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 14, 2005

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its ninth meeting on September 14, 2005, at the Pooks Hill Marriott in Bethesda, Maryland. Dr. Roderic I. Pettigrew, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), served as Chairperson.

In accordance with Public Law 92–463, the meeting was open to the public on Wednesday, September 14, 2005, from 8:00 a.m. to 12:30 p.m. for the review and discussion of program development, needs, and policy. A quorum was achieved for this meeting.

Council members present

Dr. Ronald L. Arenson
Dr. Carlo J. De Luca
Dr. David J. Dzielak
Dr. Don Giddens
Dr. Augustus O. Grant
Dr. Robert I. Grossman
Dr. Linda C. Lucas
Dr. Norbert J. Pelc
Dr. Rebecca R. Richards-Kortum
Dr. Stephen A. Williams
Dr. Frank C. Yin
Dr. James A. Zagzebski

Ex officio members present:

Dr. James G. Smirniotopoulos
Dr. Andrew Watkins

Ex officio members absent:

Dr. Elias A. Zerhouni, Jr.

Executive Secretary:

Dr. Anthony Demsey

[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.

NIBIB staff present for portions of the meeting:

Ms. Lillian Ashley
Dr. Prabha Atreya
Ms. Sheila Barrett
Mr. Ryan Bess
Ms. Angela Burks
Ms. Nancy Curling
Dr. Bonnie Dunn
Ms. Cheryl Fee
Ms. Shirley Finney
Ms. Rajal Ganatra
Dr. David George
Ms. Colleen Guay-Broder
Dr. John Haller
Dr. Donald Harrington
Dr. William Heetderks
Ms. Christine Hollingsworth
Dr. Christine Kelley
Ms. Mary Beth Kester
Dr. Henry Khachaturian
Dr. Brenda Korte
Ms. Danielle Lewis
Dr. Alan McLaughlin
Mr. Todd Merchak
Mr. Nicholas Mitrano
Dr. Peter Moy
Mr. Aaron Nicholas
Ms. Donna Pearman
Dr. Grace Peng
Dr. Roderic Pettigrew
Dr. Belinda Seto
Ms. Karen Shields
Ms. Theresa Smith
Ms. Casey Stewart
Ms. Angela Taylor
Dr. Carol Torgan
Ms. Shana Townsend
Ms. Florence Turska
Ms. Stacy Wallick
Dr. Fei Wang
Mr. Elijah Weisberg
Ms. Carolyn Williams
Ms. Li-Yin Xi
Dr. Yantian Zhang

Members of the public present for portions of the open meeting:

Dr. Richard Baird, Washington University
Ms. Pat Ford-Roegner, American Institute for Medical and Biological Engineering
Dr. Gary Glover, Stanford University
Ms. Mariana González del Riego, Rose Li and Associates, Inc.
Ms. Jeanie Kennedy, AAOS
Dr. Rose Maria Li, Rose Li and Associates, Inc.
Mr. Ed Nagy, Academy of Radiology Research
Dr. Robert Nerem, Georgia Tech
Ms. Liz Parry, American Institute for Medical and Biological Engineering
Mr. Gene Russo, Research Policy Alert

Other Federal employees present:

Dr. Sally Amero, CSR
Dr. David Brown, FDA
Dr. Mrunal Chapekar, NIST
Dr. Peter Kirchner, DOE
Dr. Albert Lee, NIST
Dr. Zhenya Li, CSR
Dr. Kyle Myers, FDA
Ms. Michelle Rodrigues, SRI
Dr. Ross Shonat, CSR
Dr. Richard Swaja, DOE

I. Call to Order: Dr. Anthony Demsey

Dr. Demsey called the ninth NACBIB meeting to order. He reminded attendees that since the morning session of the Council meeting was open to the public, comments about applications should be reserved for the closed afternoon session. Dr. Demsey informed attendees about an orientation session and ethics update that was held for new members the previous afternoon, as well as a change in the method for handling the annual ethics update for some continuing members. The Office of Government Ethics recently ruled that the annual ethics update now can be completed using distributed reading materials and Web sites, as opposed to mandatory attendance at an orally delivered presentation. Dr. Demsey introduced Dr. Pettigrew, who formally welcomed all participants.

II. Opening Remarks: Dr. Pettigrew

New and Transitioning Council Members

Dr. Pettigrew identified and welcomed three new Council members:

- Dr. Augustus Grant, Director of the Section of Clinical Electrophysiology at Duke University Medical Center
- Dr. Ronald Arenson, Chairman of Radiology at the University of California, San Francisco
- Dr. Don Giddens, Dean of Engineering at the Georgia Institute of Technology

Dr. Pettigrew also announced that:

- Dr. Rebecca Richards-Kortum recently moved from the University of Texas to Rice University.
- Dr. Janie Fouke, former Council member, moved from Michigan State University to the University of Florida.
- Dr. Richard Swaja will be leaving NIBIB on September 23, 2005, to assume a new position at the Oak Ridge National Laboratory (his actual employer during the time he has been working with NIBIB).
- Dr. Mrunal Chapekar has joined NIBIB on a 1-year detail from the National Institute of Standards and Technology (NIST).

III. Director's Report: Dr. Pettigrew

Dr. Pettigrew summarized the progress made by the Institute since the January 2005 Council meeting, the budget outlook, significant events, and scientific highlights and initiatives.

NIBIB Budget

As discussed at the last Council meeting, the NIBIB fiscal year (FY) 2005 budget is approximately $298 million. The President's proposed budget for FY 2006, which already has been endorsed by the House, is approximately $300 million. The Senate has suggested a slightly higher amount of $309 million. The percentage of the total budget distributed to each activity remains as it was last year, the one exception being a 1-percent increase in expenditures for developing the Intramural Program. Dr. Pettigrew mentioned that the announcement for a new Scientific Director of the Intramural Program will close on September 15, 2005, and that the search committee will review the applicants to recommend a short list to the Institute Director. In reviewing the grant award history from FY 2002 through FY 2005, Dr. Pettigrew observed that

awards tracked the large budget increase from FY 2002 to FY 2003. This jump largely was due to a one-time transfer of $150 million in start-up monies (consisting of grants and uncommitted funds) to the Institute. An interesting part of the history of NIBIB is that the number of investigator-initiated applications has continued to rise each year. From FY 2002 to FY 2003, there was a 250-percent increase in these applications, with the real total increase being closer to 500 percent when taking into account the 10 requests for applications (RFAs) that were issued during that period. A further 100 percent increase in investigator-initiated applications was experienced from FY 2003 to FY 2004, and a 30-percent increase was seen from FY 2004 to FY 2005. The NIBIB received approximately 1,700 applications this past year. Dr. Pettigrew noted that NIBIB receives 3 percent of the applications that are submitted to the National Institutes of Health (NIH) yet operates with only 1 percent of the total NIH budget.

Funding for New Investigators
Dr. Pettigrew described the first-year impact of the NIBIB policy to increase the pay line for new investigators by 5 percentage points. In FY 2005, there were 14 new investigators funded at the 20th percentile (the nominal FY 2005 NIBIB pay line) and 5 additional new investigators funded between the 20th and 25th percentiles.

NIH Roadmap Funding
The current NIBIB contribution to the Roadmap program is approximately $1.8 million. The Institute is leading two initiatives: (1) Robotics/Instrumentation Technology Development, and (2) Development of High-Resolution Probes for Cellular Imaging. NIBIB also plays a significant collaborative role in overseeing the National Centers for Biomedical Computing. Taken together, these initiatives contribute a total of $6.8 million in Roadmap funds to benefit projects in the NIBIB community.

NIBIB Initiatives
Dr. Pettigrew directed the Council's attention to the 2006 House Appropriations Committee Report Language that cited NIBIB as an Institute that has taken a leadership role in examining "scientific questions that can be addressed by collaboration between a life and physical scientist." As a result of this report, NIBIB has developed a new policy that gives special consideration to research grant applications that bridge and integrate the life and physical sciences. This special consideration would be applied to applications just below the payline, and/or when considering select pays.

Dr. Pettigrew updated Council members on the upcoming initiative for Quantum projects, which are highly focused, collaborative research and development projects that require technological approaches and will result in significant (quantum) improvements in health care within 7 to 10 years. The approach is to begin by making five to seven 3-year exploratory grants (Phase 1). These will provide sufficient funds to assemble an interdisciplinary team, develop the research plan and infrastructure, perform feasibility studies, demonstrate capabilities, and subsequently prepare a detailed application for Phase 2 support. The RFA will be issued in late 2005 with the goal of making awards in late FY 2006. These five to seven exploratory grants are expected to form the basis from which larger establishment grants (Phase 2) will be awarded in late FY 2009 in order to conduct focused research and achieve the stated goals. The strategy will be to seek collaboration during Phase 2 between the private sector and the appropriate Institutes and

Centers (ICs) for the medical condition that is being addressed.

NIH Operations and Policies
A recent draft bill from a committee chaired by Congressman Joseph Barton (R-TX) includes some rather significant changes to the structure and operation of the NIH. This bill proposes to:

- Classify existing ICs into two major categories—mission-specific Institutes and science-enabling ICs.
- Establish within the Office of the NIH Director a Division of Program Coordination, Planning, and Strategic Initiatives.
- Limit the total number of ICs to the current number, capping the number of mission-specific ICs at 14 and capping the number of science-enabling ICs at 10. (NIBIB falls within the latter category.)
- Establish a common fund for trans-NIH research activities (overseen by this new division in the Office of the Director).
- Establish four specific authorization of appropriation line items for FY 2007 through FY 2009.
- Authorize the NIH Director, in conjunction with the Director of the National Science Foundation (NSF) and the Secretary of Energy, to allocate funds to ICs to award grants focusing on bridging and integrating life and physical sciences, as well as high-risk/high-reward research.

Dr. Pettigrew also reported that both the Office of Management and Budget and the NIH Office of Extramural Research have requested input from the community on the way the NIH recognizes principal investigators (PIs) on grants. Currently, only a single PI per grant is recognized. With more senior scientists collaborating on interdisciplinary efforts, there is interest in conferring recognition to multiple PIs on a single grant. Dr. Pettigrew urged any interested Council member to comment on this issue.

Meetings and Workshops
Dr. Pettigrew highlighted three important NIBIB grantee meetings and a workshop that were held recently: (1) The annual grantee meeting focusing on investigators who received awards in response to the 10 RFAs issued between FY 2002 and FY 2003, (2) the interdisciplinary Bioengineering Research Partnership (BRP) grantee meeting, (3) the P41 grantee meeting, and (4) the Neural Interfaces Workshop.

Honors and Awards
Dr. William Heetderks recently was honored by the Alfred Mann Foundation for excellence in the field of functional neuromuscular systems. Specifically, Dr. Heetderks' work on the radio frequency (RF)-powered control over neural prosthetic implants was the initial inspiration for the development of the Alfred Mann Foundation's new project on the microstimulator/sensory system. Dr. Heetderks' continued work in the areas of closed-loop control of functional neuromuscular stimulation, cortical control of neural prostheses, spinal cord stimulation, and cochlear implants has inspired a community of scientists across the world.

NIBIB Web Site
In fall 2005, a redesigned NIBIB Web site will be unveiled thanks to the hard work of Dr. Carol

Torgan and Ms. Colleen Guay-Broder. The new site will be improved in both appearance and functionality. The aim is to provide more useful information to the grantee community, as well as to inform the general public about how the various funded technologies are being used to address common medical problems.

Scientific Highlights
Dr. Pettigrew highlighted the work of three NIBIB grantees in the areas of targeted vascular delivery systems and nuclear magnetic resonance (NMR) structural studies of membrane proteins.

- **Dr. Jeffrey M. Davidson**, Vanderbilt University, has developed a platform technology in which nanoparticles can be directed at specific vascular targets (monoclonal antibodies or homing peptides) on the basis of selective addressing. These nanoparticles can carry various payloads that allow for both imaging and therapy applications.
- **Dr. Katherine Ferrara**, University of California, Davis, has been working on a similar system in which one ultrasound frequency is used to move gas-filled oil droplets with homing particles on the outside toward specific endothelial targets. A different ultrasound frequency then is used to fragment the nanoparticle in contact with the target, delivering a drug contained in the oil shell.
- **Dr. Stanley J. Opella**, University of California, San Diego, is using NMR to elucidate the three-dimensional (3D) structure of drug-binding sites on G protein-coupled receptors. This work is based on the observation that the physical orientation of the nuclei that are responsible for the NMR signal can be used to decipher the 3D structure of the target by rotating the sample in the magnetic field (angular dependence). With membrane proteins that are difficult to crystallize and solubilize, this *in situ* approach offers a significant advantage over competing techniques of x-ray crystallography and aqueous solution phase NMR.

To illustrate the importance of delineating the structure of G protein-coupled receptors, Dr. Pettigrew presented some recent work involving two genes that code for a class of G protein-coupled receptors in taste receptors, which were knocked out of mice. As a result of this gene knockout, the mice do not lick the sweets that they generally prefer. Moreover, if the genes are rescued in mice by inserting a human gene such that they now begin to make G protein-coupled receptors, the mice do not prefer the class of sweets they generally prefer, but rather their taste preferences for sweets are similar to those of humans. This is fascinating because (1) it demonstrates that the preference is not just in the brain—it is controlled at the level of these G protein-coupled receptors; and (2) it shows that small differences in amino acid composition between G protein-coupled receptors in mice and in humans are responsible for the preference of sweets that humans have.

IV. Review of Regulations, Policies, and Procedures: Dr. Demsey

Council Regulations, Policies, and Procedures
Dr. Demsey summarized the elements of the Government in the Sunshine Act and the Federal Advisory Committee Act that govern all Advisory Council meetings. These acts require the Department of Health and Human Services to open Advisory Committee 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, except for the review of individual grant applications.

In briefing Council members on guidelines for conflicts of interest and confidentiality issues, Dr. Demsey emphasized the importance of maintaining confidentiality in all settings, formal and informal. Members were given examples of when these guidelines should be applied and were offered the opportunity to ask questions to clarify any areas of uncertainty.

Attendees also were reminded that for the duration of the meeting, they were special government employees bound by Federal standards of conduct and, therefore, not allowed to engage in lobbying activities.

Future NACBIB Meeting Dates
The next NACBIB meeting is scheduled for January 24–25, 2006, at the Marriott Bethesda North Conference Center. Dr. Demsey acknowledged the Council's preference for holding future meetings on Fridays or Mondays but stated that it was probably too late to change the January meeting dates. He suggested that the May meeting be held on Friday, May 19, 2006, at the Marriott Bethesda North Conference Center.

Approval of May 25–26, 2005 NACBIB Meeting Minutes
A motion was entertained to approve the minutes of the May 25–26, 2005, NACBIB meeting. The minutes were approved unanimously without modification.

V. Joint Report of Strategic Plan Development and Training and Career Development: Dr. William Heetderks and Dr. Henry Khachaturian

Strategic Plan Implementation
Dr. Heetderks informed the Council that a major new initiative for FY 2006 would be the implementation of the Quantum project grants. In addition, a retreat would be held in October 2005 to determine priorities for the Institute in FY 2007, as well as to carve out a 5-year plan identifying high priorities.

FY 2005 Training and Career Development Portfolio
Drs. Khachaturian and Heetderks provided a summary of the many grants and programs currently being used to support training and career development as follows:

- Institutional training grants (T32) currently are supporting about 143 pre- and postdoctoral students with approximately a 2:1 ratio of predoctoral to postdoctoral students. There are approximately 27 of these awards.
- Individual fellowships also are being used to support predoctoral and postdoctoral

students in the respective ratio of about 2:1. Twenty-two trainees are currently supported.

- There are currently 21 mentored career development (K) awards, which are given for late postdoctoral or early faculty appointments. The recent K25 award mechanism recruits talented individuals who have physics/engineering/mathematics backgrounds to careers focused on biological or biomedical issues.
- Diversity supplements support individuals from underrepresented minorities, individuals with disabilities, and individuals from socioeconomic disadvantaged backgrounds. There are currently nine such awards that provide 1 or 2 years of training to a range of applicants from high school students to senior investigators.
- There are currently seven residency supplement awards.
- Loan repayment contracts are being used to repay the educational debt of clinicians who agree to devote part of their career to research. Four awards have been made.
- The Bioengineering and Bioinformatics Summer Institute (BBSI), in partnership with the NSF, currently is funding nine programs across the country to encourage those with physics and engineering backgrounds to enter the fields of bioengineering and bioinformatics. About 128 students are being supported.
- The Biomedical Engineering Summer Institute Program (BESIP) brings undergraduate students to the NIH campus to work with an NIH intramural researcher for 10 weeks during the summer. There are currently 16 trainees in this program. Like the BBSI, the BESIP is broadly targeted to mathematics, physics, computational science, and engineering students.
- The NIH-NIST Joint Fellowship Program is a postdoctoral mentoring program that currently is supporting four fellows who spend time at both agencies.
- In partnership with the Howard Hughes Medical Institute (HHMI), funds have been committed toward the establishment of the HHMI-NIBIB Interfaces Initiative for Interdisciplinary Graduate Research Training Program. This program will make 10, 3-year awards by early 2006. NIBIB will become part of the program in FY 2009 by supporting traditional training grants.

New Investigators

Dr. Heetderks reported that NIBIB is encouraging and supporting the development of new investigators in the expanding research fields of engineering, physical, and imaging sciences. In FY 2004, there were 120 applications and 15 awards. The estimated number of applications in FY 2005 is 135, and approximately 22 awards will be made. In terms of NIBIB R01 awards to new investigators from engineering and physical science departments, 52 applications were received, and 2 awards were made in FY 2004. It is estimated that 45 such applications will be received in FY 2005, and 7 awards made. Dr. Heetderks noted that the small increases in the number of anticipated applications between FY 2004 and FY 2005 were accompanied by equally small increases in the expected number of awards. Furthermore, the average age of an investigator receiving his or her first R01 grant has risen from age 34 to about age 38 over the past 20 years. There is roughly a 2- to 3-year gap between appointment as an assistant professor and first grant award. Current and planned NIBIB activities include: (1) selective funding of new investigators with priority scores within 5 percentile points of the stated pay line, (2) making mentored career development awards, (3) holding grant application-writing workshops at various meetings, and (4) conducting a training needs assessment study.

A number of Institute Directors have proposed a program to address the increasing time between postdoctoral training and fully independent research. The current thinking is that an NIH-wide combination career transition program consisting of two pieces (K22/R22) may be used to provide mentoring for 2 years before an applicant secures a position, followed by an additional 3 years of support during the R22 phase while the applicant is working toward the first R01 grant.

Although the Whitaker Biomedical Engineering Research (3-year) Grants have been instrumental in facilitating the transition between training and independent research, two other new investigator programs now are being offered by the NIH. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has been experimenting with the use of small R03 grants ($50,000) to increase the success rate of R01 applications. Other data from the past 6 years suggest that 42 percent of the investigators who received an NIAMS R03 grant were able to get a subsequent R01 grant, while only 17 percent of those who were unsuccessful in getting an R03 grant were able to secure a subsequent R01 grant. There are multiple interpretations for these data, and one must continue to look far into the future to observe final outcomes. The second program, Outstanding New Environmental Scientist, is supported by the National Institute of Environmental Health Sciences and provides a type of honorific R01 award with the following restrictions on investigators:

- Applicants must be within 8 years of receiving a Ph.D.
- Investigators must allot at least 50 percent effort to the funded project.
- Awardees must have an external Advisory Committee.

At the conclusion of this presentation, a Council member inquired about the average age at first R01 award over the past 25 years. Dr. Belinda Seto stated that a report showed that recent graduates are engaging increasingly in multiple postdoctoral appointments, followed by research associate positions, which are not considered academic appointments. The postdoctoral appointment cycle has lengthened over time, with faculty positions occurring later in a researcher's career. Dr. Seto also noted that the data analysis was performed with regard to discipline and degree only.

Dr. Khachaturian informed the Council that the Institute welcomed advice on two programs—the Residency Supplement program and the Predoctoral Fellowship program. With respect to the former and in response to the first application deadline in FY 2005, three applications were received and funded. The second deadline brought in 16 applications, of which 4 were funded. Because the Residency Supplement program has started to gain momentum, the program announcement was re-released in May 2005 with upcoming deadlines of October 21, 2005, and February 21, 2006.

Dr. Khachaturian specifically requested advice on the possibility of extending the Residency Supplement program eligibility to the fellowship years. A member of the Council endorsed this idea, noting that it has been difficult for clinicians at his institution to determine how to take a year off from their residencies to complete this training. He argued that timing such training at the beginning of a fellowship period would result in more and better applicants. Another Council member disagreed, as many residents do take a year out of their residencies to do research and manage to do well.

One Council member advised that the fellowship program should be accredited but the fellowship need not necessarily be. This Council member also expressed concern about the timing of the fellowship. Because most are 1-year fellowships, a candidate would have to apply for this program before acceptance as a fellow. During a residency program, there are 4 years in which to apply.

Dr. Khachaturian commented that the Institute has received several requests from individuals who are finishing their residencies in 6 months to extend the 1-year program into their fellowship years. In the past, the program has been quite flexible in granting these requests. A Council member expressed his support for encouraging clinicians to enter into research by broadening the program to include fellows. The logistical and temporal difficulties an applicant may encounter due to the time period in which she or he must apply for the fellowship potentially could be overcome if the fellowship were extended for a second year.

Another Council member envisioned the program funding 1 year of research training, with the second year of the fellowship funded through the normal clinical mechanism. The Council was reminded by another member that all radiology fellowships last for 1 year. Funding a second year through the normal clinical mechanism would require a change in the way most fellowships are structured. Dr. Pettigrew offered the hypothetical situation in which an applicant receives an option for a second year of fellowship at the time of application, and this second year then could be used for the Residency Supplement program. One Council member agreed that this would be a viable option. He added that there is a fair amount of discussion within radiology departments about a change in the residency structure, leading to a shorter, general residency. This would allow for more time in subspecialty fellowships incorporating research. This structure also would fit very well in the model described by Dr. Pettigrew.

Participants were reminded that this program would be applicable not only to radiology, but to any department in which there were multiple-year fellowships. While supportive of the initiative, one Council member observed that the institutions most likely to take advantage of this program are those with radiology departments, infrastructure, and funded PIs.

Dr. Pettigrew explained that the idea is to design a fellowship program that will encourage more traditionally, clinically oriented young minds to go into research. There are models in fields other than radiology, such as medicine, with extended fellowships containing a research year as a component. For example, the program in cardiology at Duke University Medical Center only requires 3 years of fellowship, but all of the fellows complete 4 years, with the last year spent in research.

Predoctoral Fellowship Program

NIBIB is one of the few Institutes that supports the Predoctoral Fellowship program. From 2003 to 2005, the number of applications has continued to increase, raising the question of sustainability. Dr. Khachaturian suggested that this fellowship program cannot continue to grow at the expense of the overall training program unless the Institute considers this to be desirable. Currently, applicants are asked to address the relevance to biomedical imaging or bioengineering, as well as the novelty of the technology. Dr. Khachaturian sought Council advice

regarding the application screening process, in particular whether special consideration should be given to institutions that do not have NIBIB training grants and whether thesis advisers who either have current NIBIB grants or are doing research that is clearly relevant to the NIBIB mission should be favored.

One Council member voiced support for awarding predoctoral fellowships to trainees at institutions that do not have NIBIB training grants, while another expressed reservations. A third member was supportive only if the institutions already have predoctoral fellows and not mostly postdoctoral fellows, after Dr. Khachaturian reminded the Council that there is a mixture of predoctoral and postdoctoral trainees with an approximate ratio of 2:1. Giving special consideration to those advisers who already have NIBIB grants or even to those that perform research relevant to the current NIBIB mission was seen as controversial. One Council member urged that relevance to the current NIBIB mission could be interpreted quite broadly.

In closing, Dr. Khachaturian proposed that prior to the formulation of formal recommendations by the Council, experience be gained from two more rounds of applications. At that point, this additional information would be brought back to the Council for further consideration. Council members who had contributed to the discussion clarified that they were supportive of the program and only were concerned about the logistics of its implementation.

VI. Scientific Presentation—NIBIB Magnetic Resonance Imaging Portfolio:
Dr. Alan McLaughlin

Portfolio Overview
Dr. McLaughlin is a Program Director in the Division of Applied Science and Technology at NIBIB. His portfolio includes magnetic resonance imaging (MRI) and magnetic resonance spectroscopy. His background is in physics, biophysics, and physiology, and he has held academic positions at Oxford University (Biochemistry Department), Brookhaven National Laboratories (Biology Department), the University of Pennsylvania (Biochemistry/Biophysics Department), and the Intramural Program at the NIH (i.e., National Institute on Alcohol Abuse and Alcoholism and National Institute of Mental Health [NIMH]).

Dr. McLaughlin provided a broad overview of the MRI portfolio, which contains approximately 110 grants in six areas. The first area, General MRI Techniques, includes a number of subtopics. In NMR Spectroscopic Imaging, proton NMR spectra are produced for each voxel in an image. These data can be used to image biochemical constituents, such as creatine and coline, in brain tissues. Several mechanisms (T1, T2, and recently iZQF) can be used to provide intrinsic contrast in MRIs. MRI also can be combined with other imaging approaches, such as optical imaging. Elastography can be used to mount the strain tensor in tissues noninvasively. The anisotropy of the diffusion tensor for water and white matter can be used to produce maps of white matter tracks in the brain. Hyperpolarized gases, such as xenon and helium, also can be used to map and quantitate airflow in the lungs.

The second area is General MRI Instrumentation, which contains four subtopics. One of the most prominent subtopics is High-Field MRI. The highest available magnetic field strength for human MRI instruments has increased from 4 tesla to 9.4 tesla during the past decade. This

improvement in field strength, and redesigned RF and gradient coils have led to improved sensitivity and high-speed parallel imaging in which MRI images are obtained in a much shorter time.

The third area, Functional MRI (fMRI), began about 10 years ago when it was discovered that the intensity of the magnetic resonance (MR) signal in the brain was increased by 1 to 2 percent when the brain was involved in a task. This finding has been used by a large number of groups to map out areas of the brain that are activated in different tasks.

The last three areas of the MRI portfolio are:

- MRI Techniques for Specific Organs involves the design of different MRI techniques for different organs;
- *In Vivo* Electron Paramagnetic Resonance Imaging, in which maps of oxygen tension in tumors are produced; and
- MRI Techniques for Physiological Measurements that can yield quantitative maps of oxygen consumption and blood flow.

High-Field MRI and High-Speed Parallel Imaging

The three central problems in clinical MRI involve improving (1) sensitivity to obtain better quality images, (2) spatial resolution to obtain finer spatial detail, and (3) temporal resolution to complete images in a single breath-hold, conduct shorter clinical exams, and decrease "distortion," "blurring," and "drop-out" artifacts. Increasing sensitivity can be achieved by obtaining data at a higher magnetic field strength. Spatial resolution can be improved through the acquisition of more data. Finally, the problem of temporal resolution can be resolved by using high-speed parallel imaging.

Redesign of High-Field RF Coils

By carefully redesigning the RF coils for high-field strength, a common problem (i.e., drop out) seen in early high-field images of the head can be removed. New coils have been designed by groups like the one led by Dr. Kamil Ugurbil at the University of Minnesota so that the RF field is constant over the entire head. This gives relatively homogeneous sensitivity and greatly improved images with good contrast between white and gray matter. At 9.4 tesla, veins in the deep gray matter and white matter tracts can be seen. These features simply cannot be observed at lower magnetic field strengths.

High-Speed Parallel Imaging

The high-speed parallel imaging technique uses a phased array of independent MR receiver coils to acquire MRI images faster by taking more data sets. The general rule of thumb is that n independent receiver coils can yield an increase in the rate at which data are acquired up to a factor of n-fold. There is a tradeoff, however, between the rate at which data can be acquired and the noise contained within the image.

High-Field and High-Speed MRI Applications

In fMRI, both sensitivity and contrast are increased in going to high-field strengths. An example of the value of this technique is provided by a series of experiments in human tonotopy conducted in the laboratory of Dr. Ugurbil. Using high-field fMRI, researchers were able to map

out sites of activation in the human primary auditory cortex in extremely high resolution and contrast in response to tones. Dr. Oded Gonen at New York University's Department of Radiology has been trying to optimize spectroscopic imaging at high fields by combining chemical shift imaging with Hadamard spectroscopic imaging. Dr. Daniel Sodickson of Harvard University and his collaborators also have increased the signal-to-noise ratio and spectral resolution successfully by applying parallel imaging to body imaging at 1.5 tesla. The time required to complete a 3D image has been reduced by a factor of 12, making the total time for scanning the abdomen 22 seconds, which can be completed easily in a single-breath hold. This technique also has been applied to produce rapid 3D coronary MR angiography. In this case, angiograms of all four coronary arteries can be obtained without having to retake all of the data.

VII. Scientific Presentation—Detection and Disclosure of Incidental Findings in Imaging Research: Dr. Gary Glover

Dr. Glover is Professor of Radiology, Neurosciences, and Biophysics; Professor of Electrical Engineering; and Director of the Radiological Science Laboratory at Stanford University. His research interests encompass the physics and mathematics of imaging with MR and presently are directed in part toward the exploration of rapid MRI scanning methods using spiral and other non-Cartesian k-space trajectories for dynamic imaging of function. Using spiral techniques, Dr. Glover has developed MRI pulse sequences and processing methods for mapping cortical brain function by imaging the metabolic response to various stimuli, with both clinical and basic neuroscience applications. Recently, Dr. Glover was the recipient of the Gold Medal Award from the International Society for Magnetic Resonance in Medicine for his development of new MR technology hardware and software.

Dr. Glover began his presentation by providing a working definition for "incidental findings" in imaging scans. In healthy subjects, these would be unexpected findings, and in patients, these would be findings that are incidental to the purpose of the clinical study. Some examples of incidental findings include arteriovenous malformation (AVM), cavernous hemangioma, and meningioma.

Incidental Findings Statistics

A recent study of healthy volunteers by the NIH (Katzman et al., *JAMA*, 1999) found approximately a 3 percent occurrence of incidental findings that required some kind of referral. Similar statistics were obtained in a pediatric study performed at Stanford University (Kim et al., *AJNR*, 2003). There were, however, twice as many incidental findings in older adults than in children, with most of those seen in males (Illes et al., *Neurology*, 2004). In summary, in the older cohort of subjects, the frequency of incidental findings was high, but all findings were classified as routine. In contrast, in the younger cohort, the frequency of incidental findings was low, but most findings were classified as urgent. In general, wide variability exists in how incidental findings are handled nationally and internationally. Furthermore, most subjects expect that if an incidental finding exists, it will be detected and disclosed (Kirschen et al., *JMRI*, 2005)

NIH/Stanford University Workshop on Detection and Disclosure of Incidental Findings in Neuroimaging Research

With rapidly increasing use of imaging in brain research, especially MR technology, and

expanding new applications for these tools within and outside of the traditional boundaries of medicine, significant questions have been raised about the standards for detecting and disclosing incidental findings in research subjects. Consequently, a workshop on the detection and disclosure of incidental findings in neuroimaging research was held in Bethesda, Maryland, on January 6–7, 2005. The workshop was designed to explore several ethical, legal, and policy questions including, but not limited to, the overall burden on the individual who discovers an incidental finding, legal and ethical considerations, the level of training that researchers should have for the detection of these kinds of abnormalities, and whether all studies should have a physician involved to review images for abnormal findings and provide a referral.

The workshop focused on five key areas in which recommendations were provided:

- Detection of incidental findings
- Institutional review board (IRB) involvement
- Communicating with subjects
- Research protocols, scanning environment and training
- Subject selection

Final recommendations are posted on the National Institute of Neurological Disorders and Stroke Web site (www.ninds.nih.gov/news_and_events/proceedings/ ifexecsummary_pr.htm). A short paper describing the recommended pathway for incidental findings also has been prepared as a result of the workshop and is in the final review stages by *Science*. Several other workshops and a Council meeting focusing on incidental findings currently are being planned by groups that were not part of the original workshop. These include the National Human Genome Research Institute, the National Heart, Lung, and Blood Institute, and NIMH. One workshop participant recently received an R01 grant on genetic incidental findings. There was also significant publicity generated by an article in the September 5, 2005, issue of the *New York Times* describing how incidental findings in a clinical study were used to save a person's life.

The Incidental Finding Case of SH

In closing, Dr. Glover shared the story of a 25-year-old Stanford University medical student whose life was saved as a result of enrolling in an fMRI research study during which a massive AVM was found incidentally in her frontal lobe. After undergoing a number of procedures over a period of several months, she returned to a fairly high-paced life. This student has written a poignant article describing her experience, which was printed in the *Stanford Medical Student Clinical Journal* and is being published in a clinical journal.

A Council member stated that at his institution, subjects are encouraged to consult with a neuroradiologist if the incidental finding is a case involving the brain. If a series of studies is going to be performed on the same subject or group of subjects, then it is recommended that a neuroradiologist be inserted into the study to review at least one of the scans in the series for the benefit of the patient(s). Dr. Glover remarked that this is a common approach as long as the expertise is easily available without having to incur high costs.

Another Council member raised the question of what to do about research subjects who respond to studies involving MR, because they are concerned about their health status, and they do not have access to health care. These are not good candidates for inclusion in a nondiagnostic study.

Dr. Glover agreed and responded that investigators at his institution are asked to screen individuals carefully before entering them into a protocol. A statement that the subject attests to being in good health could be added to the informed consent form, but it may not be effective as many people will ignore the statement if they are determined to receive the scans. Dr. Seto added that all that can be done is to inform subjects that the enrollment is for a research study and not for treatment. In the practical sense, investigators cannot ask subjects to attest to the fact that they are healthy because of the lack of a precise definition for the word "healthy."

A question was raised about the possibility that incidental findings could have been approached as a purely economic equation. For instance, how much is the cost of a false-positive result? Dr. Glover replied that this type of analysis will be performed by Dr. Judy Illes, the Workshop Chair. In her analysis proposal, she describes a three-way access approach in which costs, ethics, practicality, and the corresponding tradeoffs are considered.

With respect to IRB requirements and incidental findings made during a research study, Dr. Glover stated that the general procedure followed at his institution any time an incidental finding is observed involves a referral to a neuroradiologist to review the scan. The neuroradiologist also makes a decision that is communicated to the PI about whether the subject should be informed. Stanford University's IRB also includes specific language about incidental findings on its Web site. Another Council member commented that it is important to state in the informed consent form whether a radiologist will review the images. Dr. Glover clarified that, at his institution, the informed consent form states that scans will not be read by a trained physician, but if an incidental finding is observed, a specific protocol involving a referral to a neuroradiologist will be followed.

A final inquiry arose about the disclosure of incidental findings, which could result in changes to health insurance coverage. Dr. Glover indicated that there was a group at the workshop that discussed personal health information and third-party involvement. It was felt that the existing Health Insurance Portability and Accountability Act language would protect against disclosure of this type of information and that no additional constraints should be put in place.

VIII. Adjournment

The meeting was closed for review of applications at 12:03 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).

X. Certification

We certify that, to the best of our knowledge, the foregoing minutes and attachments are accurate

and complete.[2]

/s/

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

/s/

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, 2006, and corrections or notations will be stated in the minutes of that meeting.