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DIRECTOR'S COUNCIL OF PUBLIC REPRESENTATIVES

April 6–7, 2000 Meeting Minutes

3rd Meeting of the Director's Council of Public Representatives
Thursday-Friday, April 6-7, 2000
8:30 a.m.
Building 31C, Conference Room 6
National Institutes of Health
Bethesda, Maryland

The Council of Public Representatives convened its third meeting at 8:30 a.m., Thursday, April 6, Building 31, Conference Room 6, National Institutes of Health, Bethesda, Maryland. The meeting was open to the public.

Dr. Ruth Kirschstein, Chair, Council of Public Representatives, and Acting Director, National Institutes of Health (NIH), presided.

COUNCIL MEMBERS PRESENT:

- Theodore Castele
- Robin Chin
- Luz Claudio
- Mary desVignes-Kendrick
- Melanie C. Dreher
- Pam Fernandes
- David Frohnmayer
- Vicki Kalabokes
- Barbara Lackritz
- Joan Lancaster
- Debra R. Lappin
- Lydia Lewis
- Roland McFarland
- Isaac Montoya
- Rosemary Quigley
- Maurice F. Rabb
- Bob Roehr
- Thomas Vaalburg
- Doug Yee

COUNCIL MEMBERS ABSENT:

- Michael D. Anderson

OTHERS PRESENT:

- Public Observers
- Members of Staff, NIH

Executive Summary

The Acting Director of the National Institutes of Health (NIH), Dr. Ruth Kirschstein, began the third meeting of the Director's Council of Public Representatives

(COPR) by describing recent activities of COPR members, including their participation in the Government Performance and Results Act (GPRA); the participation of five COPR members in the June NIH budget retreat; reviews of several Institute directors who have served at NIH for terms exceeding five years; and the participation of several members as part of an Advisory Committee to the Director working group that is reviewing gene transfer clinical studies. Dr. Kirschstein also presented an update of several key issues affecting NIH, including the development of draft guidelines for overseeing the use of human embryonic stem cells in research and a review of early budget negotiations before congressional appropriations committees.

Dr. Steven E. Hyman, Director of the National Institute of Mental Health (NIMH), described a growing awareness among administration officials and global leaders of the important impact of mental illness on public health and on the economy, particularly in developing countries. NIMH has developed a new series of effectiveness trials in which a variety of treatments may be tested in relevant settings. He said that concerns about recent increases in the use of Ritalin and other psychoactive drugs to treat preschool children have helped lead Surgeon General David Satcher to convene a conference that will review available data on such use of medications in young children, and consider the design of additional preschool population studies. Dr. Hyman also answered questions concerning a recent report from the National Alliance for the Mentally Ill (NAMI). Dr. Hyman expressed concern over the inaccurate characterization of congressional instructions to NIMH. While the five disorders of greatest concern to NAMI are at the core of the NIMH mission, the Congress and the American people have many additional concerns within the NIMH mission, such as childhood mental disorders, eating disorders, youth violence, and the most common forms of depression. He also stated that it is vital for NIMH to continue supporting robust basic research on brain and behavior, and that it is the job of the NIH to make clear the importance of such basic research.

Dr. Francis Collins, Director of the National Human Genome Research Institute (NHGRI), said that sequencing of the human genome began as a pilot project in 1996, but the large international effort to map and determine the DNA sequence of the human genome really began in 1999, and is ahead of schedule and under budget. Access to data that this effort is generating continues to be a controversial subject, and the NIH position on patenting of gene sequences is that stringent criteria for their utility need to be met before patents are issued. Although genomic studies will provide insights into virtually every human disease, legislation or other assurances are needed to protect individuals against genetic discrimination. Moreover, a major effort is needed to evaluate genetic tests and to inform clinical practitioners as well as the public about their proper uses.

Dr. Yvonne Maddox, NIH Acting Deputy Director, said that a new NIH health disparities program of action involves all of NIH as well as other agencies within the U.S. Department of Health and Human Services (DHHS). Each of the Institutes at NIH submitted draft plans for this program to a working group early in April 2000; the plans are being used to set the overall NIH Strategic Research Agenda that will be discussed at the FY 2002 budget planning retreat scheduled for this summer. Health disparities are defined as differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups.

Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID), said that almost every disease entails health disparities and, therefore, every institute at NIH is studying health disparities. Dr. Fauci also pointed out that there are different types of health disparities. Some disparities are biological in nature. In addition to biological disparities, Dr. Fauci stressed other important factors that may have an impact on health disparities, such as social or economic factors. The goal of the NIH strategic research plan is to formulate a comprehensive approach to address the many aspects of health disparities. Dr. Fauci stated that the NIH plan would address questions like: Is there a disparity related to this disorder, and if so, is there a biological reason for that? If there is a biological reason for the disparity, can we address that via biomedical research? Dr. Fauci emphasized that some of the appropriate approaches may be from a research or a research training standpoint. Dr. Fauci described the overall NIH health disparities plan and stated that the plan includes the following goals: (1) Developing a five-year research agenda, (2) Recruiting and training a substantial number of investigators from minority groups, (3) Extending community outreach programs and developing partnerships, (4) Defining goals and evaluating progress in ways that enable Congress to track these programs, and (5) Enhancing public awareness of these efforts.

Dr. Gary Ellis, Director of the NIH Office for Protection from Research Risks, said that some news media accounts of patient risks stemming from clinical research exaggerate those risks while others understate them. Not all research involving human subjects is covered by regulations, as there is no federal statute extending these protections to everyone in the private sector. This NIH office oversees institutional review boards (IRBs), which are charged with responsibility for assuring the risks to subjects are minimized and there is proper informed consent-an important protective component for those who participate in such studies. Although the death in 1999 of a young man who was participating in a gene transfer protocol has focused attention on risks stemming from gene therapy research, public concern could well be directed more broadly to include other areas of clinical research, according to Dr. Ellis.

Dr. Wendy Baldwin, NIH Deputy Director for Extramural Research, said that IRBs may not have adequate resources in terms of information and funding to fulfill their mandates, and described several NIH efforts to augment those resources and to improve bioethics training among researchers. She said that OPRR is being moved from NIH to DHHS and a new committee is being established to advise OPRR. She suggested that COPR direct its initial efforts in this area to learning more about the array of reviews of human subject protections now under way.

COPR members reviewed recent activities of the council as well as its mandate and charter, and considered how best to involve the 260 members of the COPR Associates in forthcoming activities. Ms. Anne Thomas, Director of the NIH Office of Communications and Public Liaison, said that her office would draft a prototype message for this purpose and also would prepare a COPR handbook for review by the council members.

Dr. Kirschstein said that she would remind the Institute advisory councils about COPR and recommend to them that they invite COPR members to their meetings. Although COPR members said that they want to keep their agenda as flexible as possible, they agreed to establish several specific working groups, including groups focused on: (1) human research protections; (2) underserved populations; (3) outreach to other public advisors involved in NIH activities and institute committees; and (4) a process for identifying and recruiting new members to replenish the council as current members depart.

Acting Director's Report

Acting Director of the National Institutes of Health (NIH), Dr. Ruth Kirschstein, began the third meeting of the Director's Council of Public Representatives (COPR) by introducing Dr. Yvonne Maddox, who is the Acting Deputy Director of NIH. Dr. Kirschstein noted that all of the COPR members have been reappointed through the spring of 2001, when one-third of them will cycle off active membership.

Dr. Kirschstein highlighted recent activities of COPR members, including the participation by 15 of them during October 1999 with members of the Advisory Committee to the Director (ACD) in preparing a review of research outcomes of NIH conducted under the mandate of the Government Performance and Results Act (GPRA). She said that a final version of that report was recently submitted to the House of Representatives Appropriations Subcommittee to help in its review of the fiscal year (FY) 2001 NIH budget proposal. Another activity in which COPR members participated was a FY 2001 budget planning retreat, held in June 1999. A similar retreat is being planned for June 2000, to which five COPR members will be invited, according to Dr. Kirschstein.

Dr. Kirschstein said that former NIH Director Harold Varmus asked COPR members to participate in several continuing review activities, such as the review of individual Institute directors who have served at NIH for terms exceeding five years. Two such reviews have been completed this year, and two remain to be conducted. In addition, COPR members Rosemary Quigley, Bob Roehr, and Debra Lappin are serving as part of an ACD working group that is reviewing gene therapy and gene transfer clinical studies. Dr. Kirschstein also noted that NIH is working closely with officials at the Food and Drug Administration (FDA) to improve the safety and monitoring of such clinical protocols.

Meanwhile, COPR member Dr. Ted Castele participated in a public advocacy forum that focused on activities of the National Institute of Dental and Craniofacial Research, while Ms. Joan Lancaster participated in recent discussions that focused on studies of the elderly that were conducted by the National Institute of Nursing Research. Dr. Melanie Dreher is involved in a broad review of efforts to reduce the regulatory burden on researchers and grantee institutions; this review is looking at several issues, including the protection of human subjects, ethical issues involving research, the use of animals in research, and medical waste management.

Dr. Kirschstein also presented an update of several key issues affecting NIH, including the development of guidelines for overseeing pluripotent stem cell research and a review of early budget negotiations before congressional appropriations committees. She said that NIH is reviewing hundreds of comments on its draft stem cell guidelines, which will be revised by this summer. The NIH Office of Science Policy is writing a charter for an oversight body that will conduct public review of research proposals involving human stem cells. She also said that Senator Arlen Specter (R-PA) and Senator Tom Harkin (D-IA) have submitted a bill that explicitly would permit federal support of such research.

Dr. Kirschstein and the Institute Directors appeared before the House of Representatives Appropriations Subcommittee over a three-week period in a series of hearings to review the NIH FY 2001 budget proposal this spring as well as before the comparable Senate Subcommittee in a briefer hearing. Although these hearings have been cordial, the questions often have been more pointed than during the past two years, according to Dr. Kirschstein. She said that some members of Congress are asking whether NIH can use its increased funding wisely, while others are focusing their questions on spending for specific diseases, such as diabetes, Parkinson's disease, and Alzheimer's disease, and also on health disparities. Markup of the NIH budget proposal was delayed, while the overall federal budget resolution was being considered.

In response to a question about the delayed obligations in the FY 2000 NIH appropriation, Dr. Kirschstein explained that a last-minute compromise was worked out that requires NIH to delay spending $3 billion until the last day of the fiscal year; an earlier proposal would have had NIH spending $7.5 billion on the final day of the fiscal year, which could have proved burdensome. More recently, Congress lifted that last-day spending requirement.

Dr. Kirschstein briefly reviewed several recent NIH staff changes, including the departure of Dr. Neal Nathanson, Director of the Office of AIDS Research, who is returning, in September, to the University of Pennsylvania; Dr. Hal Slavkin, Director of the National Institute of Dental and Craniofacial Research, who will become Dean of the Dental School at the University of Southern California; and Dr. Norman Anderson, Director of the Office of Behavioral and Social Sciences Research, who joined the Harvard School of Public Health in April. Dr. Alan Spiegel was named the Director of the National Institute of Diabetes and Digestive and Kidney Diseases last November.

NIMH Director's Presentation

Dr. Steven E. Hyman, Director of the National Institute of Mental Health (NIMH), described several recent interactions with the public, including a first-ever White House Conference on Mental Health, presided over by Tipper Gore; the first Surgeon General's Report on Mental Health; and a more recent expression of concerns from the White House over the widespread use of psychotropic drugs such as Ritalin for treating preschool children that will lead to a conference sometime this summer.

Dr. Hyman stated that the recent increased attention in mental health issues may stem from dedicated interest from administration officials and from many influential members of Congress. There has also been increased interest in mental health issues from the recent report, "Global Burdens of Disease," prepared by experts from the World Bank, the World Health Organization, and the Harvard School of Public Health. Dr. Hyman said that this report recognizes a new paradigm in which fundamental economic improvements in developing countries depend directly on improvements in public health. This new paradigm is shaped by a new understanding worldwide, that when measures of disability adjusted life years (DALYs) are looked at, it is clear that dealing with mental disorders becomes a critical ingredient to improving public health in developing countries.

Although the "Global Burdens" report and others like it indicate that health burdens are difficult to define precisely, they now explicitly include mental disorders as an important component contributing to those health burdens, according to Dr. Hyman. Depression, for example, affects up to 10 percent of the population and is ranked as the fourth leading contributor to disability adjusted life years (DALYs), noted as one of the most widely used measure of health burdens. Dr. Hyman stated that this particular report is one of several recent indicators that some people are coming to appreciate the importance of mental diseases, particularly their impact on the economy, and to realize that in many cases effective treatments are available.

Dr. Hyman said that a large segment of the public is still asking why is it taking so long to understand mental illnesses and to mark progress in combating them. One major reason is that the brain is the most complicated biological structure to study. Another problem is that many NIMH-sponsored clinical trials in the past were designed more as typical, albeit short-term, drug-evaluation protocols than as experiments to understand the fundamentals of brain function and behavior in realistic settings. Hence, NIMH has moved to develop a new series of effectiveness trials in which specific mental health research hypotheses may be tested in relevant settings that will be able to provide information to practitioners on real consumers in realistic environments, according to Dr. Hyman. To better ensure that these studies are both relevant and scientifically rigorous, last year three members representing the public interest were added to each of the study sections

that evaluate clinical research proposals. He said that this new approach within the study sections is working very well and has added an important component to improve the public health impact of these studies.

Dr. Hyman said that a recent report published in the *Journal of the American Medical Association* indicates a substantial increase in the use of several psychotropic drugs to treat preschool children. This increase is not uniform across the population, but instead tends to be very specific to certain segments. For example, Ritalin treatment has increased sharply among upper-middle-class Caucasian boys. Although this drug is safe and effective for treating well-characterized cases of attention deficit disorder, its use for other less well-characterized behavioral disorders may not be indicated. To address such questions, Surgeon General David Satcher plans to convene a conference that will review available data on Ritalin use and discuss the design of additional preschool population studies. Dr. Hyman said that, because such studies raised perplexing ethical issues, it would be important to involve educators as well as representatives of the general public. Focusing on the needs of children is an essential component of these deliberations.

Dr. Hyman said that a recent report from the National Alliance for the Mentally Ill (NAMI) was highly critical of the NIMH research portfolio, alleging that the Institute's research portfolio neglects the five key mental illnesses that Congress has mandated it to study. For example, the report implies that NIMH redirected funds from research on schizophrenia to support research on AIDS-related mental illnesses, and it also recommends that NIMH not perform basic scientific research but focus only on specific diseases. Dr. Hyman said that the report is inaccurate on several counts, and that many members of the NAMI board of trustees had expressed to him disagreement with its conclusions. He also said that Congress requires NIMH to study mental illnesses beyond the five disorders that NAMI highlighted. Dr. Hyman pointed out that, in fact, the suggestions and encouragement from Congress was actually larger in areas other than the five areas of particular concern to NAMI. Some of these other areas included youth violence, eating disorders, and Alzheimer's disease. He also reminded the group that in reference to the report's implications about redirected funds to AIDS research, there actually is a separate AIDS budget and clearly stated that these are not fungible funds. Dr. Hyman also mentioned that it is vital for NIMH to continue supporting robust basic research.

Discussion

Ms. Lydia Lewis said that it continues to frustrate members of the mental health community that many physicians as well as members of the public do not recognize mental illnesses as real diseases. She said that it is important to deliver this science-based message to the general public. In response, Dr. Hyman said that this message is being heard in some sectors, particularly regarding schizophrenia and autism. It will help as basic research provides additional insights into the components of the brain that are involved in additional specific diseases. Although many physicians are not properly trained to deal with such illnesses, former practices based on beliefs that blamed many mental conditions on one's parents are being replaced by an understanding of the biological bases of those conditions.

In response to a comment from Dr. Melanie Dreher, Dr. Hyman agreed that mental illnesses could cause problems for entire families. He said that NIMH is seeking ways to collaborate with other Institutes and to develop new ways to improve family support systems.

In response to a question regarding genetic determinism from Mr. David Frohnmayer, Dr. Hyman stated that, while genetic studies are contributing a great many insights into mental illnesses, genes are interacting in these diseases in complex and non-linear ways. Moreover, non-genetic factors are also important contributors to mental illness. Thus, information about an individual's genetics, although helpful in establishing his or her risk for specific mental illnesses, is not determinative and should not be used to determine one's employment or insurance status.

Ms. Debra Lappin said that, because the health care system often fails to meet the mental health care needs of enrollees, NIMH officials should do more to inform health care providers and representatives of the insurance industry about the research being done on and progress being made to understand and treat mental illnesses. Dr. Hyman commented that NIMH has been providing the Senate with information about the impact of parity in insurance coverage and other health insurance issues as they affect quality of mental health care. He also said that managed care, rather than fee-for-service insurance coverage, is better equipped to provide parity for mental health needs to enrollees. One especially useful role NIMH plays is to provide burden-of-illness data to insurance companies, explaining in concrete terms how big an impact illnesses such as depression have on employees in the workplace. Hence, NIMH is redesigning certain clinical trials to delineate more clearly such impacts.

In response to a question from Dr. Luz Claudio, Dr. Hyman answered that although many specific mental illnesses strike more or less equally among very different population groups, the kinds of diagnoses, treatments, and other interventions that are available to those different groups tend to vary widely, as do outcomes. Dr. Claudio and Dr. Hyman agreed that access to health care as well as cultural differences influencing beliefs and perceptions also have an impact on the number of diagnoses, and thus apparent prevalence rates of mental illnesses in different communities. Dr. Mary desVignes-Kendrick noted that often physicians are told to assess a child's mental health status too quickly, perhaps within 15 minutes, an inadequate amount of time in which to conduct such evaluations. Dr. Hyman said that budget increases would help NIMH to reassess prevalence rates for specific illnesses among different populations.

Dr. Isaac Montoya praised NIMH for their efforts on handling the critical NAMI report and asked how COPR might assist NIH in managing similar situations in the future. Dr. Hyman said that it would be helpful if he or other NIH officials could receive comments from COPR members on tentative responses to such criticisms-in other words, if COPR could serve as a sounding board.

In response to a comment from Ms. Barbara Lackritz about how many school children now receive medication for mental illnesses, Dr. Hyman said that public health experts and educators have drifted apart from one another and he is eager to see things change. One point Dr. Hyman and Ms. Lackritz agreed on was the importance of bringing together the public health and education community on these issues. An example of this would be bringing the two communities closer together by sharing research and best practices on the most modern behavioral techniques for behavior management.

NHGRI Director's Presentation

Dr. Francis Collins, Director of the National Institute of Human Genome Research (NHGRI), said that public interest in human genomics continues to rise and that a special one-day consumer-oriented conference held last November will be repeated this fall. He said that genome studies will provide insights into virtually every human disease, from cystic fibrosis with a high genetic impact to others such as AIDS or other infectious diseases in which host factors play a substantial but considerably lesser role. The sequencing of the human genome began as a pilot project in 1996, but the large international effort to map and determine the DNA

sequence of the human genome began on a large scale in 1999, and is ahead of schedule and under budget, according to Dr. Collins. The overall program has reached a number of important milestones, including genomic sequences of several model organisms, including yeast, *Escherichia coli*, C. elegans, and, very recently, the fruit fly *Drosophila melanogaster*. After genomic mapping was done in adequate detail, sequencing of the human genome began as a pilot project in 1996, with a goal of determining the entire sequence by 2005. During the past 14 months, however, progress has steadily accelerated, and the sequencing completion date has been moved up to 2003 with a "working draft" (90% of sequence in high accuracy) this year.

By late March, about two-thirds of the human genome sequence was available in working draft form, and about 20 percent was considered unequivocally finished, according to Dr. Collins. The sequencing of chromosome 22, for example, was completed and published late in 1999. At least a dozen new disease-associated genes have been identified because specialists in those diseases have free and immediate access to sequence data through GenBank. The NIH position on patenting of gene sequences is that stringent criteria for their utility need to be satisfied before patents are issued. In other words, the bar for obtaining patents needs to be set high.

Dr. Collins said that single nucleotide polymorphisms (SNPs)-each representing a misspelling in a particular DNA sequence-occur in an average of one per one thousand nucleotides throughout the human genome. Many SNPs play a role in, or are markers for, disease susceptibility. A group known as the SNPs Consortium is investing $50 million into a focused effort to identify those disease-associated SNPs, according to Dr. Collins. This consortium consists of NIH, ten pharmaceutical companies, several additional technology-oriented corporations, and the Wellcome Trust; the data being assembled are being retained in the public domain.

These genome analysis efforts require the development and use of many specific tools, according to Dr. Collins. The NHGRI Human Genome Project has identified eight goals, including training, bioinformatics, biological functionality, development of improved sequencing technology, the study of variants, sequencing itself, and analysis of the ethical, social, and legal implications of this research. These efforts will have a great impact on human health, including on medical diagnosis, preventive medicine, pharmacogenomics involving the development of drugs specific to the molecular basis of disease, gene therapy, and the design of drugs tailored to specific diseases.

However, for the genome project to have such effects, legislation or other assurances are needed to protect individuals against genetic discrimination, according to Dr. Collins. In addition, a major effort is needed to evaluate genetic tests and to inform clinical practitioners as well as the public about their proper uses.

Discussion

In response to a comment from Dr. Maurice Rabb about sickle-cell trait screening programs during the 1970s, Dr. Collins said that there are sobering lessons to be learned from that period, such as the failure of insurance companies to distinguish between an individual carrying a genetic trait and a person actually having a genetic disease.

In response to a comment from Dr. Luz Claudio that minority communities are very concerned about genetic testing, Dr. Collins said that these concerns are reflected in a widespread reluctance among many individuals to participate in clinical studies.

Along similar lines, Ms. Barbara Lackritz said that cancer patients also are concerned that genetic information about them and their families will be misused. Ms. Pam Fernandes said that stringent safeguards to protect privacy will be needed. Dr. Collins said that laws guarding against abuse of participants or results from such studies (and similar guarantees against the misuse of medical records) are needed, other efforts will be required to re-build trust in such communities, and privacy safeguards will be essential.

In response to a comment from Mr. Doug Yee, Dr. Collins said that the involvement of scientists, including Dr. Eric Lander from the Whitehead Institute, in recent programs at the White House has generated considerable enthusiasm on the part of President Clinton and other top officials in genome research and its implications.

In response to a question from Dr. Ted Castele about the patentability of gene sequences, Dr. Collins said that genes and gene products potentially can be used in several ways, including to diagnose specific diseases or as tools for developing new treatments, and that the criteria for granting patents in this area are being made more stringent. In response to a question from Mr. Yee, Dr. Collins also said that it is difficult to explain the stock market response to the statement issued by President Clinton and U.K. Prime Minister Tony Blair about the value of genome sequencing information being in public databases for all scientists to use freely. Their statement endorsed the current practices of the Institute's human genome sequencing program.

In response to a question from Mr. Thomas Vaalburg about the degree of NIH/NHGRI cooperation involved in the fruit fly genome-sequencing program, including with researchers from the Celera Corporation, Dr. Collins said that a detailed memorandum of understanding specified that all the sequence data is deposited in GenBank. He also said that, although NHGRI and Celera Corporation covered the costs of sequencing *Drosophila*, the fruit fly, it was proving difficult to develop a similar cooperative program for the sequencing of the human genome. This difficulty is in large part because the business value of human genomic data is considered so much greater than data for *Drosophila*.

In response to questions from Mr. Frohnmayer about use of genomics data and on gene therapy research, Dr. Collins said that clinical research trials involving people with hemophilia and individuals with X-linked immunodeficiencies are showing progress, whereas studies of other disorders do not look so promising. In response to a question about genomics data, Dr. Collins said that the genome program depends on scientists working on specific diseases to use data made available through GenBank to further study those diseases.

Ms. Joan Lancaster asked about gene therapy procedures that might be aimed at enhancing individuals. Dr. Collins said that such research raises thorny ethical questions, and the science needed to implement such plans is a long way away from being available.

In response to a question about genetics and social hierarchies from Ms. Rosemary Quigley, Dr. Collins said that genetics research indicates that there is more variability within an ethnic or racial group than there is between two randomly picked individuals, each representing a different group. Thus, most recognized differences have more to do with cultural, economic, and social factors than with inherited differences.

Health Disparities Presentation

Dr. Yvonne Maddox, NIH Acting Deputy Director

Dr. Yvonne Maddox said that the new NIH health disparities program of action involves all of NIH as well as other agencies within the U.S. Department of Health and Human Services (DHHS). Although NIH has been involved for the past decade in minority health research through its Office of Research on Minority Health (ORMH), President Clinton's 1998 Race Initiative led to a DHHS response in six specific biomedical areas: infant mortality, cancer screening and management, cardiovascular diseases, diabetes, HIV/AIDS, and immunizations.

In December 1999, after it was recommended that NIH develop a strategic plan for dealing with health disparities research, a Trans-NIH Working Group on Health Disparities was reestablished within the NIH Office of Director to develop a plan of action for setting an overall NIH health disparities research agenda. The working group members include all Institute and Center directors, and directors of special OD components, such as the Office of Research on Women's Health, the Office of Research on Minority Health, the Office of Behavioral and Social Sciences Research, and the Office of AIDS Research. Each of these entities then developed their own draft plans, which were submitted to the Working Group early in April 2000, according to Dr. Maddox. In turn, those draft plans were to be used for setting the overall NIH plan and, once refined during the FY 2002 budget planning retreat, for setting overall research priorities.

The Working Group defines health disparities as differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups, according to Dr. Maddox. The current focus is on racial and ethnic minority populations and also disparities that arise from social and economic status. The Working Group draft plan calls for developing a five-year strategic research agenda, recruiting and training a substantial number of investigators from minority groups, extending community outreach programs and developing partnerships, defining goals and evaluating progress in ways that enable Congress to track these programs, and enhancing public awareness of this range of efforts.

Dr. Maddox said that the draft plans from the Institutes and other Offices are focused and innovative, describing new mechanisms for collaborations and for expanding efforts to recruit individuals from minority populations to participate in clinical research studies. Such efforts will be further enhanced as the number of investigators from minority populations increases, because their presence is expected to help develop a greater sense of trust among the population groups they represent. For instance, the participation of African American investigators in a cardiovascular study in Jackson, Mississippi, has helped to increase the participation of African Americans in that study.

In general, NIH is encouraging the career development of minority scientists through an increased focus on obtaining R01 grants and on their greater participation in the peer-review process, according to Dr. Maddox. In addition to a special focus on such investigators at NIH itself, there is an increased emphasis on partnerships with industry and foundations as well as intensified outreach to the general public. Several new programs are designed to interest students from minority groups in careers in the health sciences. Other efforts include the development of informational materials that are ethnically sensitive.

Dr. Maddox said that members of Congress have introduced several bills to establish a Center for Health Disparity Research at NIH, including one introduced by Representative Jesse Jackson Jr. (D-IL), H.R. 2391, another similar bill introduced by Senator Edward Kennedy (D-MA), S. 1880, and yet another bill introduced by Representative Bennie Thompson (D-MS), H.R. 3250. Because these bills differ in wording, there are potential administrative complications that will need to be faced as the individual bills are considered, including whether such a center is to be free-standing or housed within the NIH Office of the Director (OD). Meanwhile, the NIH Office of the Director will coordinate and accelerate development and implementation of the overall NIH health disparities research plan.

Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID)

Dr. Fauci mentioned that almost every disease entails health disparities and therefore, every institute at NIH is studying health disparities. Part of the NIAID mission, particularly as it concerns HIV/AIDS, tuberculosis, sexually transmitted diseases, autoimmune diseases, allergy, and asthma, is not merely to study the biological basis of these diseases, but how to address disparities in treatments and outcomes that may be associated with those or other diseases.

Sometimes disease disparities appear to have a direct biological basis, according to Dr. Fauci. For instance, African Americans who are infected with the hepatitis C virus do not always respond as well to antiviral therapy as individuals from other populations do. Moreover, African Americans have a higher incidence of autoimmune diseases than do others, whereas there is a higher than usual incidence of meningitis among Native American populations. Thus, one goal of research sponsored by NIAID is to understand the biological basis for those differences.

Other disparities may stem from uneven participation in available research and health care delivery programs, according to Dr. Fauci. For example, because the incidence of HIV infection is particularly high among African Americans, NIAID is mounting an effort to increase their participation in clinical trials to evaluate various antiviral drugs. Following a concerted effort by the AIDS clinical trials network, enrollment of African Americans in such trials has increased from 2 percent to 35 percent.

Another NIAID effort entails intensified recruitment of young people from minority backgrounds at the high school and college levels into clinical and research careers. Other efforts include outreach to minority communities through use of culturally sensitive materials.

Discussion

In response to a question from Dr. Isaac Montoya about potential collaborations with other federal departments, Dr. Maddox said that there have been some discussions with officials elsewhere, such as the Department of Labor, and ongoing collaborations with the Department of Education, but NIH needs to focus on its biomedical research mission. Dr. Fauci said that many of these discussions need to take place at the departmental level and that NIH must be careful not to dilute its own research efforts. Dr. Kirschstein stated that NIH should also concentrate on bolstering its research programs and on recruiting, training, and retaining scientists from minority backgrounds.

In response to a question from Dr. Maurice Rabb about the pending bill submitted by Rep. Jackson, Dr. Kirschstein said that NIH will establish an independent

center if that proposal is signed into law. In any case, NIH will do more in the area of health disparities research and related activities, using its administrative authority to invest where it can. A pending administrative problem is that the current legislative proposal could lead to establishing a center that would effectively compete with many activities now undertaken by the NIH ORMH. She said that Dr. John Ruffin, the ORMH Director, is working closely with Rep. Jackson and his staff members to work out some of these potential difficulties.

Dr. Ted Castele said that NIH needs to educate the general public about health disparity issues, which are poorly understood.

Ms. Rosemary Quigley said that stepped-up recruitment of individuals from minority groups into biomedical career tracks, even if successful, does not guarantee that they will want to work on health disparities research. Dr. Maddox said that jump-starting such careers would have a positive impact on minority communities; moreover, NIH will be working with medical organizations, such as the Student National Medical Association, to address how to retain those recruits and encourage their interests in a broad range of areas. Efforts like these will help build increased awareness so that the physicians of tomorrow will bring a health disparities perspective to their careers and the communities they serve.

Dr. Kirschstein said that provisions might be attached to the NIH appropriations bill that would ease circumstances for medical students who face high indebtedness from tuition costs. NIH has proposed in its FY01 budget request $1.4M for a loan repayment program to assist medical students who are interested in conducting clinical research in the extramural community. NIH already has such a program for clinical researchers from disadvantaged backgrounds who participate in the intramural program.

Dr. Luz Claudio raised the point that the pool of minority scientists that currently exists is often "recruited" for too many additional administrative activities. The limited pool of minority scientists is in danger of being over extended. She also advised building-in evaluative procedures for these new programs. In response, Dr. Fauci said that NIAID is tracking M.D./Ph.D. candidates who enter the Institute's program. He and Dr. Rabb both said that many young scientists and clinicians from minority groups are returning to their communities once they have completed their professional training.

Human Subjects Protections

Dr. Kirschstein provided some background information about recent events affecting the NIH Office for Protection from Research Risks (OPRR), including the recommendation from a Working Group of the NIH Advisory Committee to the Director (ACD) that OPRR be moved to DHHS. HHS Secretary Donna Shalala accepted that recommendation, decided that the office should report to the Assistant Secretary of Health, and agreed that the office should have its own advisory committee. DHHS officials also conducted a management study, and concluded that OPRR's human subject protection duties belonged in the new entity, which is to be called the Office for Human Research Protections (OHRP), within the department. However, its animal protection duties are to remain at NIH.

COPR member Debra Lappin said that a small group within COPR has had several conference calls to discuss the protection of human subjects in research and what COPR might do in this area. For this reason, the members of this subgroup invited Dr. Gary Ellis to review the activities of OPRR, whose staff of 24 individuals oversees agreements of assurance with more than 4,000 institutions throughout the United States.

Dr. Gary Ellis, Director, NIH Office for Protection from Research Risks

Dr. Ellis said that news media and public perceptions of patient risks stemming from clinical research vary widely, with some recent descriptions exaggerating those risks and others understating them. The Declaration of Helsinki of 1964 is the premise on which such considerations are built; it states that concerns for human subjects must prevail in any accounting of research risks and whenever subjects are recruited to participate in studies. The challenge faced by OPRR is to identify ways of reducing risks to individuals who agree to participate in research projects of every kind.

The statutory authority for OPRR dates to 1974 and, since 1991, it has overseen the 16 other federal agencies and departments that are signatories of the Common Rule governing the treatment of human subjects in research. (Some federal agencies that fund human subjects research have not signed this rule.) OPRR oversees assurances, informed consent, and institutional review boards (IRBs) for federal grantees. FDA has comparable rules that apply to clinical trials conducted in the private sector for products that come under its regulatory jurisdiction. OPRR defines human research broadly, and extends the definition to include any deliberate collection of biomedical information for developing generalizable conclusions.

Despite this broad coverage, not all research involving human subjects is covered by regulations, as there is no federal statute extending these protections to everyone, according to Dr. Ellis. Research institutions that do not fall under federal oversight include certain colleges and universities that receive no federal funds, *in vitro* fertilization and diet clinics, private offices and clinics of physicians and psychotherapists, and companies developing genetic tests. He cited several anecdotal cases of abuse arising from facilities not subject to federal oversight, including psychotherapists who disclosed the names and conditions of their clients and a plastic surgery private practice that evaluated two cosmetic procedures on individual patients without their knowledge or consent.

Dr. Ellis said that OPRR receives a great many inquiries, and a smaller number of formal complaints. OPRR has no authority to pursue complaints or inquiries outside its particular jurisdiction. Several reports, including one prepared in 1996 by the federal General Accounting Office and another prepared by the DHHS Inspector General in 1998, warn that the effectiveness of IRBs is in jeopardy. However, neither report provides evidence of widespread harm to human subjects. Both recommend a constructive review of the system and better education of all who are involved with it.

IRBs are charged with several responsibilities, including a continuing review at appropriate intervals of all ongoing protocols. Several examples, indicating that protocols often change as they proceed and thus risks to participant subjects may escalate, illustrate that this responsibility is not trivial and cannot be disregarded, according to Dr. Ellis.

Informed consent is another critical component of the system intended to protect human subjects from harm, according to Dr. Ellis. However, in practice, this concept often proves challenging to implement and, often, the process tends to underestimate risks and overestimate potential benefits. One major challenge is to provide informed consent documents that are written in simple language that subjects can fully understand. It also is important to avoid any form of coercion when recruiting individuals to participate in research of any kind.

Although the death in 1999 of a young man who was participating in a gene therapy protocol has focused attention on this area of research, public concern could well be directed more broadly to include other areas of clinical research, according to Dr. Ellis. An important consideration is that the need for research protection has received attention from President Clinton, who directed all federal departments in 1994 to assure compliance with applicable protective measures and has spoken out on this subject several times since then. In addition, members of the National Bioethics Advisory Commission (NBAC) in 1997 recommended universal protection for research subjects, regardless of whether protocols received federal funding or were protected under FDA regulations. Moreover, several congressional committees held hearings early during 2000 on this subject.

Discussion

In response to a comment from Ms. Barbara Lackritz, Dr. Ellis said the candidate subjects may demand to know full details about a protocol in which they have been asked to participate and that no one should sign an informed consent agreement until being fully satisfied with the disclosures. He also said that students involved in conducting research studies involving human subjects often do not receive adequate training from their mentors.

Ms. Lydia Lewis said that the NBAC 1998 report on research involving subjects with mental disorders is misleading inasmuch as some individuals with mental disorders can make fully informed decisions about participating. Dr. Ellis said that the title of that report is at fault and that NBAC members took great care to indicate that not all mental disorders lead to impaired decision making.

In response to a question from Dr. Isaac Montoya, Dr. Ellis said that systematic clinical evaluations intended to develop generalizable knowledge fall under the broad definition of research; thus, individuals who participate in such evaluations are entitled to full protection under current federal guidelines.

In response to a question from Mr. Bob Roehr about OPRR moving from NIH to DHHS, Dr. Ellis said that the office is under-staffed, with only two full-time investigators, an average investigational period of 23 months, and 163 cases now under investigation. The caseload could be much higher if the office operated proactively. Nonetheless, the recent wave of high-profile investigations and enforcement actions has intensified interest in protecting human subjects. For example, attendance at recent OPRR-sponsored workshops has increased substantially.

Dr. Wendy Baldwin, NIH Deputy Director for Extramural Research, said that IRBs may not have adequate resources in terms of information and funding to fulfill their mandates. A Web site is being established to provide useful information to IRBs, and steps are being taken to provide additional funding, possibly by raising the current 26 percent cap on indirect cost recovery from NIH research grants. In addition, a committee at NIH is reviewing how regulatory burdens could be reduced or simplified in ways that would make the job of IRBs easier, particularly in cases of multi-site clinical trials in which duplicative regulatory efforts often are required. NIH also has several training programs in bioethics for members of the research community, and a research program was recently begun whose aim is to better understand behaviors needed to achieve informed consent. Finally, NIH is working on a guidance document for investigators conducting research that involves subjects whose decision-making capabilities are impaired.

Ms. Rosemary Quigley recommended that COPR establish a working group, perhaps including COPR Associates among its members, to help deal with the many public misunderstandings that surround research involving human subjects. Ms. Debra Lappin said that it would be helpful for Dr. Baldwin to participate further during COPR deliberations and to explain more completely issues revolving around IRB operations.

April 7 Discussion

Ms. Debra Lappin reviewed several recent issues touching on the role of human subjects in research and on various measures to protect them from undue harm. She said that a federal working group is assessing current safeguards and a subcommittee of ACD is reviewing gene transfer and gene therapy clinical trials. Meanwhile, Ms. Jennifer Gorman from the NIH Office of Communications and Public Liaison (OCPL) prepared a fact sheet for COPR that summarizes how the federal system for protecting human research subjects is structured. One question facing COPR is whether it can complete its own report on this subject by next fall.

Dr. Baldwin said that a great deal is taking place, including the transfer of the OPRR to DHHS and the establishment of a new committee to advise the successor to OPRR. She said that COPR may want to delay trying to complete a report until it reviews what other groups are doing and becomes more familiar with the broad scope of these issues. She also provided COPR members with several relevant documents, including one describing bioethics training and research initiatives, resources that are available on the NIH Web site, guidelines for the participation in research of subjects whose decision-making capabilities may be impaired, and a proposal for just-in-time reviews by IRBs as a way of conserving their resources by delaying some phases of their reviews until grant proposals are provisionally approved.

Dr. Kirschstein said that there may be several congressional hearings on this topic before Congress adjourns before the November elections. She suggested that COPR devote part of its next scheduled meeting to developing a fuller understanding of these issues, with some attention to the forthcoming report of the ACD subcommittee on gene therapy and gene transfer research and also to the activities of NBAC as well as typical IRBs and institutional biosafety committees. She said that, following a request from several members of Congress, the ACD subcommittee also will address whether the NIH Recombinant DNA Advisory Committee should resume its consideration of individual research protocols, a potential change in activity that would not take place until it can be posted in the *Federal Register*. Later, in response to a question from Dr. Mary desVignes-Kendrick, Dr. Kirschstein suggested that there be a liaison between COPR and the new committee being formed to advise OHRP.

Mr. Roehr said that, following a successful conference call with the ACD gene therapy working group, it is time for COPR members to move beyond preliminary discussions about these issues. Dr. Montoya said that the IRB system may not be so damaged as some public reports suggest and that there may sometimes be maverick investigators at institutions where the IRBs are being well run. He also said that volunteer IRB members can become demoralized by excessive negative publicity. Dr. Luz Claudio said that, whatever the actual condition of the IRB system, these issues need to be addressed because the public perception is that the system is damaged. Several other members agreed, noting that public perceptions are far from uniform on this issue. Dr. Mary desVignes-Kendrick said that if COPR could identify gaps and recommend where additional resources are needed, it would be providing a useful service to the community.

Dr. Kirschstein said that care needs to be taken to explain to potential research subjects that such trials can mean that some of them will receive placebos or best-available conventional care rather than a particular experimental treatment. She also said that sometimes individuals refuse to participate because they do not understand how such trials are structured. Mr. Roehr said that the line between standard health care and treatment within clinical research projects is not so clear as it was a decade ago. Moreover, with other issues involving the participation of managed care organizations in clinical research programs in flux, COPR potentially can influence such organizations to be more receptive to having their members participate in clinical trials.

In response to a question from Mr. Doug Yee, Dr. Baldwin said that, although there are many partnerships involving university scientists and researchers in companies and these investigators embrace the principles of bioethics, there is currently not enough research being conducted on the ethical issues, practices, and principles involving human subjects.

Current Activities, Future Directions for COPR

[Thursday and Friday segments of the COPR deliberations are combined in this section.]

COPR Activities Presentation

COPR member Ms. Vicki Kalabokes, who moderated this session, said that the council is mandated to exchange information with the public. Although the breadth of capabilities among current COPR members is considerable, there is interest in expanding the capabilities by more actively involving the 225 COPR Associates in some of the council's activities.

Ms. Cate Timmerman of Palladian Partners, a contractor who is assisting the NIH, described salient demographic features of the COPR Associates. She said that they are associated with institutions in 37 states, and about one-quarter of them are interested in multiple diseases; other information is available as part of a database to which COPR members are entitled access because they are considered federal employees while they are engaged in NIH-related activity. She also said that NIH communicates frequently with the Associates, providing them a newsletter and other items describing ongoing COPR and COPR-related activities.

Ms. Anne Thomas, Director of the NIH Office of Communications and Public Liaison, said that COPR members can contact COPR Associates to determine whether they will participate in specific COPR-related activities. She said that she would draft a prototype message for this purpose that COPR members subsequently could review. Dr. Ruth Kirschstein said that, as a matter of privacy, individuals among the Associates may decline to participate or even to be contacted about pending COPR activities.

Mr. Bob Roehr asked whether additional information that would enable COPR members to contact and collaborate with members of the Institute advisory councils could be made available. Dr. Montoya suggested establishing a formal link between COPR and the members of those councils. Dr. Kirschstein said that one-third of the members of those councils are public representatives who help in deciding where to allocate NIH resources and thus the councils serve a different purpose from COPR.

Several suggestions were presented for how to communicate with and best involve the Associates in COPR activities. Ms. Pam Fernandes recommended that communications between COPR and the Associates be centralized, not fragmented and diffuse. Mr. David Frohnmayer said that COPR Associates might be affiliated with COPR by serving as members of working groups. Ms. Barbara Lackritz said that grouping Associates according to their interests might be helpful. However, Mr. Doug Yee recommended that the Associates not focus on their specialty interests when collaborating on COPR activities. Ms. Rosemary Quigley said that assigning each of the Associates to specific COPR members would help to personalize their contacts with the council.

Dr. Ted Castele said that it is important to define carefully what to expect from the Associates. Dr. Isaac Montoya suggested that the Associates help with future GPRA assessments. After further discussion, there was wide agreement among COPR members that the Associates should be considered as a pool of talented individuals from which to draw for involvement in specific, task-oriented assignments. Ms. Timmerman said that, as specific needs arise, there are efficient ways to contact all the Associates and to offer them opportunities to participate in COPR activities.

Ms. Thomas agreed to draft a general message for this purpose and also to enlist Associates to help the general public to better understand NIH through outreach efforts. Mr. Yee said that Rotary Clubs and other general public service organizations offer many opportunities to reach the general public with information about NIH programs. Information was also exchanged about the availability of a traveling exhibit sponsored the National Eye Institute.

COPR Roles and Functions and Core Operating Values

Ms. Anne Thomas said that some other federal agencies view COPR as a model and that delegations from the United Kingdom and Canada have visited NIH to learn more about its makeup and activities. She plans to write a booklet describing how COPR is constituted and the roles it can play--in part to help NIH, but also for other interested agencies.

In a presentation about the history and background of COPR, Ms. Thomas, explained how COPR was established. On September 23, 1998, NIH convened a public planning meeting where the participants concluded that a new entity was to be formed. This new entity would serve a different purpose from that of the long-standing NIH Advisory Committee to the Director (ACD) by providing publicly oriented views but also addressing issues of importance across the entire NIH. COPR would also be a sounding board for major issues, define mechanisms for obtaining broad public input for NIH, assure Congress that NIH has continuing access to such input, improve the understanding of NIH among health advocacy groups, and receive public input regarding the NIH administrative structure and decision-making apparatus.

Discussion

Ms. Lydia Lewis recommended that COPR members set priorities among the issues COPR might grapple with. Ms. Barbara Lackritz said that COPR's role is still evolving.

Ms. Debra Lappin said that, during the 1998 meeting, former NIH Director Harold Varmus helped to go beyond the initial mandate imagined for COPR by extending past its role as a vehicle for informing the public about NIH activities. Thus, it also serves as a means for members of the public to advise NIH on research priorities and to serve as a sounding board. Moreover, because COPR members do not depend on NIH for support and thus have no conflicts of interest, they are in a stronger position than they may realize to advise NIH.

Mr. David Frohnmayer said that COPR's figurative role as a firefighter—that is, in dealing in a timely fashion with controversies or other topical issues, such as the protection of human subjects in research settings—seems inevitable. Hence, COPR should not become rigid about the way it sets its own agenda. Mr. Bob Roehr agreed, noting that the council will need to react to events. He suggested that COPR might take the initiative on certain issues, maybe reach out to the advisory councils, or even build an education program about NIH in which other public advisors to NIH also participate.

Dr. Ruth Kirschstein said that she would remind the Institute advisory councils about COPR and recommend to them that they invite COPR members to some of their meetings. In response to a question from Mr. Frohnmayer about COPR's longer term future, she said that, although there is no absolute guarantee that the next NIH Director will embrace the concept, in all likelihood the COPR will continue to serve an important advisory role for NIH.

Dr. Isaac Montoya said that, although flexibility was useful for COPR, it also is important to have certain fixed functions and activities in the agenda, including receiving a report from the NIH Director on key current issues on which to provide input and also presenting a report from COPR members on important issues outside NIH of importance to it.

Ms. Thomas proposed several core operating values for COPR members to consider, including continuing open and direct dialogue between NIH and COPR on substantive issues, COPR striving to represent the views of the public at large, and all members actively engaging in ongoing activities.

COPR Interests and Operations

Establishment of COPR Working Groups

Dr. Baldwin pointed to an important area in which COPR members might provide NIH and the public with advice and improve understanding-namely the management, not the elimination, of conflicts of interest as they apply to research situations. These issues as they apply to clinical research have become increasingly complex, making it particularly difficult to handle potential conflicts as they involve institutions over and above individual investigators. Dr. Kirschstein said that these emerging conflicts of interest at the institutional level reflect the rapid growth of small biotechnology companies, many of which are founded by academic scientists and often involve their participation as officers or advisors.

Dr. Ted Castele agreed that this issue is of major importance and that providing guidelines is a valuable undertaking. Dr. Kirschstein said that COPR could form a working group that would include Dr. Castele, Dr. Montoya, and Mr. Yee. Dr. Kirschstein said that COPR should consider forming another working group to work with Ms. Thomas on identifying gaps in protections for human subjects. Ms. Lappin said that conflict of interest could be considered as a subcategory of concerns revolving around human subjects.

In response to a suggestion from Ms. Thomas that these issues can be brought together in a draft document, Ms. Fernandes said that COPR members could provide input to a writer who would prepare such a document. COPR members agreed to establish a working group for this purpose. Debra Lappin agreed to facilitate this group.

Mr. Frohnmayer asked to what audience these documents would be directed, the general public or researchers. In response, Mr. Roehr said that the working group should assemble available information into guidance documents for patients who are potential subjects of clinical research trials. Dr. Montoya said that, in some cases, the goal is also to educate principal investigators (PIs) about issues affecting human subjects. Dr. Maddox said this good idea should be extended, ensuring that not only PIs but also other research team members who are involved in explaining informed consent documents also fully understand what they mean. Ms. Lackritz said that full disclosure is essential because patients are being discouraged from participating in clinical trials.

Dr. Kirschstein said that it might make sense to develop a single document for this purpose and that NIH will need to coordinate this overall effort. Ms. Lappin recommended presenting a patient-oriented document on the NIH Web site, and that COPR should think of itself as representing the public.

Mr. Frohnmayer said that, if the document becomes too prescriptive in language, attorneys representing universities and other research institutions will object to an outside agency attempting to set standards of care. Other participants suggested that formatting the documents as flow charts or as questions-and-answers might circumvent this difficulty. Dr. Montoya said that the document should not be aimed only at the middle class, but should also be directed at others who may be unable to read or represent disenfranchised community segments.

In response to a question from Dr. Maurice Rabb, Dr. Kirschstein said that NIH staff members will facilitate efforts of COPR members to interact with other NIH committees and federal agencies. One recurrent problem is that, despite widespread interest in biomedical research, members of the general public often do not connect such activities with NIH. Ms. Thomas said that her office could prepare a "Talking About the NIH" packet for COPR members to use as a tool for outreach when they talk with outside groups. She also said that members of her staff are working with Mr. Roland McFarland on television projects addressing some of these communication challenges. Ms. Pam Fernandes said that the public could better help in shaping policies if it understood more about NIH.

Additional Planning for the Future of COPR

Ms. Barbara Lackritz asked whether additional structuring of COPR would prove helpful, particularly as new members are recruited to the council. In response to questions about COPR's mission and how new members would be chosen, Ms. Anne Thomas said that information about these matters is contained in the COPR charter, which is available on the NIH Web site. Dr. Kirschstein added that, although the Institute of Medicine (IOM) provided a basic outline for COPR, the charter goes beyond those initial IOM recommendations. In response to a comment from Ms. Vicki Kalabokes, Dr. Kirschstein and Ms. Thomas agreed to draft a COPR orientation handbook for review by council members.

Mr. Roehr said, and others agreed, that setting explicit priorities for COPR by establishing a series of working groups risks excluding potentially important issues from the future agenda. Dr. Luz Claudio said that having a checklist of key issues would be helpful for COPR members. Mr. David Frohnmayer said that potential issues identified during the course of this (April 2000) meeting should be critically reviewed.

Dr. Isaac Montoya said that evaluating the success of COPR presents a challenge, with one possibility being to rely on public opinion polls. In response to a comment from Ms Fernandes, who said that keeping records of COPR accomplishments would help toward such evaluations, Dr. Kirschstein urged all members of COPR also to keep their own list of COPR activities.

In response to a comment from Ms. Lackritz, Dr. Kirschstein recommended that COPR establish a working group to deal with research involving under-served communities. Mr. Roehr said that it is important to undertake this effort across all the Institutes at NIH, as the public perspective changes shape in each different context. Dr. Kirschstein said that Mr. Roehr should take the lead in establishing a group to work with other public advisors at NIH. Dr. Yvonne Maddox said that inviting those public members to a COPR meeting could prove valuable in enlisting their cooperation. Mr. Roehr agreed to form such a working group.

Ms. Thomas asked COPR members to form a working group to develop a process for identifying and recruiting new members to replenish the council as current members depart. Ms. Thomas emphasized that whatever selection process was used to bring new members onto the Council would need to take into account an appropriate balance of many diverse factors, including gender, biomedical interests, and geographic representation. Ms. Kalabokes agreed to coordinate this working group.

Several other items were suggested for inclusion on the agenda of the next meeting: pain research; clustering of diseases and environmental factors; a review of NIH public education and outreach efforts; and how individual Institutes communicate their research achievements. COPR members agreed that responsibility for setting that agenda should not be assigned to a working group but should be settled through conference calls and e-mail messages among all the council members. That next meeting may be structured to permit time for the working groups to assemble separately either before or after the full council meets.

Summary and Conclusions

The Director's Council of Public Representatives (COPR) of the National Institutes of Health (NIH) met on April 6-7, 2000, to consider recent events affecting the visibility of mental health research issues, developments in the Human Genome Project, plans for a new trans-NIH health disparities research plan, several issues involving human subjects protections, and plans for the future activities of COPR.

The COPR acknowledged and commented on these reports, agreed to review several draft documents that NIH officials will prepare, and COPR members agreed to form several working groups to deal with a series of specific issues.

Table of Abbreviations

- **ACD—**Advisory Committee to the Director
- **BRIN—**Biomedical Research Infrastructure Network
- **CDC—**Centers for Disease Control and Prevention
- **COPR—**Council of Public Representatives
- **CSR—**Center for Scientific Review
- **DHHS—**U.S. Department of Health and Human Services
- **FDA—**Food and Drug Administration
- **FY—**Fiscal Year
- **GPRA—**Government Performanceand Results Act
- **HRSA—**Health Resources and Services Administration
- **HPSCRG—**Human Pluripotent Stem Cell Review Group
- **IHS—**Indian Health Service
- **IOM—**Institute of Medicine
- **IRB—**Institutional Review Board
- **NBAC—**National Bioethics Advisory Commission
- **NCI—**National Cancer Institute
- **NCRR—**National Center for Research Resources
- **NCMHD—**National Center on Minority Health and Health Disparities
- **NEI—**National Eye Institute
- **NIAMS—**National Institute of Arthritis and Musculoskeletal and Skin Diseases
- **NIBIB—**National Institute for Biomedical Imaging and Bioengineering
- **NICHD—**National Institute of Child Health and Human Development
- **NIDA—**National Institute on Drug Abuse

- **NIDCR—**National Institute of Dental and Craniofacial Research
- **NIDDK—**National Institute of Diabetes and Digestive and Kidney Diseases
- **NIEHS—**National Institute of Environmental Health Sciences
- **NIH—**National Institutes of Health
- **NIMH—**National Institute of Mental Health
- **NINDS—**National Institute of Neurological Disorders and Stroke
- *NINR—*National Institute of Nursing Research
- **NHGRI—**National Human Genome Research Institute
- **NLM—**National Library of Medicine
- **NSF—**National Science Foundation
- **OCPL—**Office of Communications and Public Liaison
- **OHRP—**Office for Human Research Protections
- **OMAR—**Office of Medical Applications of Research
- **OSP—**Office of Science Policy
- **OTT—**Office of Technology Transfer
- **PI—**Principal Investigator
- **RFA—**Request for Applications

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DIRECTOR'S COUNCIL OF PUBLIC REPRESENTATIVES

October 31–November 1, 2000 Meeting Minutes

Fourth Meeting of the Director's Council of Public Representatives
Tuesday-Wednesday, October 31-November 1, 2000
8:30 a.m.
Building 31C, Conference Room 6
National Institutes of Health
Bethesda, Maryland

The Council of Public Representatives convened its fourth meeting at 8:30 a.m., Thursday, April 6, Building 31, Conference Room 6, National Institutes of Health, Bethesda, Maryland. The meeting was open to the public.

Dr. Ruth Kirschstein, Chair, Council of Public Representatives, and Acting Director, National Institutes of Health (NIH), presided.

COUNCIL MEMBERS PRESENT:

- Luz Claudio
- Melanie C. Dreher
- Pam Fernandes
- Vicki Kalabokes
- Barbara Lackritz
- Joan Lancaster
- Debra R. Lappin
- Roland McFarland
- Isaac Montoya
- Rosemary Quigley
- Bob Roehr
- Thomas Vaalburg
- Doug Yee

COUNCIL MEMBERS ABSENT:

- Michael D. Anderson
- Theodore Castele
- Robin Chin
- Mary desVignes-Kendrick
- David Frohnmayer
- Lydia Lewis
- Maurice F. Rabb

AD-HOC PARTICIPANTS:

- Marilyn Benoit
- Ellen Grant Bishop
- Evelyn Bromet
- Bob Martin
- Rodrigo Munoz

- Leonard Tamura

Executive Summary

Dr. Ruth Kirschstein began the Fourth Meeting of the Director's Council of Public Representatives (COPR) by briefing COPR members on uncertainties facing NIH because the Congress has not yet passed an appropriations bill and thus is funding NIH on the basis of a continuing resolution, meaning current resources are based on levels set for FY 2000. In addition, legislation is pending to establish a new NIH Institute of Bioimaging and Bioengineering. *(Note: This legislation was signed into law on December 29, 2000).* She also mentioned several appointments made recently at NIH as well as other appointments that are pending, reviewed many awards including recent Nobel Prizes that went to NIH grantees, and noted that a new vaccine research facility is now in operation on the NIH campus.

Dr. Kirschstein said that the NIH draft strategic plan on health disparities research is posted on the NIH Web site, and will be implemented principally by the NIH Office for Research on Minority Health *(Note: now the National Center for Minority Health and Health Disparities Research).* In addition, the final version of the NIH Stem Cell Research Guidelines was published on August 25, 2000, but NIH has not yet funded any research projects in this area. She also summarized recommendations from an ACD working group that reviewed gene transfer clinical research, thanked the three members of COPR who participated in that review, and also expressed gratitude to other COPR members who were involved in the annual Government Performance and Results Act (GPRA) review of NIH.

Several COPR members described recent COPR-related activities, including Dr. Montoya who is involved in extensive outreach activities; Ms. Quigley, Mr. Roehr, and Ms. Lappin, who participated with members of the ACD in a review of gene transfer studies; Dr. Dreher on community reactions to human genetics research; Ms. Lancaster on a site visit to Tennessee made by a delegation from NIH led by Dr. Maddox; and a future clearinghouse meeting sponsored by the NIH National Institute of Dental and Craniofacial Research that Ms. Kalabokes planned to attend.

Dr. Barry Kramer, the new Director of the NIH Office of Medical Applications of Research (OMAR), reviewed how this office develops consensus reports on medical applications and practices, and outlined several reforms that are being instituted.. For instance, he said that it might be useful to include public representatives as members of a discussion group being formed to review topics of potential interest for this office. In addition, the NIH OMAR plans to develop a curriculum for the news media describing how scientific evidence is evaluated.

Mary McCabe, Director of the Office of Education and Special Initiatives, NIH National Cancer Institute (NCI), described two recent clinical trials initiatives at the federal level, one involving efforts to improve informed consent procedures and the other to provide coverage to participants in clinical trials through the Medicare Program. She said that an NIH working group recently developed a prototype informed consent document to improve the understanding of potential participants in clinical trials. One special feature of this document is that it presents risks for the entire medical regimen to which a participant may be subject, according to Ms. McCabe. Meanwhile, based on a memorandum issued by President Clinton on June 7, 2000, Medicare was to begin covering expenses associated with clinical trials as of September 11, 2000, thereby widening opportunities for studying medical conditions among the elderly.

Dr. Tom Murray, President of the Hastings Center and a member of the National Bioethics Advisory Commission (NBAC), said that NBAC has been methodically reviewing the system for protecting human subjects who participate in research programs. The current NBAC Oversight Project involves reviewing the adequacy of the entire regulatory framework, including the Common Rule and the Institutional Review Board (IRB) system, as well as a series of specific issues. Key recommendations under NBAC consideration include: putting all oversight, both public and private, under a single federal office or agency with a uniform set of regulations; establishing a new framework for analyzing the vulnerabilities of subjects; developing a fair system for compensating subjects who are injured during their participation in research projects; better educating IRB members and investigators; increasing the participation of non-experts and personnel who are unaffiliated with the respective host institutions in the IRB system; instituting an IRB accrediting system; and providing greater scrutiny for research protocols that entail paticularly high risks for participants.

Dr. Greg Koski, Director of the HHS Office for Human Research Protections (OHRP), said that the research oversight system has limited resources with which to respond to specific incidents or to develop general policy recommendations and guidelines. Meanwhile, IRBs face a considerable challenge in trying to translate policy recommendations from OHRP and elsewhere into practice. OHRP is instituting several policy changes, including moving away from confronting IRBs, developing a certification system, and changing IRBs to be more representative of the broader community and the public. OHRP is also developing a comprehensive registry of IRBs and is asking the Institute of Medicine to help OHRP monitor its own performance as it implements various reforms.

At the end of the first day, COPR members engaged in a wide-ranging discussion of measures to protect patients and conflict-of-interest issues with Dr. Koski, Dr. Murray, and Ms. McCabe. On the second day of the meeting, COPR members and NIH staff discussed a wide range of issues pertaining to the council's current and future activities. That discussion began with a review of information materials about NIH that COPR members may draw upon when they visit various communities and are asked to describe NIH programs and activities. This discussion also broached substantive issues on the agenda of the previous day, including a lengthy colloquy on the NIH initiative to support research on health disparities and the need to secure increased funding to support this expanding effort.

COPR members representing five working groups summarized the current status of their activities. These discussions included brief reports from Ms. Lackritz (presented by Ms. Anne Thomas) on clinical trials, Mr. Roehr and Ms. Kalabokes on outreach efforts aimed at other public members participating in NIH groups, Dr. Montoya on health disparities and underserved populations, Ms. Kalabokes on COPR membership succession, and Ms. Lappin on protections for people participating in research.

Ms. Thomas led a discussion of the draft guidebook, *History, Values and Operations of COPR,* that is intended to serve current and future COPR members as well as others who are interested in the council's structure and activities. She also asked COPR members to consider several options as to how they should go about decision-making, and the group concluded that, although it will strive for consensus, a simple majority vote would be sufficient for making recommendations, with allowance for members in the minority to issue dissenting opinions. Ms. Thomas said that the next set of six new COPR members will be named in January/February, and Ms. Kalabokes said that her working group plans to recommend steps for broad distribution to identify candidates for COPR membership beyond this next selection, which primarily identified candidates from among the COPR Associates.

NIH Director's Report

Dr. Ruth Kirschstein began the Fourth Meeting of the Director's Council of Public Representatives by briefing COPR members on uncertainties facing NIH because the Congress has not yet passed an appropriations bill for fiscal year (FY) 2001 but is funding NIH on the basis of a continuing resolution, meaning that current resources during the early part of FY 2001 are based on levels set for FY 2000. These lower spending levels remain in force despite apparent congressional plans to continue increasing the NIH budget on a course to double its budget within a five-year period. She said that the House of Representatives Appropriations Subcommittee for Labor, Health and Human Services held a hearing in September (it had been scheduled for May, but was postponed) during which several Nobel Laureates testified on behalf of NIH, calling for its continued strong support. In addition, several younger scientists also testified, including two young women investigators, and representatives of patient advocacy groups.

Dr. Kirschstein reminded COPR members that NIH Acting Deputy Director Yvonne Maddox and NIH National Institute of Allergy and Infectious Diseases (NIAID) Director, Anthony Fauci, co-chaired a trans-NIH Working Group that developed a draft strategic plan on health disparities research. That draft is now posted on the NIH Web site, and it will be implemented by the NIH Office for Research on Minority Health *(Note: now the National Center for Minority Health and Health Disparities Research),* as well as by the individual Institutes and Centers.

Dr. Kirschstein said that legislation is pending to establish a new NIH Institute of Bioimaging and Bioengineering, which would encompass the work of the current Office for such activities known as the Office of Bioimaging, Bioengineering, and Bioinformatics (OBBB).

Dr. Kirschstein said that several appointments were made recently at NIH, including the appointment of Dr. Lawrence Tabak from the University of Rochester to Director, NIH National Institute of Dental and Craniofacial Research (NIDCR) and Dr. Raynard Kington from the Centers for Disease Control and Prevention (CDC) to Director, NIH Office of Behavioral and Social Sciences Research. Additional appointments are pending to Director, NIH National Eye Institute, from which Dr. Carl Kupfer recently retired; Director, NIH Office of AIDS Research, from which Dr. Neal Nathanson recently resigned; and Director, NIH Office of Equal Opportunity.

Meanwhile, a new building dedicated to vaccine research recently opened on the NIH campus. Research activities in this building, directed by Dr. Gary Nabel, will focus initially on developing an AIDS vaccine within the next decade, but other projects will include research on malaria and tuberculosis vaccines. Other signs of intensified activity at NIH came during the summer when hundreds of students from the high school to the postdoctoral level were working on the Bethesda campus.

Several sets of honors were recently bestowed on investigators with links to NIH, including the 2000 Nobel Prize for Physiology or Medicine to Paul Greengard and Eric Kandel, who were NIH grantees, as well as Arvid Carlson, who worked at NIH early in his career; and the Nobel Prize in economics, which went to investigators who were supported by NIH grants. This year's Lasker Award went to NIH investigator Dr. Harvey Alter for his work on hepatitis C and other efforts to safeguard the blood supply. Moreover, two investigators in the NIH Intramural Program received Presidential EarlyCareer Awards.

NIH published a final version of its Stem Cell Research Guidelines on August 25, 2000, after receiving a large volume of comments, but has not yet funded any projects involving human pluripotent stem cells, according to Dr. Kirschstein. The guidelines call for establishing a special advisory process to review research proposals involving unique human stem cell lines, and to report on these activities. The Senate Committee on Appropriations, Subcommittee on Labor, Health and Human Services and Education, which is chaired by Senator Arlen Specter (R-PA), has held several hearings on this issue. In response to questions from several COPR members, Dr. Kirschstein said that the special reviews will focus on unique stem cell lines and that the guidelines apply only to research being funded by the NIH.

Dr. Kirschstein said that three COPR members participated as part of a working group of the NIH Advisory Committee to the Director (ACD) that reviewed the role of NIH oversight in gene transfer research. That working group developed a series of recommendations regarding coordination of such oversight with the Food and Drug Administration (FDA), particularly in reporting adverse events. The ACD as a whole officially accepted that report on the basis of a meeting held by telephone in September. Principal recommendations include that researchers agree to provide the NIH Recombinant DNA Advisory Committee (RAC) with notification of protocol changes before enrolling patients to ensure RAC review before a clinical trial begins, that NIH attempt to harmonize its requirements for reporting adverse events with those of FDA, and that RAC establish a standing working group to review serious adverse events. The NIH Office of Biotechnology Activities, which administers RAC activities, has published these recommendations for public comment and plans to use them to amend the NIH Recombinant DNA Guidelines.

Dr. Kirschstein reviewed recent activities of COPR members, including the participation by several of them in the recently completed review of NIH that was mandated by the Government Performance and Results Act (GPRA), involvement in the June NIH retreat for budget planning, participation (by Vicki Kalabokes and Melanie Dreher, Ph.D.) in performance reviews of several NIH Institute Directors, and participation (by Maurice Rabb, M.D.) as an advisor of PubMed Central and in personnel searches.

COPR Members Report on COPR Activities to NIH Director

Dr. Montoya on Public Outreach

Dr. Isaac Montoya described several recent occasions during which he represented COPR while participating in NIH-related activities. Thus he attended meetings, including with Elaine Baldwin of the NIH National Institute of Mental Health who directs the Outreach Partners program, which communicates science-based information on mental health to people in every part of the country, NIH advisory council meetings, a meeting devoted to conflict-of-interest issues, and a scientific meeting focused on how HIV affects elderly populations. He also visited several universities to present them with information about COPR and NIH, met with the Director of the American Society of Clinical Laboratory Science, and attended several regional meetings of community and religious groups to discuss participation by volunteers in clinical trials.

Dr. Montoya said that those visits indicate to him how poorly the clinical trials process is understood, but that recently held town hall meetings are helping to correct some of those misunderstandings. He also said that he has received many inquiries about protections for subjects participating in clinical trials and about health disparities, and he has tried to refer those callers to appropriate officials at NIH.

Ms. Quigley and Others on Gene Transfer, Other Clinical Trials-Related Issues

Ms. Rosemary Quigley summarized some of her experiences as one of several COPR members who served on the NIH Working Group on Gene Transfer Clinical Trials. The Working Group concluded that the intense focus by the public on gene transfer research helps to set it apart from other types of clinical research, according to Ms. Quigley. She also said that it was valuable for several individuals to be representing the general public on the Working Group because even the bioethicists who serve on that body appear to bring a distinct viewpoint to its deliberations, but the public members can better represent the public at large. She said that the Working Group was trying to amend the process for reviewing research on gene transfer to improve its oversight without making the process too formal. The scope of that oversight remains limited to those research proposals involving genuinely novel activities, about ten percent of overall activities in gene transfer clinical research.

Ms. Quigley said that the Working Group also recommended that RAC reviews be conducted before any patients are enrolled in a particular clinical trial and that communications improve between the NIH RAC and FDA. However, those efforts are complicated because the NIH RAC and FDA adhere to different, mandated procedures when reporting serious adverse events associated with clinical trials, making it difficult to reconcile the differences in their current practices.

Mr. Robert Roehr said that, although he supports the NIH Working Group's recommendations, he would like to see data from gene transfer clinical trials treated more openly, and for the review process to be modeled after NIH rather than FDA practices. He said that he favors increased public participation, and suggested that a more open process will encourage patients to enroll in clinical trials. Subjects are more likely to protect themselves if they better understand experimental procedures through a process for informed consent that is more open.

Ms. Debra Lappin said that having COPR members serve on the Working Group was valuable, and that their presence helped to demarcate important differences between the NIH and FDA. She agreed with Mr. Roehr that NIH should go further toward openly reporting serious adverse events associated with gene transfer clinical trials. Another important component of such reporting would be for NIH to present data that might indicate trends across different clinical trials. This same approach could also prove valuable in other areas of innovative clinical research, such as clinical trials involving stem cells, or wherever else sensitive issues of patient protections might arise.

Discussion

Dr. Kirschstein said that there is intense interest in conflict-of-interest issues as they pertain to clinical trials and protecting subjects who participate in them. Dr. Kirschstein, FDA Commissioner Jane Henney, and OHRP Director Greg Koski participated in a conference focused on these issues last August. An effort is under way to reconcile differences in FDA and NIH requirements for reporting adverse events, an effort that is made more challenging because of cultural differences between the two agencies, according to Dr. Kirschstein. Adverse event reporting is further complicated because many participants in clinical trials are ill because of their underlying diseases, meaning that many of the adverse events arise from the medical condition rather than the experimental interventions being investigated.

Ms. Quigley said that data on adverse event data should be made public, even if that information discourages potential participants from taking part in clinical trials. Dr. desVignes-Kendrick agreed, noting that public trust may be eroded if participants are not fully informed about adverse events. Mr. Roehr said that such information should be made public in a timely fashion, despite technical and proprietary challenges in doing so. He said that the pharmaceutical industry, which prefers to delay the dissemination of such information, is facing a paradigm shift. Ms. Quigley said that FDA officials sometimes are put in the awkward position of being aware of studies whose results are kept proprietary even though disclosure of those results might enlighten discussions focused, for example, on adverse events arising from clinical trials under sponsorship of other, perhaps competing, companies.

Dr. Dreher on Genetic Research Issues

Dr. Dreher discussed a series of public meetings sponsored by the NIH involving members of ethnic and religious groups and their views on human genetics research. The tenor of these discussions varies widely, with some community members very eager to cooperate with researchers, while other groups are concerned that the results of genetic testing will be used to stigmatize their members. As these research efforts expand, additional discussions can be anticipated, according to Dr. Dreher. Although there appear to be no ready or simple answers to the many concerns now being expressed, open forums provide a valuable means to confront them.

Ms. Lancaster, Dr. Maddox on Tennessee Site Visit

Ms. Joan Lancaster described her recent role in initiating an NIH site visit to Eastern Tennessee. One of COPR's interests for outreach involves bringing NIH staff and resources out to states that have not previously participated fully in the research programs of the NIH. Ms. Lancaster recently coordinated a successful event in East Tennessee with Dr. Ron Geller from the NIH Office of Extramural Research. Ms. Lancaster organized an extremely impressive planning group that included medical centers, hospitals, researchers, and several local universities.

Dr. Yvonne Maddox, NIH Acting Deputy Director, also attended the site visit and led a group of NIH representatives on a visit to some of these Tennessee facilities where they discussed plans for NIH research programs on health disparities with members of that community. Dr. Maddox said that the interactions between the NIH delegation and the representatives of the local community, including medical school faculty, nurses and other health care professionals, and also members of the local news media, provided valuable insights about conducting such research with the cooperation of local communities.

Ms. Kalabokes on NIDCR Presentation

Ms. Kalabokes said that she would shortly be talking on COPR's role and structure at a clearinghouse meeting arranged by the NIH National Institute of Dental and Craniofacial Research (NIDCR) at which members of the public and scientists were scheduled to discuss research opportunities of special interest to NIDCR.

Update on the Office of Medical Applications of Research (OMAR)

Dr. Kirschstein said that members of the NIH Advisory Committee to the Director recently reviewed the NIH Office of Medical Applications of Research (OMAR),

recommending several changes in the way in which consensus statements are developed. She then introduced Dr. Barry Kramer, who was recently recruited to be the new Director of OMAR.

Presentation by Dr. Barry Kramer, Director, OMAR

Dr. Kramer said that NIH OMAR develops formal assessments of medical applications, basing decision-making on solid evidence that is carefully weighed during consensus development conferences. Over its history, the NIH OMAR has hosted some 110 such conferences, each of which is sponsored by one or more of the NIH Institutes and Centers. The choice of a topic is dictated by several criteria, including its importance to public health, whether there is a gap or controversy between current knowledge and common medical practice, whether there is an adequate base of scientific information, and whether there is sufficient public interest and investment of resources for health care in a specific area.

Dr. Kramer said that the design of each consensus conference follows a similar general outline once a topic is selected. Thus, a planning committee drafts questions to be addressed and nominates experts to participate in the formal consensus process, convenes smaller panels once or twice before the conference to refine critical issues, oversees the conference itself while allowing for broader public input before the scientific jury develops the formal consensus statement, and meets following the conference to revise the consensus statement as needed.

Currently, the operations of the NIH OMAR are being adjusted and expanded, according to Dr. Kramer. For instance, OMAR is putting together a discussion group whose rotating membership can serve as a sounding board for topics of potential interest for this office. He said that it will be useful to include public representatives as members of this sounding board, such as from the NIH COPR as well as from other federal agencies with health-related missions.

Another new activity for the NIH OMAR will be to develop a curriculum for the news media that will help journalists appreciate some of the differences between weighing solid evidence and basing judgments on strongly held opinions, according to Dr. Kramer. He said that members of the medical community recognize several levels of evidence with a distinct hierarchy in terms of credibility, with randomized control clinical trials considered at the top, followed by controlled trials without random selection, case-controlled cohort studies, ecological and descriptive studies, and opinions of reputable experts. Similarly, there is a hierarchy among different types of clinical treatment trials.

Dr. Kramer encouraged COPR members to participate more fully in the ongoing discussions of the sounding board group, which convenes more than 3 times annually to advise the NIH OMAR. He said that he would attend future meetings of COPR and would supply additional materials to the council.

Discussion

Dr. Dreher said that other professionals within the health care community, such as members of the nursing community, could provide valuable contributions to the NIH OMAR as it develops evidence-based decisions. In response, Dr. Kramer welcomed her suggestion and said that other health professionals, including experts in the methodologies of public health, participate in consensus development conferences.

In response to a question from Ms. Lappin about the long-term follow-up to consensus development conferences, Dr. Kramer said that it is a formidable challenge to evaluate the practical outcomes of NIH OMAR activities. Even designing a procedure for undertaking such evaluations represents a serious challenge. As a practical matter, the office tries to determine whether medical practices change following particular consensus development conferences, and it enlists the help of other federal agencies that keep track of such matters. In some specific cases, there have been follow-up efforts to redirect medical practitioners who implemented recommendations from consensus conferences in an erroneous fashion.

In response to several questions about how statements issued from such consensus development conferences are put to use locally or by lawyers as part of lawsuits, Dr. Kramer said that, although such information may be misused medically or exploited as part of civil lawsuits, they are not presented as official NIH positions on medical practice. Instead, consensus development statements represent the collected views of experts and are not meant to carry the weight of law or to represent policy positions of the NIH.

Making Informed Consent in Clinical Trials Understandable, as well as Other Important Updates in Clinical Trials

Presentation by Mary McCabe, R.N., M.A., Director, Office of Education and Special Initiatives, National Cancer Institute (NCI)

Ms. McCabe described two recent clinical trials initiatives at the federal level, one involving important efforts to improve procedures for informed consent and the other to provide coverage to participants in clinical trials through the Medicare Program. After providing a brief account of the history of this issue, she described details of recent efforts to improve informed consent procedures, some of which was developed on the basis of feedback provided by focus groups. Fundamental to the system is the principle that each individual who considers participating in a clinical trial has the right to authorize experimental treatment (or other inquiries) by health professionals through an informed consent process that requires full disclosure on the professional's part, comprehension on the part of the individual about the procedures and risks, and a decision made on a voluntary basis.

Ms. McCabe said that many of the informed consent documents now being written and used as part of consent procedures for clinical trials have grown increasingly complex, making them difficult to understand. For this and other reasons, an NIH working group was formed to develop a prototype document for informed consent in clear and simple language that could improve the understanding of potential participants in clinical trials and serve as a better tool for educating them about the experimental procedures in which they are being asked to participate. The prototype was designed to delineate—without overstating—potential benefits to participants in clinical research projects, and describes both risks and benefits of those experimental procedures in the context of standard care administered to patients with the medical condition that brought them into the clinical trial.

One special feature of the prototype document is that it presents risks for the entire medical regimen to which a participant may be subject, rather than referring separately to each and every specific drug or procedure to which they may be subject, according to Ms. McCabe. Moreover, risks are ranked in terms of likelihood. The document further specifies that any risks associated with the reproductive system be described for both men and women who might participate. Other

recommendations for informed consent documents include that they provide supplemental information to potential participants, be written clearly in a manner that is culturally sensitive, and that they promise to notify participants as new information related to the experimental procedure is made available. The documents also describe the likely timetable of events for participants in clinical trials.

Ms. McCabe later said that a memorandum issued by President Clinton on June 7, 2000, authorized Medicare to begin covering expenses associated with clinical trials as of September 11, 2000. This new policy will widen opportunities for studying many medical conditions among the elderly because it authorizes broad coverage of their medical costs through all phases of clinical trials. She said that officials from several federal agencies are working through some of the details needed to implement this new policy. Eventually, they plan to develop a comprehensive registry of clinical trials that are covered under the aegis of Medicare.

Discussion

Dr. Kirschstein said that federal officials are considering ways to deal with informed consent documents for participants who may not fully understand English.

In response to a question from Dr. Ted Castele about whether informed consent requires face-to-face discussions, Ms. McCabe said that such procedural decisions rest with local members of Institutional Review Boards (IRBs).

Mr. Roehr said that the lines between standard medical care and research-associated care can become blurred. He also asked whether candidate participants should be routinely notified of alternative clinical trials in which they might participate. Ms. McCabe said that the development of a comprehensive clinical trials database could help to provide investigators with information about alternative clinical trials and that such information could be shared with candidate participants, and such information already is often provided.

Ms. Barbara Lackritz, who has been involved as a patient in clinical trials, recommends that anyone considering participating in such trials obtain and read copies of the entire experimental protocol. In response to comments from Ms. Lydia Lewis about candidate participants whose decision-making capacities may be impaired for one reason or another, Ms. McCabe said that the NIH working group extensively discussed this issue and recognized that decision-making can be impaired for a wide variety of reasons.

Dr. Montoya said that, although the prototype document is valuable, it is also important to tailor it to the specific issues that arise for any particular experimental protocol. Ms. McCabe agreed, saying that the working group did not want to present a simple check-off list of issues.

In response to questions and comments from Ms. Quigley and Dr. desVignes-Kendrick about children as experimental subjects in clinical trials, Ms. McCabe said that the working group held discussions with individuals who had participated as children in clinical trials to understand some of the special issues that arose from those experiences. One result is that the working group is developing a document that takes into account some of the special needs of children, particularly adolescents, in the context of clinical trials.

Dr. Montoya pointed out that NIH requires all investigators to learn about procedures for informed consent and related matters, and provides information for that purpose as part of its Web site.

In response to a comment from Mr. Roehr about the managed care system, Ms. McCabe said that it is important to educate medical gatekeepers about informed consent and other issues relevant to clinical trials.

In response to a question from Mr. Thomas Vaalburg about international input on informed consent, Ms. McCabe said that the NIH working group members focused on concerns in the context of U.S. clinical trials, but that they benefited from contacts with representatives of several countries in Europe.

In response to a question from Ms. Lappin about potential coercion that could arise from extension of Medicare to cover clinical trials, Ms. McCabe said this possibility is not unique to Medicare, but she also said that care of a participant cannot be dropped simply because someone drops out of a clinical trial.

In response to a question from Mr. Roehr whether the new Medicare policy on clinical trials would be extended to include other groups of patients besides the elderly, such as those being supported under Medicaid programs, Ms. McCabe said that discussions on such matters are under way. She also said that implementing these changes involves wonderful cooperation among several federal agencies. Dr. Kirschstein said that these changes to enable Medicare patients to participate in clinical trials are extraordinary and that they are being implemented at a rapid pace. In response to a question from Mr. Doug Yee about the cost of implementing these policy changes, Ms. McCabe said that federal officials are tabulating the projected costs but their first estimates indicate that the incremental costs for experimental procedures on a clinical trial will not be very far above the costs of standard care, indicating the new Medicare policy is fiscally responsible.

Update from a Member of the National Bioethics Advisory Commission (NBAC) on NBAC's Human Research Protections Report

Presentation by Tom Murray, Ph.D., President, Hastings Center and Member of the National Bioethics Advisory Commission

Dr. Murray said that there are fundamental problems with the system for protecting human subjects who participate in research programs. For instance, institutional review boards (IRBs) are overworked, under a great deal of pressure, and in a virtual state of siege. Moreover, IRBs are not particularly good at monitoring research in progress. He also said that the Common Rule, which serves as the fundamental principle for protecting subjects involved in research projects sponsored by the federal government applied to some 17 federal agencies, is unwieldy because agreement among all the parties is required to make any changes to it. In addition, there is a general concern that the informed consent process is not working properly because it is being handled in an increasingly formulaic manner.

Dr. Murray said that the members of NBAC, which was established in 1995, have been methodically reviewing these matters, developing reforms that are described in a series of reports. NBAC members already have completed several reports through a transparent process that is open to the public. The reports focus on several topics, including issues of informed consent for research involving subjects who are mentally impaired, concerns revolving around the use of human tissues and other biological materials, and clinical research undertaken in developing countries.

The current focus of NBAC efforts is the Oversight Project, its most ambitious undertaking to date, according to Dr. Murray. The goal is to promote good research consistent with ethical standards, while fully protecting the safety of human subjects. He said that the project involves reviewing the adequacy of the current regulatory framework including the Common Rule and the IRB system, as well as a series of specific issues such as the scope of human subject protections, the extent to which research in the private sector is covered by federal rules, a weighing of relative risks and potential benefits to research subjects, informed consent procedures, privacy and confidentiality safeguards, and measures to protect cohorts of subjects that are unusually vulnerable. In addition, NBAC is reviewing several issues related to oversight, including how to meet specific educational needs of IRB members and of researchers, how to improve the monitoring of ongoing research projects, whether reviews can be streamlined in cases of multi-institutional cooperative projects, how to institute accountability measures such as accrediting of IRBs, and how to develop adequate resources to better support IRBs.

There are several key recommendations under NBAC consideration. They include: putting all oversight, both public and private, under a single federal office or agency with a uniform set of regulations; establishing a new framework for analyzing the vulnerabilities of subjects; developing a fair system for compensating subjects who are injured during their participation in research projects; better educating IRB members and investigators; increasing the participation of non-experts and personnel who are unaffiliated with the respective host institutions in the IRB system; instituting a system for accrediting IRBs; and providing greater scrutiny for research protocols that entail especially high risks for participants so that resources are directed to areas where oversight is most needed.

Discussion

In response to a question from Ms. Lappin about conflicts of interest, Dr. Murray said that NBAC recently drafted recommendations that focus on conflicts of interest among members of IRBs; that draft will soon be posted on the NBAC Web site for comments, along with another draft report on international research.

In response to a question from Ms. Lackritz as to whether NBAC has considered the issue of solicitations over the Internet to individuals in disease groups to participate in research projects, Dr. Murray said that, although NBAC has not spent much time on this issue, the Hastings Institute is developing a code of ethics pertaining to use of the Internet for certain research purposes.

In response to several questions about where in the federal government to locate an agency with comprehensive oversight and authority over IRBs, Dr. Murray said that NBAC might not make such a specific recommendation; its draft recommendation merely states that these responsibilities should be centralized.

In response to questions from Dr. Rabb and Dr. Montoya about the membership of IRBs and whether individuals should be drawn from outside a particular IRB's institution, Dr. Murray said that NBAC does not have comprehensive data about the make-up of IRBs. He also said that New Zealand mandates that IRB members be unaffiliated with the institutions on whose boards they serve. Although NBAC is inclined to recommend that some members of each IRB come from outside its institution, it has not recommended what that proportion should be.

Mr. Roehr asked what NBAC recommends about better informing individuals who participate in clinical trials about the experimental plans. Dr. Murray said that it is important for the public to better understand the nature of clinical trials, particularly to have a clearer picture that experimental procedures may not necessarily prove beneficial to participants in clinical trials.

In response to a question from Mr. Yee about the relative merits of the U.S. IRB system compared to protections afforded individuals in other countries, Dr. Murray said that, although the United States pioneered many fundamental concepts in bioethics for protecting human subjects in research, some countries now have surpassed the U.S., particularly in terms of monitoring research projects once they are under way.

New Directions for the Office for Human Research Protections (OHRP)

Presentation by Greg Koski, Ph.D., M.D., Director, OHRP

Dr. Koski said that investigators working with human subjects find themselves in a very different environment now compared to 30 years ago when the rules for oversight were first developed. One major difference is the enormous growth in the overall research investment compared to relatively minor changes in research oversight. Moreover, much of the research investment comes from the private sector.

The system for research oversight has limited resources with which to respond to specific incidents or to develop general policy recommendations and guidelines, according to Dr. Koski. Meanwhile, investigators and IRBs need to see this system as something other than an administrative add-on, and more as an integral part of they way they operate. The IRB system has the burden of making oversight measures work effectively, and those who serve on IRBs are supposed to conduct themselves impartially, although they cannot fully divorce themselves from the research contexts in which they operate.

The IRBs face a considerable challenge in trying to translate policy recommendations from OHRP and elsewhere into practice, according to Dr. Koski. One valuable measure to help them meet that challenge would be to make the system simpler and more uniform than it now is. He said that this goal can be achieved, in part, by pulling this oversight by many federal agencies involved in research involving human subjects under a single administrative umbrella. The Department of Health and Human Services took an important step in that direction by moving and changing the predecessor Office for the Protection from Research Risks (OPRR) from NIH to HHS, where it became OHRP. Even so, although 17 federal agencies have adopted the HHS-generated regulation known as the Common Rule, there is no common federal infrastructure to oversee its implementation and enforcement. He said that one of his goals is to make the Common Rule work as a common rule.

FDA is among the agencies that adopted the Common Rule and mandates that it be applied to privately sponsored research that comes under its jurisdiction, mainly that research funded by industry aimed at the development of new biomedical products. Because it is housed within HHS, OHRP has an opportunity to work directly with FDA officials, and this recent administrative change, namely that involving the former NIH OPRR and the new OHRP, has led already to a great deal of cooperation and progress, according to Dr. Koski. In addition to FDA and NIH, several other HHS agencies account for more than 80 percent of federally sponsored research involving human subjects. Hence, HHS appears to be an appropriate administrative home for exercising federal-wide oversight over such research. Dr. Koski said that, although legislation is pending that would formally mandate such federal-wide oversight, there is not a great deal of enthusiasm in the Congress to fund a new federal agency for this oversight purpose.

Meanwhile, OHRP is instituting several policy changes, according to Dr. Koski. One consists of moving away from confronting IRBs and instead trying to foster a broad sense of responsibility at all levels of this system for protecting human subjects. The underlying goal is that every individual within the system will come to gauge what needs to be done, what training is appropriate, and what other measures should be taken to ensure that investigators are properly trained and human subjects are fully protected when they participate in research. Part of this change will entail moving to a certification system, applying appropriate criteria to clinical investigators and to IRB members. Another change being considered is to change IRBs from having members taken exclusively from single institutions, where conflicts of interest are more prone to develop, and toward becoming unaffiliated with specific institutions and more representative of the broader community and the public.

For these measures to work, it will be essential to develop a more uniform, national system that is based on meeting performance standards that are broadly recognized according to Dr. Koski. Moreover, the system needs to operate not on a post-hoc, compliance basis, but by protecting human subjects before they enroll and while they participate in research projects.

To help in implementing a system of uniform accreditation, Dr. Koski has asked the Institute of Medicine (IOM) to develop accreditation standards. The IOM recommendations are expected to be ready by April 2001. Although these standards are being developed for OHRP, the eventual goal is for them to be accepted and implemented across all federal agencies and by the private sector.

OHRP also is developing a comprehensive registry of IRBs, one that will provide details about the types of research that each one oversees, membership, and accreditation data-in short, a national database on the IRB system that could provide a basis for becoming a "safety monitoring board that is integrated," according to Dr. Koski. One goal is to design this system to be capable of monitoring across different clinical trials for adverse events as a way of providing alerts and very quickly preventing additional injuries to individuals who are enrolled in clinical trials.

IOM will also help OHRP to monitor its own performance as it implements various reforms, according to Dr. Koski. In addition, OHRP not only will use assurances for individual institutions to help them evaluate IRB performances, but will also develop new measures to hold IRBs accountable and to help them in meeting performance standards, such as through enhanced education efforts. Efforts also will be made to educate the public about the broad benefits that come from supporting and participating in clinical research.

COPR Discussion on Human Research Protections

with Greg Koski, Ph.D., M.D., Tom Murray, Ph.D., and Mary McCabe, R.N., M.A.

In response to a question from Dr. Montoya about resources for training investigators, Dr. Koski said that materials for training investigators about issues related to patient protection are available through his office and that a new handbook is being prepared. He also said that efforts are under way to heighten awareness of these issues and to use novel approaches for educating investigators about these important matters.

In response to a question from Mr. Vaalburg about industry, Dr. Koski said that clinical research regulated by FDA comes under OHRP jurisdiction and is subject to its guidelines for protecting human subjects. This jurisdiction thus extends to the pharmaceutical, biotechnology, and medical device manufacturing industries, and several industry sector organizations are working directly with OHRP on these issues.

Ms. Lappin praised the proposed reforms in patient protection but also questioned whether there are adequate penalties or whether patients can exert any pressure on investigators to comply with safety measures. Dr. Koski said that consumers and patient groups can do a great deal already; indeed, their willingness or reluctance to participate in clinical trials represents a potent force. He also said that OHRP's authority to enforce compliance is not being put on the back burner or being weakened, and his office is contacting IRBs about their practices and is visiting various research sites, with plans to do so more frequently than did the predecessor organization, the NIH OPRR.

Ms. Lydia Lewis praised Dr. Koski for his enthusiasm but said that she was cynical about the clinical research enterprise, explaining that because researchers and industry benefit from such activities more than do patients, other measures are needed to protect patients who participate in clinical trials. Ms. Quigley added that institutions will tend to overlook guidelines to protect humans if they see those protections as not serving the institution's interests and asked whether enforcement procedures that are more potent were being contemplated. In response, Dr. Koski said that his personal experiences in Boston during the past decade provided him with a great deal of practical experience in patient protection issues and convinced him that not every injury can be prevented. Moreover, he acknowledges that industry benefits from patients who cooperate and participate in clinical trials to evaluate commercial products. With such a considerable potential for conflicts of interest, OHRP is developing points-to-consider guidelines to help in preventing such abuses. He also said that OHRP wields enormous power over academic institutions because they depend on federal funds.

Mr. Yee said that the idea of using carrots rather than sticks to induce better compliance with measures to protect patients in clinical trials is a sound idea. Dr. Koski said that accreditation programs will be instituted in the future, and that providing standards of excellence for everyone to follow will be a valuable means for improving patient protections, particularly if federal enforcement undergirds that accreditation. He also pointed out that NBAC is preparing similar proposals independently, a development that helps to validate the ideas underlying these proposals.

Dr. Koski also said that an advisory committee is being established to meet publicly on a quarterly basis and to provide OHRP with input from the research community and the public.

Dr. Murray praised Dr. Koski for his moral passion, creativity, and energy. He said that NBAC has recommended that Congress enact legislation that will extend measures for protecting human subjects to everyone, regardless of whether the research in which they are participating is funded privately or publicly. He said that NBAC expects to release its major draft report before the end of 2000 and noted that some of the commission's recommendations to Congress and to federal agencies will be pointed.

In response to Mr. Vaalburg, who recommended that focus groups be used to learn more about the views of human subjects who participate in research, Dr. Koski

said that his goal is to improve the current system and to provide robust protections to human subjects participating in research. These reforms will benefit not only patients, but also the science being done. Dr. Murray said that NBAC invited several groups of human subjects to provide input to the commission. He also noted that IRBs would benefit if they included more lay representatives as members.

In response to a comment from Dr. desVignes-Kendrick about the erosion of trust toward researchers among minority groups, Dr. Koski said that such populations have been approached in the wrong way and that it is essential to provide all populations with equal protection from research risks. He said that reaching out to such populations and respecting their needs represents an important challenge for the research community to meet. Dr. Kirschstein said that the NIH Women's Health Initiative has enrolled a very large number of women from minority groups and is implementing a number of special measures to develop their trust. Dr. desVignes-Kendrick agreed that such measures are needed to help in overcoming health disparities. Ms. McCabe said that training efforts are being stepped up to provide more health care professionals drawn from such communities.

In response to a question from Ms. Quigley about what COPR might contribute, Dr. Murray said that some suggestions, such as developing closer contacts with human subjects, provide a good start. He said that knowing COPR's opinions on whether measures to protect human subjects should be applied to both privately and publicly funded research and whether there should be a federal office with oversight over all such research would be helpful. Dr. Koski urged COPR to share its views directly with the OHRP advisory committee that will soon begin to meet.

Mr. Roehr suggested that market forces and efforts to better inform patients about clinical trials would improve protective measures and might also induce more lay individuals to participate in designing clinical trials that better meet their health needs.

Ms. Lackritz praised the prototype document on informed consent described earlier by Ms. McCabe. In response to a question from Ms. Anne Thomas about how that document is being distributed, Ms. McCabe said that it has been sent to all IRBs and to cancer patient advocacy groups and to cancer research and treatment centers. She also said that other NIH Institutes are adapting the document for use in research settings where other diseases are being studied. Mr. Roehr said that he hopes that large components of the document will remain intact regardless of the settings in which it is being used. Dr. Kirschstein said that the IOM has been asked to provide advice on how to foster wide use of this prototype document.

COPR Business Items, Wednesday, November 1, 2000

Dr. Kirschstein acknowledged and thanked the members whose terms on the NIH COPR are ending with this meeting, including Dr. Castele, Dr. desVignes-Kendrick, Ms. Lewis, Dr. Rabb, Ms. Chin and Mr. Frohnmayer (who was unable to attend the October-November meeting). In thanking them for their contributions, she also told them that they should consider themselves permanent members of the greater NIH family and that they may be called upon for additional service.

"Talking About the NIH" Packet—Anne Thomas

Ms. Thomas described a packet that was presented to the members of the NIH COPR. It contains factual information about activities and budgets, key phone numbers for individuals and organizations involved in specific disease areas, a compilation of research advances since the 1950s, a brief history of NIH, a booklet called *How NIH Sets Research Priorities,* copies of Dr. Kirschstein's testimony presented during Congressional appropriations hearings held earlier during 2000, and two video tapes, one containing information that is available to visitors to the NIH campus and the other based on the Millennium Conference held at the White House and focused on the Genome Project and the Internet. Ms. Thomas said that additional materials can also be provided, such as detailed information about NIH research spending in a particular state.

Discussion

Ms. Quigley said that the video on the 8th Millennium Evening at the Whitehouse on "Informatics Meets Genomics" was excellent, both entertaining and substantive.

In response to a question from Dr. Michael Anderson, Ms. Thomas said that inquiries about additional information should be directed to her or to Ms. Jennifer Gorman.

In response to a question from Ms. Lewis about how COPR members might respond to inquiries about recent NIH hiring trends, Dr. Kirschstein said that NIH is almost always hiring personnel and that job openings are posted on the NIH Web site, while scientific positions typically are advertised in publications such as *Nature* and *Science.* She said that, although many NIH jobs are civil service positions and require applicants to be either U.S. citizens or permanent residents, other temporary research positions are available to scientists from abroad. She also said that there may be a temporary freeze on hiring imposed on NIH and other federal agencies during the transition to the new administration early in 2001. Ms. Thomas said that the NIH Home Page has a "careers here" link to job openings.

Dr. Yvonne Maddox said that NIH recently began to do more in the way of corporate-style recruitment. She also pointed out that Mr. Steve Benowitz, Director of the NIH Office of Human Resources, produced a brochure describing career opportunities at NIH. This active recruitment approach is being used to bring more members of minority groups to NIH, as part of a campaign scheduled to begin in mid-November 2000, according to Dr. Maddox. As part of this campaign, NIH officials will hold workshops in California, Texas, and New York to encourage Hispanic Americans and members of other minority groups to join the NIH work force.

In response to a question from Dr. desVignes-Kendrick about the strategic plan focused on health disparities research, Dr. Kirschstein promised to seek increased resources to support this initiative. Dr. Maddox said that 18 of the 25 NIH Centers and Institutes now have posted on the NIH Web site their final or near-final versions of their separate strategic plans for health disparities research, and she provided members of the NIH COPR with copies of one such plan, developed by the NIH National Institute of Child Health and Human Development. Each of these plans looks at such research from three perspectives: i) research, ii) infrastructure including recruitment, training, and retention of minority group researchers and health care professionals, as well as recruitment of minority group members as volunteers in clinical or other research projects involving human subjects, and iii) and community outreach and information dissemination.

In regards to infrastructure, Dr. Maddox commented that the Institutional Development Awards (IdeA) Program would be expanded. She said that Congress

provided additional funding in the FY 2001 budget for this NIH program, enabling the development of the NIH Biomedical Research Infrastructure Network (BRIN) and the issuance of an official request for applications (RFA) that was made public at the end of September to encourage investigators to take part in this new program. She explained that RFAs, which are a device to highlight new programs of special relevance or priority, differ from the more widely used mechanism for funding research through grants that originate as investigator-initiated proposals. The BRIN RFA is expected to stimulate applications to meet a mid-winter deadline, and successful proposals will provide funding to institutions in states that currently do not receive much NIH funding, to enhance infrastructure, conduct research, and ultimately better meet the health needs of underserved populations.

These programs also emphasize community outreach and efforts in partnership development, according to Dr. Maddox. She said that the NIH efforts in Institute Director's budget retreat in June provided some of the critical planning for these activities, and these efforts are accelerating because the NIH Institutes committed nearly one-third of their requests for additional funding in these areas for community outreach activities. Dr. Kirschstein said that, once state and institutional recipients are identified, plans call for awarding each of them funding at identical or commensurate levels for three-year periods, with the option of three-year renewals if progress so indicates.

Dr. Maddox said that NIH invited state and institutional representatives within the underfunded states to participate in a workshop that was held October 20, 2000. Dr. Sidney McNairy at the NIH National Center of Research Resources can be called on for guidance in developing applications in response to the BRIN RFA or for answering questions in this general area of interest.

Ms. Lappin said that, in the two years since COPR was inaugurated, the NIH health disparities program has gained prominence and considerable momentum, and she credited Dr. Kirschstein and Dr. Maddox for elevating that program to the top of the NIH agenda. She also suggested that presentations describing the status of the outreach programs be part of the agenda for the next NIH COPR meeting. Dr. Kirschstein said that each of the NIH Institutes and Centers oversees active outreach programs, pointing to the example of the NIH National Cancer Institute's program providing materials and services into underserved regions such as in Appalachia.

In response to Ms. Lappin's comments in praise of the *NIH Record,* Dr. Kirschstein promised to share those comments with its editor.

Ms. Lappin also asked whether NIH would consider coordinating its outreach programs with those at the Centers for Disease Control and Prevention (CDC). Dr. Kirschstein said that NIH coordination with CDC tends to work best when conducted on an individual-to-individual basis rather than through more formal arrangements.

In response to a question from Mr. Roehr about whether low levels of NIH funding levels in particular regions is associated with the absence of regional medical schools, Dr. Kirschstein said that this explanation does not appear to hold. Dr. Kirschstein said that many of the NIH-underfunded states have medical schools, and one consortium of four states, Washington, Alaska, Montana, and Idaho, was created by Senator Ted Stevens (R-AK) to encourage collaborative programs in research and health care. She said that the shortages in NIH funding have more to do with problems in putting together a critical mass of people to conduct both basic and clinical research.

Dr. Kirschstein also said that the concept of outreach programs is relatively new to NIH, and it arose following lengthy discussions with various members of Congress representing those under-funded states, some of whom serve on appropriations committees. Dr. Maddox said that much of the recent growth in the NIH outreach programs also can be attributed to leadership within HHS, including from the Surgeon General and the Secretary of HHS. She said that other agencies within the department, particularly the Health Resources and Services Administration, have become important collaborators for NIH in developing community outreach programs.

In response to a question from Ms. Lancaster, Dr. Maddox said that Tennessee does not qualify for the new NIH BRIN program because Vanderbilt University is a major recipient of NIH funding. Dr. Kirschstein added that the eastern region of Tennessee in Appalachia that is adjacent to parts of Kentucky, North Carolina, West Virginia, and Virginia has access to this program through the NIH NCI, where Dr. Friedel serves as liaison. She said that she would ask him to provide relevant information about the program at the next meeting of the NIH COPR. She also said that the single "have-not" state among several states that form a regional collaboration has the right to apply for funding through the NIH BRIN program. She mentioned the Vanderbilt-Meharry alliance as another example of a cooperative, infrastructure-building program that NIH has helped to fund.

In response to a question from Dr. Rabb, Dr. Kirschstein said that Congress appears ready to pass legislation creating an NIH Center for Minority Health and Health Disparities Research with authority to issue funds through grants and contracts. Once the new center is created, its programs and administrative structure will need to be developed, and the current NIH Office of Research on Minority Health (ORMH) likely will help in this process by providing personnel, budget, and infrastructure. She later said that Dr. John Ruffin, Director, NIH ORMH, will be in charge of coordinating impending efforts to develop the new NIH Center, augment current outreach programs, and bring in additional experts to contribute to this process.

The FY 2001 budget request called for an increase of $20 million from the previous year to an overall level of $117 million for the NIH ORMH, and additional increases will be sought in the FY 2002 budget, according to Dr. Kirschstein. Ms. Thomas said that these figures understate actual NIH spending on health disparities research that is being done by the other NIH Centers and Institutes. For example, in diabetes research, much of the NIH investment may involve projects that can benefit anyone afflicted with this disease but certainly is applicable to minority populations that suffer disproportionately from diabetes. Dr. Kirschstein said that HHS has identified six critical areas of emphasis-cardiovascular disease and hypertension, infant mortality, sudden infant death syndrome, HIV/AIDS, diabetes, cancer (particularly breast and prostate), and immunizations-throughout the Department, and NIH plays a leading role in research for five of those areas.

Dr. Maddox said that the draft strategic plan for research on health disparities cites a single figure for overall NIH spending in this area, namely $1.3 billion, but if spending in related areas were included, $1.8 billion would be a better estimate of the total. However, by keeping the definition of health disparities research rather narrow for budget-tracking purposes, NIH will be better able to measure the impact of this research in the years to come, according to Dr. Maddox. She also said that research on environmental health represents another important focus of health disparities, one for NIH to follow more closely in this context in the future.

Dr. Melanie Dreher, who is participating in the review of the Director of the NIH National Institute of Environmental Health Sciences (NIEHS), said that this institute deserves praise for its outreach programs because they bring attention to core health disparities issues. She said that living in particular environments can affect one's health and may lead to many different kinds of health problems. Dr. Kirschstein said that other NIH Institutes also study environmental effects on specific health problems of minority populations, such as the Asthma Project that involves a coordinated effort among the NIH NIEHS, National Heart, Lung and Blood Institute, and the National Institute of Allergy and Infectious Diseases (NIAID). Dr. desVignes-Kendrick said that the National Association of County and City Health Officials (NACCHO) as well as the Houston City Health Department have designated environmental impacts and racial disparities in health outcomes a priority issue, indicating that other entities besides NIH and CDC are taking on this issue, which will require a concerted effort if progress is to be made.

Ms. Lappin requested that Dr. Maddox present information at a future meeting regarding lack of subspecialty care for rare diseases of childhood. There is a growing shortage of specialists to care for sick children-for instance, one pediatric rheumatologist serves five Western states. She said that, in effect, this situation amounts to another kind of health disparity. Dr. Maddox said that there are similar shortages in other specialty areas. Dr. Kirschstein said that, despite the importance of this issue, shortfalls in the delivery of health care because of changing trends affecting the training of health professionals is not and cannot be a primary focus for NIH, which must maintain its focus on health research. Dr. Maddox added that NIH is concerned about the inclusion of children as subjects in clinical research, particularly those focusing on rare diseases, and NIH has an office devoted to such issues that helps to coordinate research related to rare diseases among the NIH Institutes and Centers.

In response to a question from Dr. Anderson about clinics on indian reservations, Dr. Kirschstein said that the Bureau of Indian Affairs is within the Department of the Interior but the Indian Health Service (IHS) and its hospitals come under HHS. She said that there are more than 500 separate tribes, many with independent treaties and separate agreements with HHS on specific arrangements for health care. Although NIH had little interactions with the Indian Health Service in the past, Dr. Clifton Poodry at NIH recently developed a Native American round table to foster programs involving both NIH and IHS.

Ms. Quigley, referring to issues discussed at the June NIH budget retreat, asked for a status report on industry-NIH research collaborations. In response, Dr. Kirschstein said that the NIH National Institute on Aging and the NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases are working jointly with several companies on osteoarthritis research projects. She said that arranging such cooperative efforts presents challenges, particularly because NIH seeks to ensure that the results of federally sponsored research remain freely accessible. The NIH Office of Technology Transfer is in charge of negotiating agreements that attempt to do this while allowing for patenting and licensing of proprietary information. She said that an effort will be made to put this issue on the COPR agenda. In response to a comment from Mr. Roehr about the NIH NCI negotiating cooperative research agreements for research on rare diseases, Dr. Kirschstein said that, even here, problems arise when companies back away from developing products because numbers of patients with a particular disease are very low.

Updates from COPR Working Groups

Clinical Trials Working Group—Report prepared by Barbara Lackritz

Because Ms. Lackritz could not attend the meeting, Ms. Thomas presented highlights from her working group's report. In a review of information on clinical trials provided by the Institutes on the NIH Web site, Ms. Thomas said that the working group concluded that some of the clinical trials listed on the Web site are identified clearly as to whether they are sponsored by industry or by one of the NIH Institutes. The working group did, however, report that for many of the listed clinical trials, it is unclear who is the sponsor of the trial. The group recommended that this unevenness be corrected. Similarly, patient protections and rights are not being consistently reported, and Ms. Thomas said that she would bring this discrepancy to the attention of the communications directors of the various NIH Institutes and Centers. Ms. Thomas said that the FDA Modernization Act mandates the NIH to bring all such information—including trials funded by industry and by other federal agencies—into a single database, which will be accessed through its Internet site, clinicaltrials.gov, as this system becomes more fully developed.

Ms. Quigley said that, when pharmaceutical companies sponsor clinical trials, information about them needs to be disclosed in a much more forthright manner, not only in the fine print of informed consent documents. Following a discussion among several participants about how various NIH Institutes and programs handle such matters for clinical trials that they co-sponsor with industry, Ms. Thomas agreed to discuss this issue among her communications colleagues and to take steps to ensure that sponsorship of clinical trials is routinely disclosed. Dr. Kirschstein added that Ms. McCabe would welcome suggestions for making such disclosures part of the prototype informed consent document she described to the NIH COPR members. Mr. Roehr said that notice of NIH sponsorship of a clinical trial carries weight because it typically means the planning of the trial is sound and the results will not be biased, factors that encourage people to enroll in the trials.

Outreach to Other Public Members Participating in NIH Groups—Working Group—Bob Roehr and Vicki Kalabokes

Mr. Roehr said that he would like to see COPR members form networks with other public advisory groups at NIH. However, in meeting with NIH public liaison officers in June 2000, he learned that there are many practical obstacles to overcome before even preliminary steps toward this goal can be undertaken. Although someone at that meeting suggested that a focus group might help to identify ways to develop such networking efforts, Mr. Roehr advocated moving forward despite those many obstacles. Thus, he welcomed the availability of a partial list of public members within the NIH community that was compiled by Ms. Jennifer Gorman, the NIH Public Liaison Coordinator. He also agreed with the recommendation from one of the NIH public liaison officers that membership in the group that he envisions should not be limited to individuals who are officially public representatives but should include anyone with a genuine interest in the group's activities. He noted that he planned to meet soon with an NIH NIAMS advisory group.

Ms. Kalabokes said that she planned to meet the next day with the Coordinating Council of the NIH NIDCR and, eventually, other public representatives associated with other NIH Institutes and Centers.

One other current activity is to forge closer ties with the NIH COPR Associates and, with help from Ms. Gorman, efforts are under way to contact members of this group. In general, they are enthusiastic about developing deeper involvements with NIH, according to Ms. Kalabokes. One plan calls for asking them to serve on COPR working groups and, to facilitate forthcoming requests for them to do so, Ms. Gorman will provide COPR members with necessary information for contacting COPR Associates.

Health Disparities/Underserved Populations Working Group—Isaac Montoya

Dr. Montoya thanked Ms. Gorman for her help in coordinating the working group's efforts, which overlap extensively with those of the working group headed by Ms. Lappin that is focusing on human research protections. His working group, which has developed an outline of its plans, is considering what format of a report would be most helpful to NIH. So far, the input for this report has come mainly from communities connected to members who serve on the working group, but plans call for reaching out more broadly. One consistent comment from those who have been contacted is to try to define underserved populations not so much in terms of racial-ethnic distinctions but in terms such as geography, disabilities, and socioeconomic and educational factors.

Rotation and Transition Working Group—Vicki Kalabokes

Ms. Kalabokes said that the members of the working group conferred by telephone to consider how the first and subsequent rotations from membership on the NIH COPR should be handled. For the first phase, enough members identified themselves as willing to rotate off active membership, that the question of finding an equitable selection process for those who are first to retire was easily resolved. In terms of finding the first set of replacements, former NIH Director Dr. Harold Varmus had agreed that the COPR Associates would make up the primary pool of candidates for the next new group. The six new COPR candidates will primarily be selected from the COPR Associates pool. The six COPR members rotating off active membership of the council will end their terms on March 31, 2001. The six new members will be selected by February 2001 and will officially begin their terms as of April 1, 2001. However, for subsequent selection rounds, the members of this working group will work with NIH staff to make sure an open call for nominations is widely distributed every few years, in order to replenish the COPR candidate pool.

Human Research Protections Working Group—Debra Lappin

Ms. Lappin, who participated in deliberations conducted by an ACD working group on gene transfer research, said that those discussions in fact applied working group on more broadly to other areas of clinical research. Moreover, discussions on clinical research in other forums, including during the COPR working group sessions held on the previous day, indicate a changing landscape, particularly in terms of concerns being expressed to bolster measures to protect patients, according to Ms. Lappin. She said that COPR can provide an important, unique, and useful voice representing the public in these continuing discussions.

The working group members planned to meet later on November 1, 2000, to identify specific areas of concern and to recommend additional issues for OHRP to consider, according to Ms. Lappin. Those issues include informed consent, patient confidentiality, the role of IRBs, conflicts of interest, underserved populations, patient recruitment, regulatory burden, and concerns related to behavioral research. She said that the working group plans to prepare a discussion paper.

Discussion

In response to Dr. Montoya about whether NIH staff members could join in working group activities, Ms. Thomas said that Dr. Wendy Baldwin and Dr. Belinda Seto would be participating in the working group's meeting. Ms. Thomas said that she and other members of her staff also will be available to the working groups. However, Dr. Kirschstein said that neither she nor Dr. Maddox should be listed as members of the COPR working groups, which may make recommendations to NIH, but that both of them would be pleased to serve as resources to the working groups.

Discussion of Feedback from COPR Members on the History, Values and Operations Guide of COPR

Ms. Thomas turned the discussion to the draft guidebook, *History, Values and Operations of COPR,* and said that, when completed, it will be helpful to address some of the many inquiries she has received about COPR, including from individuals outside the U.S. Because an additional purpose of the guidebook will be to help orient new members of COPR, the draft was distributed to the current members for their comments about a month before the October-November COPR meeting. One comment received from several members was that it should be more explicit about the time commitment required of COPR members.

Dr. Montoya said that the guidebook, along with the *Talking About the NIH* resource kit, will provide useful tools for COPR members to interact with the public, and also for enhancing communications between NIH and the public. He said that, in interacting with the public on behalf of the NIH COPR, he spends the great majority of his time listening rather than describing NIH. Nonetheless, having these resources and tools will be helpful to COPR members as a concise means for describing NIH activities.

Dr. Castele said that the guidebook should include a list of typical COPR activities outside its meetings at NIH. Dr. Dreher said that it is also important to say that COPR meetings are scheduled well in advance, enabling more of its members to attend. Mr. Roehr said that the guidebook should say COPR members are expected to participate actively in working groups. Dr. Montoya said that COPR is increasingly becoming a resource for the NIH Institutes, an activity that adds further to the time commitment of COPR members. Dr. Castele pointed out that there are typically daily e-mail messages among COPR members. Ms. Quigley said that it would be helpful to describe that the role of the NIH COPR member, although not visible every day, can present itself at any time.

Mr. Vaalburg asked what the primary focus of COPR members is expected to be. In response, Ms. Thomas said that some members prefer special assignments, whereas others prefer working group assignments. He also said that many people he encounters in his work activities are surprisingly unfamiliar with NIH. Dr. Kirschstein said that other organizations are dedicated to educating the public about NIH. For example, Research America! recently commissioned a survey to determine whether it is doing enough in that regard. Because NIH is part of HHS, it is constrained in what educational and promotional activities it may conduct.

Ms. Thomas asked the COPR members to consider several options as to how the group would conduct and run its decision-making process. In response, Mr. Roehr said that consensus is a prescription for paralysis and recommended that a simple majority vote would be the best general option to embrace. Dr. Castele agreed with this suggestion.

Dr. Kirschstein asked whether COPR members would feel constrained in any way if their individual votes were recorded and whether that practice might lead to a sense of invasion of privacy. In response, Mr. Roehr said that holding recorded votes is not likely to be common for COPR. Moreover, because COPR serves in an advisory capacity, it seems unlikely that public pressure would be brought to bear on individual members. Dr. Kirschstein said that the minutes of the NIH ACD or other advisory groups typically do not list how each member voted on particular issues, but merely an overall vote count. Ms. Quigley said that it would be appropriate for COPR vote counts to be similarly recorded but she also noted that its members strive for consensus. Mr. Roehr said that it is important to preserve

the right to present minority reports in those cases where consensus is not reached, or some members disagree with the majority viewpoint.

Ms. Thomas then asked the COPR members to think about the slate of six new members to be named in January/February 2001, who are very likely to be drawn from the COPR Associates, as was indicated by former NIH Director Varmus. That group of candidates is very diverse, but some thinking is needed about how to maintain that diversity and what process to use in future rounds of identifying candidates for COPR membership. Dr. Kirschstein said that the choice of COPR members from such candidate pools is at the discretion of the NIH Director. Ms. Kalabokes said that her working group will provide recommendations for selections expected in 2002, 2003, and beyond.

In response to a discussion among several COPR members whether Americans Indians are represented in the current group of COPR Associates, Ms. Thomas said that an effort to identify such candidates was made initially, and this effort would be extended, including through the Indian Health Service. Ms. Lappin said that it will be a challenge to fill this gap and to identify other appropriate candidates while rotating in new members of COPR. Part of the challenge is deciding whether to fill specific "interest" vacancies or to seek again nominations representing broad constituencies. Mr. Roehr said that adding an international component, particularly to reflect the importance of global infectious diseases should be considered. Ms. Quigley said that, although COPR members tend to be categorized according to what interest group they come from, in fact the members tend to represent amalgamations of varied interests. Dr. Castele pointed out that all three physicians now on COPR are part of the first group to rotate off active duty.

Mr. Roehr said that some of those among the Associates will need to be asked again whether they continue to be interested in joining COPR. In response, Ms. Thomas said there have been efforts to contact them. Ms. Cate Timmerman said that the Associates have responded to such a survey, and most of them have registered whether they can serve or not.

Mr. Roehr said that it is valuable to have good chemistry among the COPR members, but Ms. Lappin said that identifying candidates who are likely to interact well with the group is not an easy task. Dr. Kirschstein said that the final selection remains her responsibility, and that efforts were made to speak with but not interview candidates during the initial round of choices to constitute this version of COPR.

Dr. Castele suggested that the COPR Guide describe potential responsibilities for COPR alumni. He also thanked COPR members and NIH staff for their collegiality during his tenure on the council.

Mr. Roehr pointed to the first sentence of the draft COPR Guide and said that it might be re-phrased to better reflect the public as equal stakeholders in public input. He volunteered to rewrite that section.

There was a brief discussion to set the dates for the next meetings of COPR as May 1st and October 23rd, 2001, to avoid conflicts with various holidays and other meetings. Ms. Thomas then suggested that agenda items for the April meeting be discussed in a forthcoming conference call and agreed to reserve time for working groups to meet. Dr. Kirschstein further suggested that time be reserved on October 24, 2001, for COPR members to participate in the GPRA review of NIH.

As the meeting adjourned, the several departing COPR members, David Frohnmayer, Maurice Rabb, M.D., Ted Castele, M.D., Robin Chin, Mary desVignes-Kendrick, M.D., and Lydia Lewis, again thanked their colleagues and NIH staff for their cooperation and collegiality throughout their COPR undertakings.

Summary and Conclusions

The Director's Council of Public Representatives (COPR) of the National Institutes of Health (NIH) met on October 31–November 1, 2000, to consider reforms being instituted by the NIH Office of Medical Applications of Research, several matters affecting human subjects protections, and a series of activities of COPR working groups.

The COPR acknowledged and commented on these presentations, made several specific recommendations about measures to protect people participating in research and on research on health disparities, agreed on procedures for how COPR will develop recommendations, and acknowledged that several working groups continue to develop specific recommendations and plans for dealing with a variety of other issues.

Table of Abbreviations

- **ACD—**Advisory Committee to the Director
- **BRIN—**Biomedical Research Infrastructure Network
- **CDC—**Centers for Disease Control and Prevention
- **COPR—**Council of Public Representatives
- **CSR—**Center for Scientific Review
- **DHHS—**U.S. Department of Health and Human Services
- **FDA—**Food and Drug Administration
- **FY—**Fiscal Year
- **GPRA—**Government Performanceand Results Act
- **HRSA—**Health Resources and Services Administration
- **HPSCRG—**Human Pluripotent Stem Cell Review Group
- **IHS—**Indian Health Service
- **IOM—**Institute of Medicine

- **IRB**—Institutional Review Board
- **NBAC**—National Bioethics Advisory Commission
- **NCI**—National Cancer Institute
- **NCRR**—National Center for Research Resources
- **NCMHD**—National Center on Minority Health and Health Disparities
- **NEI**—National Eye Institute
- **NIAMS**—National Institute of Arthritis and Musculoskeletal and Skin Diseases
- **NIBIB**—National Institute for Biomedical Imaging and Bioengineering
- **NICHD**—National Institute of Child Health and Human Development
- **NIDA**—National Institute on Drug Abuse
- **NIDCR**—National Institute of Dental and Craniofacial Research
- **NIDDK**—National Institute of Diabetes and Digestive and Kidney Diseases
- **NIEHS**—National Institute of Environmental Health Sciences
- **NIH**—National Institutes of Health
- **NIMH**—National Institute of Mental Health
- **NINDS**—National Institute of Neurological Disorders and Stroke
- *NINR*—National Institute of Nursing Research
- **NHGRI**—National Human Genome Research Institute
- **NLM**—National Library of Medicine
- **NSF**—National Science Foundation
- **OCPL**—Office of Communications and Public Liaison
- **OHRP**—Office for Human Research Protections
- **OMAR**—Office of Medical Applications of Research
- **OSP**—Office of Science Policy
- **OTT**—Office of Technology Transfer
- **PI**—Principal Investigator
- **RFA**—Request for Applications
