"Training in the Responsible Conduct of Research"
Conference Summary

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Introduction:

Seven prominent researchers and Federal officials working and writing on issues related to scientific integrity spoke at the "Training in the Responsible Conduct of Research" conference. Dr. Baruch Brody spoke about how conflict of interest in research came to the public's attention with the advent of biotechnology firms and products in the 1980's, about various responses to this conflict, and about the results of his own recent research in this area. Dr. Drummond Rennie spoke about the need to keep responsibility closely associated with credit in authorship. Dr. David Resnik spoke on the various aspects of data access and ownership. Chris Pascal and Dr. Alan Price addressed issues related to new Federal guidelines for scientific misconduct. Dr. Tony El-Hage talked about how the Food and Drug Administration (FDA) handles cases of fraud. Dr. Jeremy Sugarman emphasized the importance of respecting the people who choose to participate in research by ensuring that the research is scrutinized in every case, and that its regulation is a public activity.

Baruch Brody: Conflict of Interests in Research

Dr. Brody is the Director of the Center for Medical Ethics and Health Policy at Baylor College of Medicine and Rice University. He has written extensively on conflict of interest and the responsible conduct of research (RCR) more generally.

Dr. Brody began by taking a look at the historical origin of the awareness of financial conflict of interest in human subjects research. He discussed the thrombolytic trials of the 1980's involving tissue plasminogen activator (TPA), a new, relatively expensive drug. Many of the major investigators in these trials were substantial equity holders in Genentech, a young company at that time, and whose financial fortunes were closely related to the results of the thrombolytic trials.

Three different kinds of conflict of interest arose in these trials. The first concerned the actual design and conduct of the study. An example is the major pivotal trial that compared TPA with streptokinase, the only trial that showed that TPA was better than streptokinase. TPA was given in a bolus immediately, whereas streptokinase was given as a steady continuous infusion, which meant that TPA was bioavailable earlier. Many people think this raises a question as to whether the trial showed anything about the superiority of TPA.

A second kind of conflict of interest that arose in the trials concerned the possibility of clinical trial centers losing participation in a trial for insufficient enrollment of subjects and the possible loss of grant income. The third kind of conflict of interest was exemplified by a continuing medical education program run by Genentech in which one of the speakers, a prominent figure in the field of cardiology, spoke impressively about the value of TPA and downplayed the cheaper drug streptokinase. That individual received a substantial amount of consulting income from Genentech.

The bottom line is that there is a tremendous potential for conflicts of interest to arise in

various ways: in the design and conduct of trials, in the enrollment of subjects, and in the interpretation and publicity that results.

One approach that can be taken to avoid these problems is to prohibit investigators from having any financial interest in the companies involved in clinical trials. This was the response taken immediately - in the late 1980's by a few groups, and the approach taken in some major clinical trials. A second approach was mandatory public disclosure, which is the policy currently used by the *New England Journal of Medicine* and some other journals. In this approach, the investigators can have equity interests and other financial conflicts, but must make a public disclosure, i.e., notify everyone concerned. This allows people to be on guard.

NIH took a different approach. In 1994-1995, a policy came into effect whereby internal disclosure was all that was required. Information had to be provided by clinical investigators only to their own institutions. With this type of policy, the institution is given great discretion, and the process is entirely internal. While this policy was being adopted, an important article was published in which the views of people involved in a controversy over the effectiveness and possible lethal effects of calcium channel blockers seemed to correlate with their financial support from companies that produced these drugs. There was an appearance of bias.

Recent studies have cast considerable doubt about the effectiveness of reliance on purely internal management. Dr. Brody recently published a study in the *New England Journal of Medicine* in which he looked at institutional policies, journal policies, and agency policies. He surveyed 297 institutions that received more than $5 million a year in grants from the National Institutes of Health (NIH) and the National Science Foundation (NSF). He also queried 50 leading journals, and every Federal agency that is a signatory to the common rule about human subjects research, as well as the FDA. Fifteen institutions reported that they have no policy at all, and yet as a condition of getting the grants they had certified to NIH and NSF that they have many policies, including a policy on conflict of interest. Among the other institutions, most had no rules for how disclosure should be managed. In other words, what the institution should do if informed of conflicts of interests.

Furthermore, of the 50 journals, only 20 even had a policy about disclosing a conflict of interest. Consequently, if the institution would like to mandate disclosure in a journal, this can be difficult. Fortunately, this is now in the process of changing. The Department of Agriculture and the FDA have policies, and require information be submitted along with the data in applications for approval of a new drug or device. The Department of Health and Human Services (HHS) and NSF do not require that they be told what institutions have done about any conflicts of interest. Dr. Brody found that most other Federal agencies don't have any conflict of interest policies.

When asked who was told about the conflict, invariably "someone at the institution" was told, but only 3/235 times was it the official policy that the Institutional Review Board (IRB) be told, only 3/235 times that the research subjects be told, and only 3/235 times was a journal told. Consequently, there are real concerns about the effectiveness of reliance on internal management.

The new version of the Declaration of Helsinki, which has been criticized for being deficient in other areas, may be on the right track regarding new proposals for conflict of interest. It requires that the research subjects be told, something that is unprecedented. The American Medical Association (AMA) has come out in support of this approach.

Other institutions have moved in yet another direction. The response taken by some groups in the late 1980's—prohibiting people from having conflicts of interest—is being reconsidered under some circumstances. At Baylor College of Medicine, conflict of interest is not allowed for certain types of research, i.e., validation research (phase 3 pivotal trials). What is of concern in these situations is equity interest and property rights.

In conclusion, in drafting a conflict of interest policy, Dr. Brody explained that what ought to be considered is not just equity interest and intellectual property rights, but also other income from the sponsor such as consulting fees, private support of the research, and fees for enrolling subjects. Conflicts of interest of family members, and conflicts of interest in trust funds should also be disclosed. Disclosure should be made not just to officials, the IRB, funding agencies, journals, and subjects, but also at every presentation of data and results, and in every publication. We need to see institutions confronting the question of their own institutional conflicts of interest. Further, because research teams have a stake in enrolling subjects and continuing the research trials, we need to look more carefully at the impact of conflict of interest on the informed consent and enrollment processes, and also on the ongoing monitoring and decision making which determines whether trials should be allowed to continue.

Drummond Rennie: Authorship

Dr. Drummond Rennie began by noting that authorship is where "every sort of rubber hits the road." Authorship is the means by which new work is communicated between scientists and scholars. It gives credit, establishes priority, and is of critical importance to every scientist. Crucial to authorship is trust and mutual responsibility between co-authors, and that people are willing to take responsibility for work published. This is particularly important as more and more research is being done collaboratively.

It is of critical importance to link credit with responsibility. But in many situations this is not done. Dr. Rennie cited one extreme case where well-known individuals are offered authorships by corporations for research they did not do and for papers they did not write and receive monetary compensation for doing so. This means a total dissociation of responsibility.

How then, can we associate the two? A simple way, Dr. Rennie says, would be for the authors to explain in their own words the particular contributions of each and every individual in the byline. This proposal is in the tradition of openness and allows us to see precisely what each person contributed, shedding additional light on the nature of work being listed in a researcher's Curriculum Vitae.

Dr. Rennie noted that this is not a new idea and detailed the efforts he and others have made to demonstrate that there is a problem with authorship and convince journals to adopt this practice. Initially the Lancet, the British Medical Journal and The Annals of Internal Medicine

required authors to specify their specific contribution. Now many journals make such requirements. The International Committee of Medical Journal Editors (ICMJE) and the Council of Science Editors support the practice as well.

The assignment of credit by explaining what each person actually contributed to the paper is just one among many the things editors ask for - none of which can be completely checked. Saying what each person did reminds people of their responsibilities in the same way that signing a conflict of interest form reminds them of conflicts. They have to ask themselves whether they truly take responsibility.

This process, Dr. Rennie suggested, turns out to have been quite successful in helping to solve a major problem with authorship. We can expect to benefit, he says, from explaining exactly who did exactly what in credit attribution. It is a process, he says, that makes us become a great deal more open.

During the question period, Dr. Price asked Dr. Rennie whether technicians could be listed as co-authors in a paper, in light of the ICMJE statement. Dr. Rennie responded that in his view it is right to include technicians as coauthors who do a lot of the work. It makes a lot of sense to say exactly what they did. Dr. Rennie noted that he thinks we need someone who is a guarantor for the whole—someone who could say: yes, the work was done. Dr. Rennie mentioned Dr. Francis Collins, head of the Human Genome project in this regard. When a coauthor was caught faking the data, Dr. Collins immediately went public with it and took responsibility.

David Resnik: Data Access and Ownership

Dr. Resnik, who is from the Brody School of Medicine, East Carolina University, began by explaining that data are recorded information researchers use to prove, disprove, suggest, or derive hypotheses. Data include handwritten note pages, laboratory notebooks, diskettes, instrument outputs, photos, audiotapes, videotapes, graphs, and charts. Further, it is of two kinds: primary and secondary. The secondary data have undergone more processing than the primary. He went on to make suggestions regarding the way that data should be kept, including that data should be well organized, no data should be erased, and that laboratory notebooks should be signed.

He also discussed several reasons that good practices in data recording should be maintained. One reason is being able to check for possible scientific misconduct. Data may also be used in marketing a product, or for making intellectual property claims.

Another topic discussed was openness in data sharing. A part of the modern scientific ethic is openness, and so the question arises as to who should have access to data prior to its publication. Collaborators on the same project ordinarily have access. The IRB or other data monitoring board may also have access, as well as the sponsor, the FDA, and the Office for Human Research Protections (OHRP). Access to the data may be required after publication as well.

Dr. Resnik mentioned that there is some controversy about whether the public at large can get access to unpublished data. Under the Federal Freedom of Information Act, the public can have access to data that have been funded by a Federal grant after the data are published. In the case of a company, on the other hand, there may be no obligation to freely share information.

Dr. Resnick said there are many reasons not to share data. They include protecting results before publication to insure credit when the work is published. He noted that Darwin waited 20 years to publish, then published when he heard Wallace had the same ideas. It took 50 years for the Dead Sea Scrolls to be published. Reasons not to share data also include protecting confidential information related to peer review and protecting patient-subject confidentiality. Reasons not to share data, and sometimes not to publish as well, include that the data would reveal business secrets, military secrets, or that there is a wish to shield the research from public criticism, or that there is a need to protect potential or actual intellectual property claims.

Private companies have an especially strong interest in the protection of intellectual property. Pharmaceutical companies sponsor $26.4 billion dollars in research and development (R&D) annually, and biotechnology companies sponsor $11 billion. Total private R&D is $100 billion. On the other hand, the entire NIH budget is only $15 billion. Companies need a return on these interests, so they need to be able to protect their intellectual properties.

Dr. Resnik also discussed the question of why we should have property rights for intangible property. He suggested that the main reason, as stated in the Constitution, is to encourage the progress of science, technology and the arts. Property rights reward investors and artists and provide incentives for private investment and entrepreneurs.

Universities became interested in intellectual property and patents with the Bayh-Dole Act, which allows technology funded by the government to be transferred to the private sector and to be patented by the company. This was so the many technologies developed by the public sector, but not completed by them, would be completed and brought to market by the private sector.

Most universities own all patents generated by faculty, though they usually pay faculty a percentage of the income from these patents. In contrast, the faculty themselves ordinarily own copyrights. In the case of companies, however, since the work comes under the category of "work for hire," the company owns the copyrights as well. There is some question as to whether university faculty work is sometimes, also, work for hire. The question becomes increasingly important as Internet distance education becomes prevalent.

Chris Pascal and Alan Price: Defining Misconduct

Chris Pascal

Chris Pascal explained that the new federal-wide regulation had been in development for a number of years. The Office of Research Integrity (ORI) had a statutory advisory group called the Commission on Research Integrity in the early to mid 1990's. In 1995 the Commission made several recommendations, including creating a common federal definition of research misconduct. In 1996, under the auspices of the Office of Science and Technology Policy (OSTP), there was a subcommittee put together to work on a definition and policy.

In December 2000, OSTP issued new guidelines. Under these guidelines, the Federal agencies, including not just NSF and the Public Health Service (PHS), but also the Department of Energy, the Department of Veteran's Affairs, the Department of Agriculture, National Aeronautics and Space Administration (NASA), the Environmental Protection Agency and the Department of Defense will be monitoring allegations of research misconduct and imposing expectations on research institutions to respond to those allegations.

The guidelines are not self-implementing; the research agencies must implement them through their own processes. OSTP has a group that meets every few months with Federal research agency representatives to discuss how the policy is being implemented. The agencies had been asked to implement the guidelines by December 2001; but no agency had done so by the time of this conference. It is expected to take at least through the year of 2002 for implementation. The regulations of NSF and the Public Health Service (PHS) will have to be amended. Until the new policy is implemented by each of these agencies, of course, the older standards remain in effect.

The policies provide general guidance only. In order to meet these guidelines, ORI and NSF are in the process of amending their regulations. OSTP is attempting to get uniform implementation, but there is no single format required. Mr. Pascal emphasized that the institutions should be interested in monitoring the process, so there will be fewer differences among agencies. If implementation is not uniform, then it will be harder for institutional officials to do their job with all these various agencies.

In the new Federal government regulations for scientific misconduct, misconduct is limited to fabrication, falsification, and plagiarism in proposing, performing, or reviewing research, or in reporting research results. This definition is different from former definitions in that it deletes the "other serious deviations" clause. Another change is that in the older definitions, scientific misconduct including plagiarism during the peer review process was only implied. In the new guidelines, plagiarism in the peer review process is explicitly covered. Mr. Pascal explained that in his view, the regulations will also cover the review of manuscripts in the publication process for federally-funded research.

Another part of the older definition is that scientific misconduct requires a significant deviation from standard practices. This is also part of the new definition. For instance, omission of data may be falsification, but sometimes it is a commonly accepted practice. So you have to show, first that it is falsification, fabrication, or plagiarism, and second that it is a significant

departure from standard practice.

The legal standard for determining whether misconduct has occurred has been that it is an intentional, or knowing act. This is the standard PHS has been following. In the new guidelines "reckless acts" have also been added. Slightly less deviation from acceptable practice is required for a reckless act than an intentional one. The legal standard has also been preponderance of evidence, and this is true for the new standard as well.

While the regulations have changed in these ways, the responsibility of the institutions has basically remained the same. That is, the institution must provide policies to ORI upon request, it must inform administrative and scientific staff of its policies, and it must take action when misconduct is suspected or alleged. It must inform, and cooperate, with ORI. If it receives an allegation, it must assess the allegation and decide whether to go forward with an inquiry. The federal agency retains responsibility for oversight review.

If you receive an allegation and your investigation committee recommends misconduct, somebody at the institution, often a senior official, makes the decision of whether or not it is misconduct before taking it to the Federal agency. Many institutions also have an appeals process. That process will remain the same. The ORI will continue to refer most allegations directly to the institutions. The institution also still has the authority to have a broader definition of research misconduct than the PHS or the other Federal agencies, e.g., by including violation of research regulations. Institutions will continue to be responsible for all the other aspects of research integrity, including educational programs, and questionable research practices such as conflict of interest and authorship disputes.

In closing, Mr. Pascal noted that the misconduct investigation process is hard on everyone; nearly everyone finds the misconduct investigation difficult, including the respondent, the witnesses asked to testify, the members of the lab where the accused is located, the research integrity officer and support staff, and the whistle-blower. In nearly every case, however, at the end of the process, most whistle-blowers have not doubted that it was the right thing to do, and would do it again.

Alan Price

Dr. Alan Price, Associate Director for Investigative Oversight at ORI, talked about some cases that are not considered scientific misconduct by ORI. These include authorship or credit disputes. Misconception about ownership of data is one of the most common sources of allegations of misconduct that institutions and ORI hear about. Researchers ask should I be an author? A coauthor? Should I be a co-PI in an application? Should I get credit for the work I have done? Plagiarism is considered by ORI to involve only those cases where the people involved have not worked together or shared information. It can be either plagiarism of words, or of ideas. About 20 percent of ORI's allegations involve plagiarism. In contrast, NSF has 60-80 percent of its cases involve plagiarism and intellectual property disputes. Many of these so-called plagiarism allegations involve intellectual property disputes between collaborators or former collaborators. Basically the ownership rights are seldom clear. So ORI doesn't get involved in those cases, but leaves them to institutions to resolve.

Dr. Price went on to discuss specific cases to illustrate these questionable research practices that are not actually cases of scientific misconduct. One example involved a graduate student who had been working in the lab on a drug that has been used in a human population to try to prevent a certain disease, and she had samples of blood and tissue that she had analyzed while working on her master's degree. But she had been having a terrible time with her mentor. After four months of aggressive arguments, the mentor terminated her as research assistant on his grant, promising to publish her work, and give her access to all the data and reagents and materials. He said she had done enough for a master's, and that he would help her to finish her thesis. She was not happy and left the laboratory and took all the reagents, the tissue samples, the blood samples, the data, and went home and kept them there. The investigator demanded that they be returned to him. He had a Federal grant, so he had to report on the progress of his research.

This was not a case of scientific misconduct. It was a case of theft, and a reasonable response would be to call the police. Unfortunately, the institution involved permitted the student to keep these materials for over a year, and at her demand, even assigned her a new committee to complete her thesis and publish her paper without demanding the materials back. She got a new committee, wrote up her paper, submitted it with the help of the institution, and did not cite the professor's grant, and did not show him the work.

In response, the professor accused her of scientific misconduct on the grounds that she had plagiarized his work by stealing his materials. The university treated this as a scientific misconduct case, and did a full investigation. They found her guilty of plagiarism and unauthorized retention of materials, even though the university officers had let her keep those materials for a year.

The case came to ORI, which settled it appropriately. ORI required the graduate student to return the materials and comply with research guidelines. This was a case where a dispute over who is going to control the data and publish it led to an enormous case, reported by Science magazine, but which was not, Dr. Price said, a case that really should been handled as a scientific misconduct case.

In the question and answer period, a participant noted that in the kind of alternative dispute resolution that should have taken place (in the example Dr. Price discussed), there is a conscious effort made to resolve the case without using the formal allegation and investigation process. Dr. Price said that while alternative dispute resolution can deal with some cases of questionable research practices, he cautioned that in the cases of true scientific misconduct, institutions are obligated to inform ORI and to go through the formal allegation and investigation procedures.

Tony El-Hage: Fraud in Bioresearch and the Consequences of Fraud

Dr. Tony El-Hage works in a Division of Scientific Investigation at the FDA, where he has been the branch chief for good clinical practice for more than 20 years. He has administrative and supervisory responsibilities for bioresearch monitoring activities including monitoring clinical investigators, sponsors, contract research organizations, and IRBs. FDA inspects clinical trials that have a pending application for marketing approval. In routine surveillance, Dr. El-Hage said, the FDA finds the submissions for approval to be fraudulent 3 percent of the time, and in their program for whistleblowers, 25-26 percent of the time.

Dr. El-Hage emphasized that when fraud is found, one person has the sole responsibility. This is the clinical investigator. The investigator and not any of the staff working at the site is legally responsible for all results. He or she is, furthermore, expected to have direct involvement in the clinical trial, and must either work at the site, or visit it routinely. This usually excludes a principal investigator from working in one state, and the research being done in another.

In detecting fraud, there are certain signs that indicate there might be a problem at a given site. Such signs include reported ranges of values for laboratory work that are too narrow and have no outliers, that every subject always took the medication as outlined in the protocol, or that every subject benefitted from the medication. Other signs are that all the consent forms are in the same handwriting, or the investigator is recorded as having seen the patient on a certain date but in fact, patient interviews indicate he was not available at that time. Dr. El-Hage reported also that when FDA calls for a site investigation, the site sometimes expresses resistance, e.g., asking that another site be visited instead, or when the visit is made, the clinical office at the site looks perfectly clean and in order. These are signs that there may be a problem at the site.

One of the FDA requirements is, of course, accurate reporting. Other requirements include maintaining accurate and adequate records - including the original data forms - making records available for review, strictly adhering to the protocols, assuring blinding and randomization, avoiding bias generally, and getting written informed consent. Study records need to be kept for two years after the Investigative New Drug (IND) has been discontinued, and two years after New Drug Approval (NDA) has been given. The principal investigator, further, must be a physician.

One way that fraud occurs is in the recycling of subjects, e.g., sometimes an electrocardiogram (EKG) is taken which is a long strip. It is cut and pasted, and multiple subjects are made up out of the one. Cases pending in this vein include an investigator who created 9/10 subjects, another who altered 4/25 EKGs, and another who submitted 4/17 identical ones. When fraud has occurred, data are sometimes lost, and excuses are made, e.g., a flood, a hurricane or a boating accident. Loss of records should be reported at the time they occur. The investigator often blames others, and sometimes silences the staff. However, if others are in some way the cause of violations, the problem is, at root, lack of supervision, and this is ultimately the investigator's fault.

If fraud is suspected, an investigation will be initiated, a monitoring visit will be made, and all documents required by FDA regulations will be examined, including case report forms, appointment books, correspondence files, EKG's and x-rays. An unannounced monitoring visit can be made to a sponsor and a monitoring report requested. There are 20 people at FDA who review the reports, 10 are MDs and 10 are consumer safety officers.

After an FDA investigation, a post-inspection letter will be sent, of which there are three kinds: no deviation from regulations, minor deviations, and major deviations. Only in the latter case is a regulatory action taken. If the violation is serious enough, but may not warrant a disqualification, a warning letter will be posted on the web explaining that if the violation occurs again, the investigator will be disqualified. If the violation is serious enough, the disqualification process will begin. There is also a restricted qualification, e.g., for a period of 3-5 years, and clinical trials not to exceed 20 patients each until reinstatement.

"Disqualification" means no longer being permitted to receive investigational grants, and doing no clinical trials, although medicine can still be practiced. If the letter sent to the investigator is a disqualification letter, it will contain a detailed explanation of what the FDA has observed. The FDA will ask that a Consent Agreement be signed. The investigator will be given the opportunity to explain, although, since the FDA proceeds to this step only when it has seen what it takes to be incontrovertible evidence for violations, explanation is difficult.

An investigator can choose to fight the disqualification. In this case, if the physician does not give an adequate explanation, nor sign the Consent Form, the physician and his or her lawyer meet with the FDA and their lawyer. After both sides have presented their cases at the hearing, the presiding officer will make a decision whether to accept or reject the disqualification. That will take years. It is a long haul during which the physician will not do studies. Once disqualified, there are guidelines for reinstatement.

In 1998, there were 5 disqualifications, in 1999 there were 3, and in 2000 there were 3.

Jeremy Sugarman: Human Subject Protection and Ethics

Dr. Jeremy Sugarman is a professor of Medicine and Philosophy at Duke University and the founding director of the Center for the Study of Medical Ethics and Humanities at the Duke University School of Medicine.

Doing research with human participants, Dr. Sugarman said, is a public act. The U.S. Government has been important in the international community in formulating guidelines for human subject research. As a direct response to Nuremberg, the U.S. instituted many guidelines such as obtaining voluntary consent, anticipating scientific benefits, ensuring that benefits outweigh risks, performing animal experiments first, and avoiding suffering, intentional death and disability.

Nevertheless, in 1994, it was revealed that the U.S. Government had funded and conducted more than 4,000 human radiation experiments in health care institutions across the country, none of which had the consent of subjects. Although only one subject had been

physically harmed, the 4,000 subjects had been wronged. And there were other experiments in the U.S. that were similarly in the wrong, including hepatitis experiments. Institutionalized retarded children, were inoculated with hepatitis to study its development. The parents gave permission in exchange for admission of the child into the institution. This practice was not prohibited at the time, was not secret, and was prospectively reviewed by the funding agency, the March of Dimes. Other unacceptable experiments performed in the U.S. included injection of liver cancer cells into hospitalized elderly patients without their consent at the Jewish Chronic Disease Hospital.

Governmental protection of research subjects came about partly as a result of the scientific research that produced new effective drugs in the 1960's, including cancer chemotherapeutic agents and new antibiotics, when NIH funding increased dramatically. The head of NIH decided protective measures ought to be taken, the most significant of which were written consent, and having research checked by someone else before it was conducted by the scientists.

Then in 1972, the Tuskegee study was exposed in which, beginning in 1932, treatment had been knowingly withheld from subjects diagnosed with syphilis. As a result of this case, it was determined that a new regulatory framework was needed. Institutional Review Boards were needed, informed consent was needed, the selection of subjects needed to be monitored and special regulations were needed for children, pregnant women, and prisoners. The Commission that made these decisions also issued the Belmont report.

The first of the three principles of the Belmont report concerned respect for persons. This included the idea that individuals ought not to participate in experiments without their permission, as well as having a right to confidentiality. It also included the idea that consent requires competency, and so fully understanding the research risks is of major importance. The second principle of the Belmont report is beneficence, or the obligation to improve health. One of the implications of this is that it is not ethical to use placebos when the outcomes of lack of treatment are long lasting and serious, and there are known effective treatments, or when there is no sure monitoring for safety. People think that research is for their benefit, but this is a misconception and we have to compensate for that. Also important in weighing research risks is that sometimes it is not right to assign subjects randomly to two procedures even when the benefits of both are unknown. It is not right when the projected risks are of different kinds and there are personal preferences regarding the kinds of risks.

The third and final principle of the Belmont report is justice, and it has a bearing on the selection of research subjects, e.g., the least well off should not be the sole research subjects. Justice also has a bearing on the question of when access is important, and when protection should win out. For example, in the case of AIDS medication, activists rallied for its availability, even when not fully tested. In a slightly different vein, only 20 percent of drugs used in children have been tested in children; and women use between 4-6 prescription drugs during pregnancy, but most of these have not been tested in pregnancy. Our desire to protect children and fetuses has led to a blatant lack of knowledge of how medications affect them, and an argument can be made for access to these kinds of experiments. Finally, with regard to justice, minorities should not be excluded from research as they have been in the past, partly

because of their distrust of the research system and partly because of long-standing discriminatory problems.

Recently, we have been seeing critiques of the current system, including lapses in the informed consent process. This has led to the closure of major academic centers, and increased Federal oversight and reorganization. Recently, we have also seen the death of research participants, and we will see new requirements in the wake of these scandals.

The regulation of research has been a public activity. It is not just decided behind closed doors. Ethics is embedded in the process of research, and it is essential to respect those who choose to participate. It is essential that we all realize how important this activity is.