DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY COUNCIL FOR BIOMEDICAL IMAGING AND BIOENGINEERING

Summary of Meeting[1]
September 17, 2007

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 15th meeting on September 17, 2007, at the Marriott Suites Bethesda in Bethesda, Maryland. Dr. Roderic I. Pettigrew, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), presided.

In accordance with Public Law 92–463, the meeting was open to the public from 8:30 a.m. to 12:45 p.m. for the review and discussion of program development, needs, and policy. The meeting was closed to the public from 1:30 p.m. to 3:45 p.m. for the discussion and consideration of individual grant applications.

Council members present:
Dr. Ronald L. Arenson
Ms. Rebecca M. Bergman
Dr. David J. Dzielak
Dr. Richard L. Ehman
Dr. Katherine W. Ferrara
Dr. Gary H. Glover
Dr. Augustus O. Grant
Dr. Percival McCormack
Dr. David Satcher

Council members absent:
Dr. Don Giddens
Dr. Mae C. Jemison

Ex officio members present:
Dr. P. Hunter Peckham, Veterans Administration
Dr. Judy A. Raper, National Science Foundation
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences
Dr. Andrew Watkins, Centers for Disease Control and Prevention

Ex officio members absent:
Dr. Anne Plant, National Institute of Standards and Technology
Mr. Michael Leavitt, U.S. Department of Health and Human Services

[1] For the record, it is noted that members absent themselves from the meeting when the Council is discussing applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure only applies to applications that are discussed individually, not to "en bloc" actions.

Dr. Elias A. Zerhouni, National Institutes of Health

Executive Secretary:
Dr. Anthony Demsey

Also present:
NIBIB staff present for portions of the meeting:

Ms. Lillian Ashley
Dr. Prabha Atreya
Mr. Angelos Bacas
Dr. Richard Baird
Ms. Barbara Cantilena
Ms. Shirley Coney-Johnson
Ms. Nancy Curling
Ms. Angela Eldridge
Dr. Zeynep Erim
Ms. Cheryl Fee
Ms. Carol Fitzpatrick
Dr. David George
Ms. Pam Glikman
Dr. Valery Gordon
Dr. Ruth Grossman
Dr. John Haller
Dr. John Hayes
Dr. William Heetderks
Dr. Lori Henderson
Dr. Rosemarie Hunziker
Ms. Jeanellen Kallevang
Dr. Chris Kelley
Ms. Mary Beth Kester
Dr. Brenda Korte
Dr. Lixin Lang
Dr. Albert Lee
Mr. Bryan Linares
Dr. Hector Lopez
Dr. Xiao-Zhong (James) Luo
Dr. Ying Ma
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Nicholas Mitrano
Mr. Larry Morton
Mr. Joe Mosimann
Dr. Peter Moy
Mr. Aaron Nicholas
Ms. Donna Pearman
Dr. Grace Peng
Dr. Karen Peterson
Dr. Roderic I. Pettigrew
Ms. Patty Runyon
Ms. Katie Serrano
Dr. Belinda P. Seto
Ms. Casey Stewart
Ms. Florence Turska
Ms. Stacy Wallick
Mr. Matt Wise
Ms. Li-Yin Xi
Dr. Yantian Zhang
Dr. Ruixa Zhou

Other Federal employees present:
Mr. Chris Anderson, U.S. Food and Drug Administration
Dr. David Brown, U.S. Food and Drug Administration
Mr. Francis Costello, National Institutes of Health, Office of the Director
Ms. Allyson Gibson, US Food and Drug Administration
Dr. Kyle Myers, U.S. Food and Drug Administration
Dr. Lawrence Tabak, National Institutes of Dental and Craniofacial Research

Members of the public present for portions of the meeting:
Ms. Jennifer Ayers, American Institute for Medical and Biological Engineering
Ms. Stephanie Darby, Biomedical Engineering Society
Ms. Mariana González del Riego, Rose Li and Associates, Inc.
Ms. Jeanie Kennedy, American Academy of Orthopaedic Surgeons
Dr. Kullervo Hynynen, Sunnybrook Health Sciences Center
Ms. Rachel Levinson, Arizona State University
Dr. Frances McFarland-Horne, Rose Li and Associates, Inc.
Mr. Robert Rains, Government Relations Representative, ASME

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey welcomed attendees and called to order the 15th NACBIB meeting. He reminded attendees that because the morning session of the meeting is open to the public, comments about applications should be reserved for the closed session. Dr. Demsey introduced Dr. Pettigrew, who formally welcomed all participants.

II. Director's Remarks: Dr. Roderic Pettigrew

A. New Members

Dr. Pettigrew welcomed three new members and one new ex officio member to the Council:

- **Dr. Gary Glover** is Professor of Radiology and the Director of the Radiological Sciences Laboratory at Stanford University. In the early days of the NIBIB, Dr. Glover served as a consultant both to the NIBIB Director and to the Institute in general. He offers considerable experience with the NIH, both as a grantee and as former Chair of the Diagnostic Imaging Study Section. He is well recognized for theoretical and experimental developments in computed tomography and magnetic resonance. Dr. Glover was employed for 20 years at General Electric, where he was responsible for critical developments in these technologies. His work has also focused on functional magnetic resonance imaging (fMRI) as a means not only for diagnosis, but also for treatment. For example, Dr. Glover has studied ways to use the fMRI signal as a means for biofeedback to help patients control sites of brain activity. This technique has been used to help patients treat their pain.
- **Dr. Percival McCormack** is a professor of bioengineering, biophysics, and physiology at the University of Illinois in Chicago. He holds an M.D. and a Ph.D. in nuclear physics. His research focuses on fluid dynamics and Doppler ultrasound in the measure of arterial wall elasticity, and on contrast echo developments in myocardial contractility. Dr. McCormack is interested in the use of MRI for angiography, and he has published on other areas, including neuroscience and lacuna cerebral lesions in divers.
- **Dr. Mae C. Jemison** was absent at this Council meeting. She is the first African-American woman to travel in space. She is founder and president of BioSentient Corporation.
- **Dr. Judy Raper** is the new ex officio member to the Council from, and Director of the Division of Chemical, Bioengineering, Environmental, and Transport Systems at, the National Science Foundation (NSF). Dr. Raper joined NSF as a Program Director in 2006, after serving as Chair in the Department of Chemical and Biological Engineering at the

University of Missouri. Her research interests include fluid and particle dynamics, and she is now focused on the bioengineering applications of drug inhalation and on nanoparticle characterization and analyses.

B. Council Accomplishments

Dr. Pettigrew acknowledged NACBIB member Dr. David Satcher, who along with Dr. Rubens Pamies has published a book, *Multicultural Medicine and Health Disparities.* A book signing was held in August at the National Medical Association annual meeting. Dr. Satcher will give a presentation focused on health disparities at the January 2008 NACBIB meeting.

C. New Staff

The following staff additions were announced:

- **Dr. Ruth Grossman** has joined the Office of Scientific Review as a Scientific Review Administrator. Dr. Grossman comes to the NIBIB from the Constella Group, a private Government contractor that supports peer review. While at Constella, Dr. Grossman supported a wide variety of reviews, including the Department of Defense Breast Cancer Research Program and the Centers for Disease Control and Prevention (CDC) Director's Health Protection Research Initiatives. Dr. Grossman received a B.A. in political science from Goucher College and a D.D.S from the University of Maryland School of Dentistry.
- **Dr. Zeynep Erim** has joined the Division of Interdisciplinary Training as a Program Officer. Dr. Erim received a B.S. in electrical engineering from the Istanbul Technical University; an M.S. in biomedical engineering, also in Turkey; and a Ph.D. in biomedical engineering from Boston University. She went on to become a research assistant professor at Boston University, where she focused on neuromuscular research. In 2002 Dr. Erim took a position as a Senior Research Scientist in the Sensory Motor Performance Program at the Rehabilitation Institute of Chicago, where she later became Associate Director for Research. Dr. Erim has also served as a Research Associate Professor in the Department of Physical Medicine and Rehabilitation, Feinberg School of Medicine, and Adjunct Faculty in the Biomedical Engineering Department, McCormick School of Engineering, at Northwestern University.

D. Budget Update

The NIBIB is currently operating under the 2007 Joint Resolution budget, which is slightly less than $297 million. A 2008 budget is not yet in place, but the President's budget marks $300 million for the NIBIB, and the House and Senate marks are slightly higher. Therefore, the 2008 budget is likely to be somewhat higher than the 2007 budget, and it will be distributed in a manner similar to that seen in past years. Dr. Pettigrew noted that the 2007 NIBIB budget had marked $4 million to be contributed to the NIH Roadmap. However, the budget passed by Congress funded the NIH Office of the Director at a level sufficient to complete funding of the Roadmap, and the contributions made by individual Institutes and Centers (ICs) have been returned to them. As a result of this and a reprogramming of the intramural budget line, the NIBIB was able to dedicate additional funds to research project grants, effectively increasing the payline from the 17th percentile to the 19th percentile.

E. Significant Events

Dr. Pettigrew reported several events:

- From May 31 to June 1, 2007, the NIBIB held a Fifth Anniversary Celebration, which consisted of a dinner and symposium. Dr. Satcher spoke at the opening dinner; former U.S. Senator and Apollo Astronaut Harrison "Jack" Schmitt, the last man to have walked on the moon, provided the keynote address; and Dr. Charles Townes, Nobel laureate and inventor of the Laser, spoke at the symposium. The First NIBIB Landmark Achievement Award was given posthumously to Dr. Paul Lauterbur, who passed away unexpectedly a month before the celebration.
- The strategic plan from the Multi-Agency Tissue Engineering Science (MATES) Interagency Working Group has been published. This working group was spearheaded by Dr. Chris Kelley of the NIBIB and Dr. Rosemarie Hunziker of the National Institute of Dental and Craniofacial Research (NIDCR), who is now with NIBIB, and included several Federal agencies. Copies of this report were made available during the NACBIB meeting.
- The Division of Bioengineering and Biophysics will be transferred to the NIBIB as of October 1, 2007. This division is involved in several areas of research, including supramolecular structure and function, dynamics of protein assembly, complex biological systems, immunochemical nanoscale analysis and diagnostics, pharmacokinetics and drug delivery, and noninvasive optical imaging.
- Proposals for the Armed Forces Institute of Regenerative Medicine (AFIRM) are due October 19, 2007. AFIRM is a consortium of research institutions comprising the U.S. Army Medical Research and Material Command, the Office of Naval Research, and the NIH. The NIBIB is leading this effort on behalf of the NIH, and the NIDCR and the National Institute of Arthritis and Musculoskeletal and Skin Diseases also support these activities. AFIRM focuses on developing regenerative medicine approaches to battlefield injuries. The intended funding level is up to $10 million per year for 5 years.
- In response to the 2006 NIH Reform Act and specific requests, the NIH will work with the NSF and the Department of Energy to develop demonstration projects that illustrate the synergy of the life and physical sciences. A Bridging the Sciences Demonstration Oversight Group has been convened, and includes five IC directors and other senior officials from the NIH. The NIBIB and the National Institute of General Medical Sciences (NIGMS) will serve as lead institutes. The oversight group has had its first meeting and is in the process of defining specific demonstration projects.
- The NIBIB and India's Department of Biotechnology will sign a memorandum of understanding to collaborate in addressing global health disparities and improving global health. Specific areas of focus will include low-cost diagnostic and treatment technologies, low-cost biomedical imaging technologies, telehealth, and neonatal health technologies. The signing is expected to take place during the first week of October 2007.
- The Institute of Medicine (IOM) of the National Academies has conducted a study to review the state of the science in nuclear medicine, identify needs, and make recommendations. This study was co-funded by the NIH and the Department of Energy. The report has been completed and will be released to the public on September 20, 2007.
- The NIBIB has begun a series of program progress reviews, starting with a review of the Optical Imaging Program. These reviews are intended to evaluate the state of the science, to establish a baseline of information from which to measure the progress of the program and

inform the design of future initiatives, and to suggest any corrective measures that may be necessary. The Optical Imaging Program Progress Review was a one-day meeting that brought together experts in the field to assess the program portfolio and discuss opportunities and challenges. The written report from this meeting was provided to Council members for comment via e-mail prior to the meeting.

- The NIH is undergoing a comprehensive examination of its peer-review system, with the intent to update the system so that it is consistent with the types of science supported by the NIH in the 21st century. This examination is also a response to recent challenges, such as the increasing number, complexity, and interdisciplinary nature of the applications. Dr. Pettigrew informed the Council that Dr. Lawrence Tabak, Director of the NIDCR who serves on both the external Advisory Committee to the NIH Director on Peer Review (ACD) and the internal Steering Committee Working Group on Peer Review, would discuss the process in more detail later in this meeting, and take any feedback from the Council to the respective working groups.

F. Awards and Recognition

Two NIBIB grantees, Dr. Bradley Efron of Stanford University and Dr. Robert Langer of the Massachusetts Institute of Technology, have received National Medal of Science awards. Dr. Efron received the 2005 award for his contributions to theoretical and applied statistics, geometric insight into nonlinear statistical problems, and applications in medicine, physics, and astronomy. Dr. Langer received the 2006 award for his work in the development of polymeric-controlled release systems and tissue engineering as well as synthesis of novel materials that have led to new medical treatments.

Dr. John P. Donoghue, Director of the Brain Science Program at Brown University, received the 2007 K.J. Zülch Prize, Germany's top neuroscience award, for pioneering BrainGate, the mind-to-movement device that allows people with paralysis to control assistive devices using thoughts alone.

Dr. Jacqueline A. Johnson has received an R&D 100 Award for her work on an ultra-high resolution mammography system that records radiographic information digitally, resulting in lower costs and offering a higher quality alternative to digital radiography. Several notable improvements over common x-ray films and scintillating screens include reusability, a wide dynamic range, and direct digitization.

G. NIBIB Outreach

The NIBIB continued its series of grantsmanship workshops with one in Keystone, Colorado, on June 20, 2007. The next workshop will be held in conjunction with the Biomedical Engineering Society meeting, which will take place on September 26, 2007, in Los Angeles, California.

III. Review of Council Procedures and Regulations: Dr. Anthony Demsey

Dr. Demsey noted for the record that Council member Dr. Mae Jemison and ex officio member Dr. Anne Plant were unable to attend today's meeting. He added that Council member

Dr. Richard Ehman was unable to attend the morning session but would be present during the closed session.

A. Council Regulations, Policies, and Procedures

Dr. Demsey summarized elements of the Government in the Sunshine Act and the Federal Advisory Committee Act that govern all Advisory Council meetings. These Acts require the U.S. Department of Health and Human Services to open Advisory Council meetings to the public except when proprietary or personal information is discussed. To comply with these regulations, the NACBIB meeting is open to the public for all but the review of individual grant applications. Dr. Demsey reviewed the guidelines with Council regarding conflict of interest, confidentiality, and lobbying.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for January 25, 2008, at the Marriott Suites Bethesda, in Bethesda, Maryland. Dr. Demsey asked Council members to inform him of major conflicts with upcoming meeting dates.

C. Approval of the May 16, 2007, NACBIB Meeting Minutes

A motion was forwarded and seconded to approve the minutes of the May 16, 2007, NACBIB meeting. The minutes were approved unanimously.

IV. Report of the Joint Strategic Plan Implementation and Training and Career Development Working Groups Meeting, Dr. David Satcher

Dr. Satcher reported on a meeting of the Strategic Plan Implementation and Training and Career Development working groups. Discussion topics included the Institute's strategic plan for reducing health disparities and the NIBIB health disparities portfolio, which encompasses telehealth, low-cost imaging, and point-of-care technology. The working groups also discussed diversity training programs supported by the NIBIB; this discussion will be presented in more detail at the January 2008 NACBIB meeting. Also addressed were interactions between the NIBIB and the National Center for Minority Health and Health Disparities (NCMHD) and how they relate to a recent IOM report assessing the NIH's efforts to address health disparities. These interactions, which included teleconferences and a solicitation for feedback from the research community, are expected to result in an increase in the number of small business research applications, particularly in the areas of telehealth, low-cost imaging, and point-of-care technology. Dr. Satcher reported that discussions of the working groups were lively and that members asked challenging questions about what to accomplish, why it should be accomplished, and how to determine whether it had been achieved.

The working groups felt that the NIBIB could aim to improve access to quality health care through the implementation of technologies such as telehealth, which already provides people in Louisiana, Mississippi, and Alabama with mental health services they would not otherwise have. Working group members also recognized the need for more technology to assess the physical

environment. It is clear that minority and underrepresented groups are more likely to be exposed to environmental problems because of where they live and work. The NIBIB should determine ways to identify these environmental problems and to increase the access of minority and underrepresented groups to health care. These technologies are also needed for the general population, both to help people monitor their own health habits and, as illustrated by the health problems encountered by rescue workers of the September 11, 2001, attacks, their exposure to harmful environmental agents.

Several examples of health disparities have been identified. For example, mortality rates associated with cardiovascular disease are higher among African Americans compared with Caucasians, and rates of infant mortality within the first year of life are approximately twice as high among African Americans and Native Americans compared with Caucasians. An article published in the *Journal of Health Affairs* (Satcher et al, 2005) assessed mortality data from 1960 through 2000 and concluded that had health disparities been eliminated during the last century, in year 2000 alone, approximately 83,500 fewer African Americans would have died from heart disease, HIV/AIDS, primary causes of infant mortality, diabetes, and breast cancer, and 2.5 million more African Americans, including 620,000 children, would have had health insurance coverage. This study also looked at morbidities and the number of people living with pain and discomfort. Altogether, these are measurable outcomes that provide a way to assess future interventions. As supported by the 2002 IOM report entitled *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*, developing strategies to address cost, access to technology, and quality of health care in minority communities will have a significant impact on the quality of overall care.

In the book *Multicultural Medicine and Health Disparities* (Satcher and Pamies, 2005), five target areas are identified to address health care disparities:

- Access to care
- Improving quality of care
- Lifestyle enhancement
- Improving environmental quality
- A balanced research agenda

Dr. Satcher pointed out that diversity can influence several factors. A study conducted at the Harvard School of Business concluded that incorporating diversity is good for businesses, increasing innovation and improving interpersonal relationships in the workplace, and allowing businesses to better develop and market their products to different communities Similarly, incorporating more diversity in research will have a positive impact on the research enterprise, redefining research agendas, priorities, and its relevance and impact on different communities.

Discussion

A Council member commented that much of the NIBIB's work focuses on bringing forward low-cost technologies to investigate conditions yielding high disparity rates. However, in some areas (e.g., imaging), the cost of a machine may not be a significant barrier to dissemination of these technologies in small communities. Furthermore, as development of many of these technologies is supported via small business grants, large corporations may be unable or unwilling to build more affordable versions. He noted that the working groups had suggested packaging

technologies together and identifying communities where such technologies could be introduced to reduce health disparities. Another member added that other agencies, such as the CDC, had identified more effective ways to work with communities. He suggested preparing solicitations with other agencies, such as the CDC, with input from community leaders on how to best reach members of their communities. This approach, which differs from the traditional one taken by the NIH, could be packaged with delivery systems (e.g., telehealth), monitoring devices (e.g., glucose monitoring in the home), education, and ways of measuring outcomes.

Dr. Satcher further clarified these comments by describing the CDC REACH program, which supports well-organized and well-founded community organizations that contract with academic health centers or local health departments and provides these organizations with the ability to offer more input into how programs are implemented. These partnerships have resulted in several positive outcomes including a reduction in the number of amputations among individuals living with diabetes. The working groups suggested that, rather than attempting to access the community, the NIBIB should partner with a program such as REACH, which already has a community presence.
A Council member pointed out that the NIBIB is a cosponsor of the Jackson Heart Study and noted striking, early data indicating broad disparities in the use of best practices with minority patients versus non-minority patients. These disparities extend to something as simple as prescribing aspirin for individuals known to have heart disease. Therefore, efforts to address health disparities should focus not only on the patients but also on the health care providers.
Dr. Satcher noted that these disparities are symptomatic of a general problem with the provision of health care in the United States. Disease prevention is not occurring because of health care priorities and reimbursement issues. All groups suffer from this failure, but minority groups suffer disproportionately. Making prevention practices available to people living in areas least likely to have access to health care will contribute tremendously to reducing disparities. Making technology easier to use and reducing the amount of training time needed to operate this equipment also could be beneficial.

Dr. Satcher emphasized that, even though much remains to be done, the United States continues to make progress. For example, in 1950, the rate of infant mortality among African Americans was more than 50 per 1,000 births. At present, that rate is 14 per 1,000 births. Dr. Satcher noted that more targeting of such problems is needed and that efforts to eliminate health disparities will benefit everyone in the general population.

V. NIH Efforts to Enhance Peer Review: Dr. Lawrence A. Tabak

Dr. Tabak provided an overview of the NIH's approach, which includes seeking input from investigators, scientific societies, grantee institutions, and voluntary health organizations, as well as NIH staff. It is apparent that the NIH peer review system must adapt to emerging and rapidly changing fields of science and to new and growing public health challenges, and it must adapt in a way that is efficient and effective for applicants and reviewers alike. Dr. Elias Zerhouni, NIH Director, has issued a broad mandate to assess how science is supported. Because peer review is a key component of scientific support, the NIH, in partnership with the scientific community, has undertaken a self-study to strengthen its peer review process.

Two groups have been established for this purpose. The external Advisory Council to the Director (ACD) Working Group on Peer Review includes representatives from academic institutions, scientific societies, and the NIH Director's Council of Public Representatives as well as ex officio members, Dr. Norka Ruiz Bravo, Director, Office of Extramural Research, and Dr. Toni Scarpa, Director, Center for Scientific Review (CSR). The internal Steering Committee Working Group on Peer Review includes directors from several NIH ICs, as well as ex officio members from the Office of Budget and the Office of General Counsel. These two working groups are coordinating with CSR to ensure an alignment of effort, as CSR is also engaged in initiatives addressing the mechanics of peer review, including review cycles, study section alignment, application length, and electronic reviews.

Phase I of the NIH self study is diagnostic, beginning with a request for information (RFI) soliciting feedback about unique challenges in NIH research support and peer review as well as solutions. The RFI also asked about core values of the peer review process, the scoring system, and the appropriateness of the peer review process for investigators at all career stages. Although the RFI closed on September 7, 2007, Dr. Tabak pointed out that feedback could still be provided via e-mail at PeerReviewRFI@mail.nih.gov. In addition to the RFI, two teleconferences and regional town meetings have been held. The first regional town meeting took place on July 30, 2007, in Washington, DC, and involved professional organizations. Another town meeting was held on September 12, 2007, in Chicago. Three more such meetings are scheduled for New York City, San Francisco, and Washington, DC. The last meeting will be directed to patient advocates.

The ACD Working Group has selected a series of science liaisons to enhance outreach to stakeholders, and the Steering Committee Working Group has held three meetings and posted a Web-based survey to gather comments from ICs relative to their own missions. The Steering Committee Working Group is also analyzing the literature related to peer review and considering approaches followed by other agencies (i.e., the NSF, the Department of Energy, the Department of Defense, and the Howard Hughes Medical Institute). A psychometric analysis of study section models is also under way. Dr. Tabak and Dr. Jeremy Berg, who co-chair the Steering Committee Working Group, are meeting with all NIH advisory councils during the fall to gather feedback from their members.

Dr. Tabak pointed out that this self study is on a fast track. Reports to the ACD and Steering Committee Working Groups will be completed by early December 2007. NIH leadership will consider input from the RFI and working groups and determine next steps, including pilot initiatives, by February 2008. Pilot initiatives and their evaluations will be designed and implemented by March 2008. The results of these pilots and analyses will be used to develop a long-range implementation plan, with briefings for NIH staff, scientific societies, NIH councils, advocacy organizations, the trade press, and legislative bodies. These efforts will result, ultimately, in the expansion of successful pilots and the development of new NIH peer review policy. Dr. Tabak emphasized that pilots will be based on the best ideas, not necessarily the most popular ones, and that all ideas are under consideration.

To stimulate discussion, Dr. Tabak presented some ideas culled from the responses analyzed to date, and emphasized that the ideas were not presented in priority order or as approaches the NIH would necessarily pursue.

Numerous comments centered on review criteria and focus as well as application structure. Many people questioned whether funding decisions should be made based on the project or the applicant. Some noted that the intramural process is a retrospective one, whereas extramural reviews are prospective. There were also requests for separate application modes and review criteria for projects that lack preliminary data versus those that are extensions of current work. The track for new projects would eliminate the preliminary data section so that more attention would be paid to significance rather than feasibility.

Review mechanisms were another emerging theme. Suggestions included:

- A two-stage peer review process, with the first stage involving technical subject matter and content review and the second stage involving an editorial board model that considers applications based on the content of reviewers' comments.
- Electronic review.
- Virtual dialogue between the applicant and reviewer, allowing applicants to answer questions or address any reviewer errors that might affect the outcome of the review.
- Different review processes for different types of science. For example, less than 10 percent of new applications are funded, but most clinical trial applications are new applications.
- Ensuring that the right reviewers are assigned to Small Business Innovation Research or Small Business Technology Transfer applications.
- Having investigators designate one application as their primary application, then using different criteria to review and fund nonprimary applications.
- Providing useful feedback for all applications from new investigators, including clearer ranking for unscored applications or the elimination of triage.
- Rethinking design of original applications to avoid clogs in the queue. A redesign could include shorter pre-applications to provide rapid identification and separation of competitive applications from noncompetitive applications as well as meaningful advice to applicants.

Comments also focused on review and reviewer quality and culture, including how much information reviewers would need to have an appropriate context for an application, and publication of reviewer identities. Suggestions for maximizing review and reviewer quality included:

- Added incentives for reviewers
- Mandatory service by grantees
- More flexible service opportunities
- Increased support for reviewers
- Rating reviewers and scientific review administrators

Comments also focused on scoring issues, such as binning and triaging, and several individuals wanted more information to help applicants decide whether to resubmit their application. Dr. Tabak described a common scenario where an investigator revises and resubmits an application, only to receive a similar score. This can happen because reviewers change or

because they hesitate to rate an application poorly. A two-score system was suggested as a way to address this problem. In such a system, the applicant would receive a score based on the application's potential, for example if the idea is sound but the application itself requires further work, in addition to the usual score of technical merit.

In closing, Dr. Tabak mentioned another proposed idea to limit the percent effort that can be recovered on grants for principal investigators or to increase the percent effort for principal investigators to 50 percent.

Discussion

In response to a question, Dr. Tabak commented that the NIH Strategic Plan influences the peer review process indirectly. Although an examination of the strategic plans of the NIH and the various ICs shows that the type of science supported by the NIH is changing, many sense that the peer review process has not caught up. For example, many have called for more community-based research, but the review process needed for these applications differs from that for basic science applications. For this reason, patient advocacy groups have been included in the NIH self study.

A Council member mentioned the Clinical and Translational Science Awards process, which provides some continuity for successful, large programs. He asked whether there was some way to transition to more guaranteed, longer term support for large interdisciplinary groups with a significant training effort. Dr. Tabak cautioned that the NIH does not want mechanisms to become entitlements. That said, Dr. Tabak acknowledged that the most expensive part of interdisciplinary science involves building the team and gathering resources to maintain that team. He also noted that often, when projects end, institutions no longer have an incentive to maintain the team, and he agreed on the need for a retrospective process to evaluate projects deserving of care and maintained support. He emphasized that the right review criteria must be built into the process.

Another member of the Council mentioned that most study sections do not give as high priority to applicants who develop a dataset or invention and wish to disseminate it to other groups, as they accord innovations. Dr. Tabak responded that this issue could be addressed via review criteria discussions. Public health importance is another such issue. ICs can set review criteria and design a subset of applications to provide infrastructure or resources, but flexibility in weighting of review criteria is needed. Dr. Tabak also cautioned that ICs need to communicate to prevent a duplication of mechanisms.

In response to questions about matching funds, Dr. Tabak commented that the NIH is not legally allowed to require matching funds. To do so may result in a situation where a select group of investigators or institutions disproportionately benefit because of large endowments that can be used to match funds. Dr. Tabak also pointed out that strong investigators can be found in unexpected places that may not have matching funds.

Another Council member was skeptical about the utility of a "blinded" review process and felt that the prior record of an investigator must be included in the evaluation. He also pointed out that four years after the American Heart Association had implemented a process where all

reviews were blinded, American abstracts tended to fare worse than they had before the anonymous process began. Applications from prestigious institutions fared worst of all. Dr. Tabak responded that there may still be some value in anonymous processes although implementation will prove challenging.

Concerns regarding score variance also were discussed. One participant wondered how much scores fluctuate depending on who reviews the application, the order in which applications are reviewed, who is in the room at the time the application is reviewed, and who makes comments during the review. He also questioned whether the ranking of grant applications would be the same if the review were conducted with the same group of reviewers a second time. Scores often imply a precision that is beyond the capability of the study sections. Dynamics within a study section can vary widely, and ad hoc reviewers add another layer of complexity. Altogether, precision cannot be easily measured or indicated.

Dr. Tabak agreed with these observations and added that reproducibility and precision most likely will not be high, simply because of human nature. Even so, the scientific community should attempt to find solutions on multiple levels, aligning scoring to better reflect reality. Simply having study section members become acquainted is a first step toward a solution. Dr. Tabak also pointed out that although some IC directors would like to banish binning, others derive some security from the numerical designations.

A suggestion was also made to divide large study sections into smaller subsections to work with a specific category of application. For example, one subsection could review all magnetic resonance applications and another could review all computed tomography applications. Although Dr. Tabak agreed with the suggestion, he cautioned against the extreme of too many subsections and emphasized the importance of finding the right balance. In turn, another Council member recommended a process where criteria are developed in such categories as methodology and quality and rigid criteria are used to bring scores together. This process may have many disadvantages, but it also may provide more logic to scoring. Again, an appropriate balance is needed.

Dr. Tabak encouraged Council members and visitors to reach out to their constituencies and to e-mail him or Dr. Pettigrew with comments.

VI. Staff Presentation: Ultrasound Research Program, Dr. Hector Lopez

Dr. Lopez focused his presentation on diagnostic ultrasound, starting with a brief history of the development of medical ultrasound. This technology began at the end of World War I with the development of echo-sounding sonar and the advent of nondestructive testing. Medical ultrasound was initially conducted in a manner similar to sonar; he gave an example of an individual who was placed in a gun turret filled with water to produce the first ultrasound scans. In the 1960s, ultrasound technology was based on the development of the piezoelectric transducer, which generates pressure waves when stimulated electrically; echo pressure waves are then converted back into electrical signals that are used to produce ultrasound images. Image quality continued to improve through the 1980s with the development of transducer arrays; many single transducer elements are connected together to form an array so that their signals can be

synchronized and coordinated to produce multiple image frames per second, thus producing moving images in real time. This development in ultrasound technology allowed focusing and steering of ultrasound beams at selected depths and positions in the body.

Image quality improved further in the 1990s with the advent of four-dimensional (3D plus motion), real-time ultrasound, and in the 21st century, with the addition of functional ultrasound display methods and other imaging approaches, which have yielded ultrasound image quality that often equals or exceeds that of other imaging modalities. Many new types of transducer technologies have also been developed, including capacitive micromachined ultrasonic transducers (CMUT), which are relatively inexpensive to build, and also acousto-optic transducers. These new types of transducers present the possibility of revolutionizing ultrasound capabilities, applications, and uses.

Research supported by the NIBIB Ultrasound Research Program includes high-frequency ultrasound, image-guided technologies, and tissue characterization. Other grant-supported areas include therapeutic ultrasound, molecular imaging, physical measurement technologies, transducer development, and contrast agent development and applications. Dr. Lopez highlighted several of the program's success stories:

- Reconfigurable arrays**: Dr. Kai Thomenius**, General Electric (GE) Healthcare, and colleagues have taken advantage of CMUT technology to produce reconfigurable arrays. The ultimate goal of this work is the development of low-cost, handheld ultrasound systems, which would be useful to emergency technicians and health care providers.
- The Sonic Window: **Dr. John Hossack**, University of Virginia, and colleagues are working on developing a small ultrasound device called the "sonic window" that is based on C-scan imaging. This device is held over a part of the body, for example, to locate a blood vessel and could be useful for biopsies and for emergency medicine situations.
- High-frequency ultrasound transducers: High-frequency ultrasound offers the advantage of higher resolution but the disadvantage of lower penetration. **Dr. Kirk Shung**, University of Southern California, and colleagues have developed the world's first high-frequency array operating at 30 MHz with 64 transducer elements, which was used to generate an illustrative cross-sectional image of the eye. This group also has made high-frequency ultrasound images of a pregnant mouse with a 45 MHz, single-element transducer.
- Chirp-code excitation and annular arrays: **Dr. Jonathan Mamou and Jeffrey Ketterling,** Riverside Research Institute, has adapted a technology originally developed for radar and applied it to high-frequency ultrasound for imaging of the eye. They have produced images that overcome the problem of limited penetration at distant locations within the eye, such as the fundus of the bovine eye, with increased signal strength and lower noise.
- High-frequency ultrasound detection: **Dr. John Hossack**, University of Virginia, and colleagues are using ultrasound to examine the velocity of motion in the walls of normal and infarcted mouse hearts.
- The opto-acoustic "smart" needle: **Drs. Matthew O'Donnell and Shai Ashkenazi**, University of Michigan, and their colleagues have developed a "smart" needle that is similar to a biopsy needle; it uses fiber optics to produce and detect acousto-optic ultrasound signals at high frequencies to generate high-resolution images of the body.
- The fiber-optic, high-frequency hydrophone probe: **Dr. Peter Lewin**, Drexel University, has created the first fiber-optic hydrophone transducer designed to calibrate other transducers in

the 0 to 100 MHz range. The probe has a fiber tip that is smaller than that of traditional hydrophones, thus eliminating spatial averaging of the acoustic field within a plane, and is sufficiently sturdy to withstand high-intensity focused ultrasound beam calibration.

- Molecular imaging: **Dr. Paul Dayton**, University of California, Davis, and collaborators have developed a technique for attaching unique ligands to ultrasound bubble agents that can bind to specific cellular structures such as those involved in angiogenesis. This type of targeted molecular ultrasound imaging provides a new tool for locating specific tumors or other structures in the body, and may be useful for targeted drug delivery.

Dr. Lopez also highlighted work that, although not supported directly by the NIH, represents important advances in the field of imaging. An example is intravascular ultrasound elastography, which distinguishes hard tissue from soft tissue within blood vessels and can be used to evaluate vulnerable arterial plaques. Other work involves the development of ultra-high frequency 1 GHz transducers for acoustic microscopy, with resolution that is capable of imaging individual cells, and he presented a time-series of images of cell division. The use of ultrasound microscopy offers the advantage of overcoming some problems usually encountered in photon imaging, such as photobleaching, breaking chemical bonds, and other challenges associated with traditional light and electron microscopy, and has the potential for applications in tissue engineering. Dr. Lopez closed by noting the possibilities afforded by all these advances.

VII. Scientific Presentation: Image-Guided Treatments Using Focused Ultrasound, Dr. Kullervo Hynynen

Dr. Hynynen is Professor, Department of Medical Biophysics, at the University of Toronto. He received his Ph.D. in biomedical physics and biomedical engineering from the University of Aberdeen, United Kingdom. His main research interest is the use of High-Intensity Focused Ultrasound (HIFU) and Focused Ultrasound Surgery (FUS), which include applications in noninvasive surgery, vascular surgery, targeted drug delivery and gene therapy.

Dr. Hynynen focused his presentation on therapeutic ultrasound, and opened his presentation by providing a historical background of focused ultrasound surgery (FUS). The field of FUS began in 1942 with the targeting of brain lesions after removing the skull. In the 1950s and 60s, William and Francis Fry used targeted x-ray to combat Parkinson's disease and focused methods were used in Japan for cancer treatments. In the 1970s and 80s, FUS advanced with the development of diagnostic ultrasound guidance by Francis Fry and colleagues and the invention of diagnostic ultrasound guidance systems for the eye and the prostate. In the 1990s, clinical ultrasound-guided systems were developed for the liver, kidney, bladder, bone, and breast. At the turn of the century, several companies in China began developing these clinical devices, some of which have been successful.

He noted that ultrasound can interact with tissues in several ways and produced different bioeffects. One such effect is temperature elevation, which results from a beam of high energy at a sufficiently high power. Continued temperature elevation beyond a certain time point results in tissue necrosis, and the threshold varies with the type of tissue. Extremely high temperature elevation results in tissue vaporization. Temperature elevation effects can be exploited to sensitize tissue for chemotherapy or x-ray or to induce apoptosis, necrosis, or vascular changes.

Ultrasound-guided FUS, which also takes advantage of temperature elevation effects, has been tested in clinical trials for prostate tumors. Patients are now in their 15th year of follow-up, and the treatment appears to be working well, with an 87-percent rate of negative biopsies and only 5 percent of patients experiencing complications. Although this technique allows a beam to be aimed, it does not yet allow quantifying exposure.

Dr. Hynynen discussed research using magnetic resonance imaging (MRI)-guided FUS to treat uterine fibroids. This work, which began in 1991 with an NIH grant and in collaboration with GE Healthcare, exploited temperature elevation effects, using focused ultrasound to target and ablate the fibroid without hitting other structures. This approach offered the added advantages of improved targeting, online temperature monitoring and exposure quantification, and online tissue effect evaluation. Dr. Hynynen stressed the importance of online monitoring because of the amount of variation among locations and among patients. Follow-up imaging has shown that MRI-guided FUS results in reduced fibroid volume, and the majority of women treated in this manner report reductions in symptom frequency and severity. Few complications have been reported worldwide. The U.S. Food and Drug Administration approved the use of MRI-guided FUS in 2004 for the treatment of uterine fibroids, and approximately 50 systems are now in use worldwide.

In Phase I and II clinical trials, FUS has resulted in 97-percent destruction of breast tumors, with one complication from operator error. Investigators also have developed a system to adapt FUS for the brain. This type of treatment has been difficult due to challenges in transmitting ultrasound through the skull and potential problems associated with heating of the bone; when ultrasound reaches bone, there is a spike in intensity, resulting in high temperature elevation. Dr. Hynynen described an InSightec Mark3 prototype that overcomes this problem by arranging transducers in a 3D array around the entire head. In clinical trials, this system appears to focus the ultrasound beam precisely, with no temperature elevation anywhere else in the brain.

Vascular occlusion is another type of treatment exploiting temperature elevation. Dr. Hynynen showed examples of vascular occlusion in the kidney and noted that this treatment could be useful on the battlefield. Nerve blockage is yet another type of treatment area. Sonication produces a temporary block, and in 80 to 90 percent of cases, the nerve recovers. This type of treatment may be useful to treat pain. Another treatment, histotripsy, uses multiple short bursts of HIFU to vaporize tissue and form a cavity. Histotripsy has been tested in the dog heart *in vitro* and *in vivo* and may have some applications in medicine. Ultrasound or MRI-guided thermal coagulation of tumors also takes advantage of temperature elevation effects.

An additional bioeffect associated with ultrasound is cavitation that arises from the formation of and interaction of gas bubbles with ultrasound. Vibrations occur at ultrasound frequencies that can cause bubble oscillations, leading to streaming, mechanical stress, or membrane effects. Limited power is needed; milliwatt power levels can produce large effects in tissue, with no heating effects. At higher amplitudes, interacting gas bubbles do not oscillate. They grow and collapse, resulting in high local temperature and pressure, generation of shock waves and free radicals, and mechanical tissue disintegration. This effect, known as sonoporation, can be exploited to enhance the permeability of cell membranes or blood vessel walls, thereby aiding in targeted drug delivery. Dr. Hynynen described an example in which sonoporation was used to

introduce a silencing RNA to suppress enhanced green fluorescent protein expression. He also described the use of targeted ultrasound to open the blood-brain barrier for drug delivery. This approach occurs rather quickly, within approximately a minute from the start of sonication.

MRI-guided, focused ultrasound has also been used to deliver chemotherapy to the rat brain, and allows investigators to monitor how much agent has been delivered. This approach has been tested for liposomal doxorubicin and for an antibody-based agent. Several studies have shown the feasibility of exploiting microbubble effects to deliver gene therapy, and other studies are underway to explore the use of ultrasound to activate drugs that have been injected into the blood stream.

Dr. Hynynen discussed the CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA) trial, in which recanalization occurs within 2 hours in 25 percent of patients receiving ultrasound and transluminal balloon angioplasty (TBA) bolus, compared with 8 percent of patients receiving TBA bolus alone. This percentage could increase with the ability to focus ultrasound through the skull. Although this treatment may work through radiation force effects, the mechanism of action is not known and must be identified and studied before it can be improved.

In closing, Dr. Hynynen predicted that in the future, FUS will play a key role in clinical interventions and in many cases make current treatments and surgeries, such as open heart surgery, obsolete. He anticipated that FUS will become increasingly useful in stroke treatment, tumor and vascular surgery, cardiac ablation for arrhythmias, image-targeted molecular delivery for the brain, image-targeted drug or gene delivery, pain treatment, and radiation and chemotherapy.

Discussion

A Council member acknowledged that FUS is a promising technology, but expressed concern that this procedure will occupy an expensive MRI machine for a significant duration given the extensive time needed to complete a case. This Council member also asked about the cost-effectiveness of FUS compared with radiofrequency ablation and whether the cost curve could be overcome. Dr. Hynynen acknowledged that the cost is high at present but that the development of array technologies will reduce the time requirement. He noted that the time required for brain treatments using FUS is comparable to that required for traditional brain surgeries. For nerve blocks and bone tumors, emerging technologies will allow the monitoring of thermal effects using diagnostic ultrasound rather than MRI, which should greatly reduce the cost of treatment.

Another Council member expressed concern about ultrasound-associated changes in fibrosis and tissue boundaries, which may make it difficult to determine whether the entire tumor has been removed or to monitor the patient following treatment. The Council member noted that many surgeons specializing in breast cancer are reluctant to adopt FUS for this reason. Dr. Hynynen acknowledged difficulties in making FUS effective in breast cancer treatment and suggested that this approach be tried on locally advanced tumors following chemotherapy but prior to traditional surgery. He also pointed out that FUS most likely would be applied to situations like prostate cancer, where the risk for complications associated with traditional surgery is high.

In response to other questions about FUS versus radiation seed techniques, Dr. Hynynen noted that FUS is faster and less invasive, and offers controlled delivery; however, the advantage of one approach over another is not yet clear. In response to other questions, Dr. Hynynen noted that MRI guidance offers good visualization of the nerve bundle in the prostate. The ultrasound beam can be focused to 1 mm or less.

Encouraged by the development of FUS for stroke intervention, a Council member asked how Dr. Hynynen envisioned future research in terms of intervention with thrombotic and hemorrhagic stroke. Dr. Hynynen noted that it is difficult to penetrate bone to determine exposures; however, advances in technologies for delivery may make such technologies useful for emergency response. The key is understanding the mechanism, the side effects, and ways to treat the stroke without breaking blood vessels.

Another member of the Council noted that FUS presents a new paradigm for minimally invasive therapy, and agreed that MRI offered the added advantage of temperature monitoring. The Council member asked whether there were less expensive ways to monitor temperature. Dr. Hynynen responded that some work in ultrasound-based temperature mapping has been conducted in which coagulation of tissue was detected in phantoms, and could be used as an indirect indicator of temperature rise in the tissue. However, this problem has not yet been solved *in vivo*, and Dr. Hynynen was unsure whether this type of ultrasound temperature mapping would work. He further pointed out that the use of ultrasound for stroke treatment would work because it is not done at a high-enough power for temperature effects to be an issue.

VIII. Adjournment

The open session of the NACBIB meeting was adjourned at 12:45 p.m.

IX. Closed Session

This portion of the meeting, involving specific grant review, was closed to the public in accordance with the provisions set forth in Section 552b(c)(4) and 552b(c)(6) Title 5, U.S. Code and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2). The closed session was adjourned at 3:45 p.m.

X. Certification

We certify that, to the best of our knowledge, the foregoing minutes and attachments are accurate and complete.[2]

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Anthony Demsey, Ph.D.
Executive Secretary,
National Advisory Council for Biomedical Imaging and Bioengineering
Director,
Office of Research Administration
National Institute of Biomedical Imaging and Bioengineering

_____

Roderic I. Pettigrew, Ph.D., M.D.
Chairperson,
National Advisory Council for Biomedical Imaging and Bioengineering
Director,
National Institute of Biomedical Imaging and Bioengineering

[2] These minutes will be approved formally by the Council at the next meeting on January 25, 2008, and corrections or notations will be stated in the minutes of that meeting.