years. The scrutiny of those kinds of relationships is not as tight as it probably needs to be, but it is getting tighter. Within the companies themselves, there are strict guidelines. Regulatory agencies and clinical physicians formulate policies that protect the company from liability during marketing, while still allowing for their products to be visible. We fall into trouble when we do not have a regulatory department that has been down that road before and does not bring up issues that might expose the company to adverse headlines or jail.

Question (Dr. Sandra Hanneman, UT-Houston School of Nursing):

I am a clinical nurse researcher. One time, when I was much younger, I did some device research because I thought it was important to patient care. The manufacturer did not offer to support the research, nor would I have accepted any support had it been offered. My first question is: because I am a woman and was a junior colleague, does that mean that is why they offered no financial remuneration, or is it that nurses and women and junior colleagues are more ethical than senior colleagues? Joking aside, the question I would like to pose to the panel is: Might there not be other methods for promoting industry-research relationships without introducing the potential bias that has been discussed this afternoon? Are there no mechanisms to pool industry money where there are ways of getting the work done without there being a direct relationship between the investigator and industry? I would appreciate your comments.

Dr. Phillips:

In my experience, which is fairly limited, I have seen a range of interests by corporations and university relations. Some companies really want something specific for their gift. Other companies are willing to give with fewer strings. One of the things we explore at Rice is giving a corporation a chance to make a gift to an endowment for graduate students or something that does not result in direct financial gain for the researcher. That is one way to reduce bias. Some companies are willing to do this. Other companies really want something more specific for their buck. There is a whole range of ideas about what is acceptable and what is not. I have colleagues who are perfectly happy owning stock in companies that they consult for and do NIH-related research for. I know other people who would not touch that situation with a 10-foot pole. It just very much comes down to personal integrity and your own belief in what is right. This is where institutional leadership can help to evolve some standards that would include fair treatment for junior women researchers if they are being discriminated against in this way.

Dr. Ko:

That is a good question. The patient signs a consent form that says it is their free will to take this experimental treatment. I guess what is not stated is: "And by the way, we are

going to make \$10,000 if you complete the study." I do not know if that needs to be said or not. Does it need to be said in a way that highlights the filthy lucre part of it? Does it need to be stated in a way that is different from an experimental treatment that comes out of health food remedies, or the notion that you can take the bark of a plant and put it into massive clinical trials? I am not sure. How far do you take it?

Question (Dr. John Grabowski, UT-Houston Medical School):

You could ask that question about NIH money, too. Should you say, "Well we have a grant for \$500,000 to do this project." In the end, NIH gives you less money than you need to do the work. Companies actually pay you what it really costs to do the work. So it is not as though you are getting the money to put into your pocket. Also the institutions are pretty careful about what they do with the money. I just can't imagine telling a subject that.

I have a question about publication, about the issues that you raised, Dr. Phillips, and not having any constraints put on it. When the company says: "Look, we want to test this drug at 12 sites around the country. We are going to collect the data and analyze it and give the data to the FDA." I have no expectation at all that I should be permitted to look at those data.

[Text lost due to tape change]

Dr. Phillips: (in response to audience question)

If you have students involved in the research, you cannot tell them this cannot be in your thesis. The freedom to publish and the involvement of students requires that their scholarly interests be protected. It does not mean that the university cannot enter into research contracts where you deliver certain things for money or whatever. That to me is more like what clinical trial arrangements should be. You always want to have in mind if it is consistent with the mission of the institution. If you are supposed to be promoting scholarly work, then you want the eventual results of that clinical trial to be published. If you are a research institution that makes money delivering clinical trials for a company, then at the end of the day you deliver so many patients and you know you are done with that site from the medical ethics component.

Question: [inaudible]

Dr. Ko:

We would check that out very carefully. We would get several people to do it before we moved on to the next phase. We are working to do what we can, the best and most efficient way that we can, and to do what is right by the patient, too. It would not do any good for the company to try to exploit that. There are situations where I can see that coming up. For instance, if you were in the venture capital game trying to churn up interest, you might want to get an early read just to get people interested in investing in your company's stock. There are a lot of ethical issues about that--not just the biomedical pieces, but the issue of what goes on in the stock market. No reputable company that wants to be around a long time has any interest in that kind of behavior.

Question: [inaudible]

Dr. Phillips:

It depends on the outcome of that research. For example, it is obvious that no company would want some dangerous product to be recommended or approved. Where the case might arise would be in areas that are sort of gray, where the product would not do any harm but might not be particularly beneficial. The temptation would be greater in that area than it would be in other areas.

Question (Ruth Clanton, Division of Ophthalmology, Stephen F. Austin State University):

I just want to follow up with what Dr. Phillips was saying. We have a master's level program that we are looking to partner with. We ran into a lot of resistance with a company's views on setting up a contract where we can publish. Is it just a matter of setting up standards?

Dr. Phillips:

It is usually a matter of setting up the research agreement, or whatever kind of agreement you have with the company. There was a case in our department where a student was asked not to talk about part of his research at his Ph.D. defense because that would constitute divulgence of information for which patent protection had not yet been established. That is bad style for a university. What we have done is try to set a time limit for a company to review the material. Then it goes to a publisher. This gives the company time to file for whatever patent protection they might want to seek and get the ball rolling before there is any divulging of information. There are times when a student is not supposed to talk about something until that process has taken place.

Question: [inaudible]

Dr. Phillips:

It takes longer than that to get a patent. I am sure Dr. Ko can talk more about that. The academics want it as short as possible, and industry wants it long as possible, so it is whatever the two parties can agree upon.

Dr. Ko:

The issue seems to be secrecy versus free knowledge to advance the state of humankind for the university. An earlier question asked whether industries could get together to set up a pool of grant funds? Why should they? What is in it for them? They will do it individually. They will spread grants around to support various fellows. They will make individual contracts with people that are specifically targeted for a particular project. To be sure, there is tension between the urge to put knowledge out for public

consumption and to further people's academic careers versus the secrecy that an industry believes it needs to safeguard a particular proprietary piece of information.

Dr. Sandra Hanneman:

I would like you to join me in thanking our panel for a stimulating discussion. Thank you all very much. We have a final conference wrap-up that is going to be delivered by none other than our distinguished microphone stimulator, Dr. John Grabowski. John is Professor and Director of the Center on Substance Abuse in the Department of Psychiatry and Behavioral Sciences at the University of Texas-Houston Medical School.

**John Grabowski, Ph.D.
Professor and Director of Substance Abuse Research Center
Psychiatry & Behavioral Sciences
University of Texas-Houston Medical School**

First, there is a comment I want to make. I was asked to summarize this conference, and to pretend to summarize the content of the last two days would be unethical. It would be self-deception even to attempt it. When we think back about everything that has been said over the past few days, I would like to synthesize and raise some concerns. You heard me raise questions about some of them over the last two days. When we discussed John Glenn going into space and his influence on the system of science, it occurred to me that I had forgotten something. When I was at the NIH, National Institute of Drug Abuse in the early 1980s, there were a series of studies done at the behest of Senator Inouye from Hawaii. He demanded that studies be done on airline cabin air quality. A whole series of studies were done, and the Institute of Medicine collated the data. As a result of this study, you don't have smoking in airplanes anymore. The reason he initiated the study was that he got tired of having to put up with people blowing smoke in his face when flying between Washington, D.C. and Hawaii. I think it had to do with getting older as well. It is an anecdotal instance of people in high places having a profound effect on the direction of science, if you will.

I will, as Dr. Reiser did, confuse the terms of fraud and misconduct. ORI uses the word misconduct with a purpose, as I understand it. Fraud has the legal requirement of proving intent. They avoided this by coming up with rules and regulations that ironically exclude honest errors in this definition of misconduct. It seems to me that leaves only dishonest areas, and those do have intent. That gets pretty close to fraud. It is an interesting linguistic problem, and I will use both words.

Each of us is first and foremost a member of the public. The conference format necessitates the way we divided it up during the last few days. I would like you to believe that these are labels for very similar human systems. There is not a lot of difference between government, which is commonly abused, and industry, which is commonly abused, and academia, which also takes its hits. The systems are very similar. They fault each other occasionally. I think when we hear the attacks on government, for example, the FDA and NIH, that the attacks are categorical attacks on attorneys and the media.

There is essentially no fundamental difference between the people in academia, industry, and government with respect to the conduct of science. Dr. Ko works for

industry, Dr. Groesch works for the government. There are FDA staffers who take a lot of heat and justifiably so. Basically, each sustains the ethical conduct in a complementary fashion. It is true that occasionally each group's goals and rules annoy the other group, and that one group's rules are viewed as impediments by the others. But the systems are more similar than dissimilar. Do people try to circumvent the guidelines for devious reasons? I do not think so. The essence of the endeavor depends on the individuals who are involved in these processes. One universally big annoyance is the terse statement that we all have heard- it is company policy, or it is university policy, or it is government policy. That is garbage. Somebody, somewhere managed to do these restricted things, and you can always get down to the source of the restriction.

Research depends on ethical conduct and training and the goals of all involved. The conference focused on ethics from philosophical and cultural viewpoints with some pragmatics intermixed. There was some discussion of who should be the first author and the last author, and the like. But the discussion has been on these factors as modulators of scientists' behavior. We can categorize the lapses by individual, as did Dr. Macfarlane. I think the assumption that ethics is simply a question of training is an unwarranted assumption. Ethical conduct is heavily dependent on satisfactory training in science and is a consequence of skill and good practice. Risk is reduced, benefit enhanced, and fruitless activity diminished with good methods. Good scientific method is not common sense, which is, I think, the most common form of human ignorance. I think many errors that might be labeled as unethical or misconduct derive from poor training, and not from deception.

It is my belief, and the point was alluded to by Dr. Bulger, that conducting a study that is not of the best practical design is as unethical as manufactured data. It is not an issue of formal training in ethics. Lack of training is intentionally remedied in students. They are in school to learn, and they are learning how to do research. There are more problematic issues in terms of poor training. A scientist embarking on unfamiliar areas may be well trained in his or her own right, but may not be an expert in the area required for the next step. Only the arrogant scientist does not ask for assistance in that regard.

Dr. Reiser commented on the recombinant DNA scientists at Harvard who acknowledged they had little knowledge about the spread of disease. We would all, I think, acknowledge that the Mayor of Cambridge was a little odd to stop the research there. The fact is that the scientists did not look at some of the possible implications of some of their research. At times, scientists will need extra training and should seek it out, or seek out the expertise.

There are some very specific cases that I think are more likely to generate problems. For example, when clinicians in private practice become contract researchers. This is an issue that industry has to struggle with. In the past in my own field, uninformed clinicians and academics in science have created much havoc. I was pleased that Dr. Macfarlane made her point very clear about this issue. My understanding of it comes from the same source as hers. People who really do not know how to do research are recruited to do it and this poses a dilemma. It can take years to overcome the results of botched trials. Tom Costin of Yale, after he heard of a particularly odious unblinded clinical trial, said use it quickly before someone does a double-blind study and discovers it does not work. It is a very serious problem.

Oftentimes we think about imposing ethical premises but much of the ethics, or at least the misconduct, stems from the lack of appropriate scientific training. I was interested in the comments by the representatives of the biotech and pharmaceutical companies, mentioning opportunities by which scientists can make substantial amounts of money. How does this influence science? Is it different from other areas? We seem to think it is. Yet two days ago, a professor at Carlton College in Minnesota received the Templeton Award, \$1.1 million, for his work in religion. Even I, not a particular devotee of religion, could do a lot of work for that kind of prize. Was he, more or less susceptible to temptation of striving for an award than any other Nobel prize contender who gets rewarded for scientific activity? I do not know.

We talked yesterday about the issue of protecting subjects. Participation in research takes many forms and each provides opportunities for deception and fraud by subjects. We have not focused on the ethical burden of subjects, or whether they even understand their ethical burden. This issue should be an ongoing one for IRBs, and probably for ORI. In our concern for subjects, we cannot overlook how they affect any given study, which in turn, affects society. Subjects have goals and motivations that conflict directly with ongoing science. Dr. Vanderpool noted this but in a rather different way. Part of the social contract is that subjects agree to participate because the study may help others. If they behave deceptively, it puts others at risk. Before we castigate them, though, I would say we cannot disassociate ourselves from the subjects. Individuals among us could be in the study or could have relatives who are involved and who, through self-deception or intentional act, could adversely affect the scientific endeavor. It is not always possible to have good controls. Let me give you an example. A friend of mine came to the Texas Medical Center to be treated for a lethal disease. When he met with the investigator, he told the investigator he would not participate if he were not in the particular group receiving a particular kind of treatment. This was a study where you could not do a very good control because there were three separate arms to it. The investigator said he would check as to which group he would be in. There was one chance in three he would be in the experimental group of interest to him. The investigator walked out of the room, came back and said: "it just happens that the next number up happens to be for that group." There is a 33% chance of that. My friend was delighted that he was going to get the treatment. I wondered how that decision was made.

There are inherent differences in the probability of successful fraud. We can look at some of the systems and rule out fraud in some of them. Large clinical trials have little room for fraud and misconduct as was attested to in part by Dr. Ko. There are many people involved and many controls in that system. Yet we know of fraud in the breast cancer trial. An investigator in Montreal did not adhere to the inclusion/exclusion criteria and the assignment criteria. Fortunately, in large clinical trials, there are many sites. The end result is that they can put the data together. If something is particularly odious, they can drop it and still see an effect. Clinical trials are not an area where fraud easily occurs.

Problematic in any area of science is self-deception as a result of ignorance or arrogance. It is a problem of method. In clinical studies it takes the form of nonrandomized, unblinded trials. To believe that one can develop a study, recruit subjects, do the gels or whatever, know the treatment, actively participate in application, and not be prone to bias is naïve and arrogant. There is far too much room for investigators to

confound, whether they are honest or dishonest. One can go through a series of laboratory environments and make some estimation. In each one of those environments you find mitigating factors that diminish the likelihood of fraud and misconduct.

Underlying all of this is the external fact that there is an inevitable replication. Someone, somewhere is going to base research on the alleged positive findings. More importantly, the more public the research, the more certain this is a reality. Two decades ago, in tissue transplant research, mice were treated with magic markers to make them look a little bit better. This action was fraud that was doomed to be revealed. There was no way that could escape notice.

In high-technology research involving several specialists, I think that the sort of collusion or the likelihood of fraud is relatively low because you are not going to find too many people willing to participate. In a very real sense, I think that science, given the way it is conducted, is an area in which crime does not pay. If discovery is the metric, people are discovered. In fact, it is worse than that. The system is difficult and demanding.

Even scientists with the highest integrity are caught up in doubts. Recently, and well summarized in the journal *Science*, the trials and tribulations of Judah Folkman were catalogued. They provide an exemplar of the issues that have been discussed. He and his collaborators conducted impeccable work with understaffing. You heard a little about this earlier today, but you did not hear it all. What Dr. Zwelling did not mention was that others could not replicate the work. There were approximations that were done. There were even extensions of the work that was done. But they could not actually replicate the work until they sent someone to the laboratory who did everything the way it was done in the laboratory environment. Then they were able to replicate it. I think the scientific community will work out the conditions under which this work can be done. Here you have a well-known, highly regarded, ethical scientist who was instantly questioned when replication was not immediately possible. I think what happens is that science is a more difficult endeavor than fraud because of the rigor with which people's results are examined.

Drs. Reiser, Bulger, and Vanderpool suggested that the current situation is the result of logical development. I think that is probably not true. Not all experiments are good experiments. In many things, including the progression of science to a breakthrough, we seem to reconstruct the story so that it sounds logical. That is a deception in and of itself. It is quite amazing how science progresses in odd ways sometimes. If we live long enough, we might be reminded that our rendition of ethical conduct is really a mirror of the moment. Even now, Dr. Vanderpool struggles with certain issues and revisits some basic premises.

Ethicists are in agreement on many issues but, like economists, are in substantial disagreement on others. This may derive from their own culture and personal boundaries. Some are quite open to new strategies. Some less so. There are those who might stop science altogether. We have progressed in codifying an ethical and humanistic stance in research, but it is far from immutable. As this conference has shown, we have impressed on scientists of today how important it is to act responsibly in their scientific endeavors. The efforts of ORI have led the world in that regard.

What I would like to do is move on to some issues that seriously concern me. Dr. Reiser says that we are in the fourth phase. Dr. Vanderpool states there is a need to revisit

issues. I think we have reached a plateau and should reflect on the requisite dose of ethics. We should not develop standards of ethical conduct to procedures and ignore them. The activity of ethicists should be subject to demonstrations of efficacy. How, in fact, do these courses in ethics work? Are they in fact efficacious? Do they have a desirable consequence? And does the cultural milieu change? It would not surprise me in the least if the public were much more enthusiastic about cloning and thought of it as being much less blasphemous when they understand the potential benefits. Can we be assured that there are ethicists who will resist the notion of cloning? Ethicists themselves have to look at some of these issues and investigate their own behaviors as well. The speakers alluded to these final points and their task is to apply them to their concepts and strategies, to the problems that affect science, but are often not of science.

We have to address training. I think that a particular area of training in science that is unfortunate and problematic is the “in my hands” approach. The phrase itself should probably be banished. “In my hands” seems to convey the need for questions, if not distrust. There has to be education about science--what to expect and what not to expect from it. There are interminable requests for breakthroughs or the appearance of breakthroughs. There are hindrances that are imposed by funding agencies, the media, and ultimately the public.

Secondly, and specifically in human research, there is a need to make clear what it means to be a subject. I have already mentioned this. I think that industry, NIH, and ORI can all play a role in making it clear. Perhaps industry could do it in some of those wonderful advertisements we have seen on TV about new medications. Perhaps by addressing the issue of science, how subjects are enrolled, and what their responsibilities are would make clearer what science is about.

Several speakers have referred to the public interest in science. Often the public interest, I think, reflects mythology and misunderstanding and an anti-science perspective that currently prevails. Society expects remedies for health, for electronics, for transportation modes that would solve their problems. It is an impatient society and the problem is represented in many venues. How do you train societal patients? An example of an impatient public and irresponsible corporate entities and pandering scientists is the domain of so-called behavioral, alternative medicine. If we clearly define our terms of medicine, a procedure or an approach can be either rigorously demonstrated to be superior to other interventions and placebo or not. Here is a brief history of medicine. Here, eat this root; that root is healing; say this prayer; that is superstitious. Here, drink this potion of snake oil; here swallow this pill. That pill is ineffective; here take this antibiotic. That antibiotic is artificial. Eat this root.

An issue underlying many of the presentations is the example of special interest groups. I raised the issue this morning and this concerns me tremendously. I still have some concern about this. There was an article in the *New York Times* a few weeks ago about a couple who had a child with an autosomal recessive metabolic disturbance. It clarified for me the lengths to which people will go in their disease lobbying. I think it is very problematic. These people threatened scientists. They threatened the IRB at Tufts. They were very wealthy people who collected \$40,000 a year from the government for their handicapped child. It presented a terrifying problem. Beyond this, one finds unseemly

infighting, special interest groups lobbying Congress and distorting the scientific process by having funds earmarked for their disease at the exclusion of others.

I served on an Institute of Medicine panel where the focus was stigmatization of scientists and clinicians and sufferers of substance abuse disorders. The founders of an organization lobbying for a closely allied overlapping mental disorder, depression in that case, disavowed the notion of collaborating with drug abusers even though there is often dual diagnosis across these things. They did not want to be associated with it. We had a committee bring in the leader of a breast cancer group. She had been invited to address the issue of activism. She described how she had explicitly disavowed any interest in considering the importance of other cancers because it would weaken their message.

On the brighter side, there is an organization called Research America that focuses broadly on the importance of science and does not lobby for any particular special interest or special disease. In this group, there are administrators who are responsive and resistant to some of these pressures. Yet we find that some of these special disease interest groups now want to be on scientific merit review committees. They think they know more about the science than the scientists do. There are places where their ethical comments are certainly welcomed, but I think that bringing them into the scientific process is not an adequate metric for determining the adequacy of science.

A final example is the animal rights groups. While Dr. Reiser seemed to approve of them, I am somewhat less supportive of the concept. I have some really serious concerns about the ways in which scientists themselves lobby in their own self-interest. Yet this morning I was told it was all right. We should really do that. We do have to look at how these forces distort science because they are much more active today than they were some years ago.

In conclusion, I offer the following points: codification of ethical constructs has been beneficial even if Dr. Vanderpool had some doubts about it. I think cross-cultural differences and cultural changes over time require periodic revisiting of these issues. There will always be room for ethicists. Rigorous scientific inquiry and training of science practitioners will minimize misconduct as much as, but not to the exclusion of, the need for ethical training. These are interactive things. The interactive character of academia and industry, foundations, and government systems further minimize the likelihood of misconduct. I fear public distortion of that process. I think it requires attention. I wonder whether there will always be jobs for scientists. The threats become too profound after a while and might drive people from the field.

Dr. Sandra K. Hanneman:

I would like to extend my sincerest thanks to the University of Texas-Houston, the University of Houston, the University of Texas M. D. Anderson Cancer Center, Prairie View A & M University, Texas Southern University, and Texas Woman's University-Houston Center, as well as the Office of Research Integrity. All of these institutions contributed financial resources to enable this conference to take place, and we are indebted to them. I hope you return to your particular roles and institutions with some new ideas, and those who work here can count on some new policies coming out. Thanks very much for your fine participation.