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]
May 20, 2014

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 35[lll] meeting on May 20, 2014, at the Bolger Center in Potomac, Maryland. Dr. Roderic I. Pettigrew, Director ofthe National Institute of Biomedical Imaging and Bioengineering (NIBIB), presided as Council chairperson. In accordance with Public Law 92-463, the meeting was open to the public from 9:00 a.m. to 12:30 p.m. for review and discussion of program development, needs, and policy. The meeting was closed to the public from 1:30 p.m. to 2:00p.m. for the consideration of grant applications.

Council members present:
Dr. Kristi Anseth, University of Colorado, Boulder, CO
Dr. John C. Gore, Vanderbilt University Medical Center, Nashville, TN
Dr. W. Eric L. Grimson, Massachusetts Institute of Technology, Cambridge, MA
Dr. Nola M. Hylton, University of California, San Francisco, CA
Dr. Cato T. Laurencin, University of Connecticut, Fannington, CT
Dr. Raphael Lee, University of Chicago, Chicago, IL
Dr. Mark Musen, Stanford University, Stanford, CA
Dr. James Thrall, Massachusetts General Hospital, Harvard Medical School, Boston, MA
Dr. Bruce Tromberg, University of California, Irvine, CA
Dr. Sheldon Weinbaum, The City College ofNew York, New York, NY

Council member attending by telephone:
Dr. Etta D. Pisano, Medical University of South Carolina, Charleston, SC

Ex officio members present:
Dr. P. Hunter Peckham, U.S. Department of Veterans Affairs, Cleveland, OH
Dr. Anne Plant, National Institute of Standards and Technology, Gaithersburg, MD
Dr. Sohi Rastegar, National Science Foundation, Arlington, VA

Council members absent:
Dr. Michael Yaszemski, Mayo Clinic College ofMedicine, Rochester, MN

Ex officio members absent:
Dr. Francis Collins, National Institutes of Health, Bethesda, MD
Ms. Kathleen Sebelius, U.S. Department of Health and Human Services, Washington, DC
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences, Bethesda, MD

Chairperson:
Dr. Roderic I. Pettigrew

Executive Secretary:
Dr. Anthony Demsey

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[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 occur. This procedure applies only to applications that are discussed individually, not to "en bloc" actions.

Also present:

NIBIB staff present for portions of the meeting:

Ms. Holly Atherton
Mr. Ryan Aziz
Mr. Angelos Bacas
Dr. Richard A. Baird
Ms. Barbara Cantilena
Ms. Shirley Coney-Johnson
Dr. Richard Conroy
Ms. Desi Conway
Ms. Christine Cooper
Ms. Zoe Ann Copeland
Ms. Nancy Curling
Ms. Monique Day
Mr. Jeff Domanski
Mr. Anthony Dorion
Dr. Henry Eden
Ms. Kate Egan
Ms. Angela Eldridge
Ms. Kathryn Ellis
Dr. Zeynep Erim
Mr. Anthony Fransella
Dr. David George
Ms. Marie Gill
Ms. Pam Glikman
Dr. Ruth Grossman
Dr. John Hayes
Ms. Eunica Haynes
Dr. William Heetderks
Ms. Alisha Hopkins
Dr. Rosemarie Hunziker
Dr. Thomas Johnson
Dr. Heather Kalish
Dr. Chris Kelley
Ms. Margot Kern
Dr. Antony Koroulakis
Dr. Brenda Korte
Dr. Steven Krosnick
Dr. Richard Leapman
Ms. Karin Lee
Dr. Christina Liu
Dr. Guoying Liu
Dr. Hector Lopez
Dr. Xiao-Zhong (James) Luo
Dr. YingMa
Dr. Shadi Mamaghani
Ms. Jessica Meade
Mr. Todd Merchak
Mr. Joe Mosimann
Dr. Vinay Pai
Dr. Grace Peng
Dr. Karen Peterson
Ms. Vicki Rein
Ms. Christel Richardson
Mr. Rolando Romero
Dr. Antonio Sastre
Dr. Oscar Ferreira Silvestre
Mr. Shaun Sims
Dr. Manana Sukhareva
Ms. Jessica Tucker
Ms. Florence Turska
Mr. Kwesi Wright
Dr. Ruixia Zhou
Dr. Steven Zullo

Non-NIBIB National Institutes of Health (NIH) employees:

Dr. Tiffani Bailey Lash, National Heart, Lung and Blood Institute

Members of the public present for portions of the meeting:

Dr. Claudia Angeli, University of Louisville
Dr. Reggie Edgerton, University of California, Los Angeles (UCLA)
Mr. Michael Kalutkiewicz, Academy of Radiology Research
Mr. Damon Kelly, Bolger Center
Mr. Josh Narotsky, National Capitol Captioning, LLC
Mr. Michael Peters, American College of Radiology
Ms. Kathy Sedgwick, NOVA Research Company
Dr. Osman Ugur Sezerman, Sabanci University, Istanbul, Turkey
Dr. Nick Terrafranca, Neurorecovery Technologies

I. Call to Order: Dr. Anthony Demsey

Dr. Anthony Dcmscy called to order the 35th meeting of the National Advisory Council for Biomedical Imaging and Bioengineering. He reminded attendees that the morning session of the meeting was open to the public, welcomed attendees, and introduced Dr. Roderic Pettigrew, who formally welcomed all participants.

II. Director's Remarks: Dr. Roderic I. Pettigrew

A. Incoming Council Members

Dr. Pettigrew introduced new members Drs. Kristi Anseth and James Thrall to the Council. He highlighted their career achievements and the expertise they bring to the Council.

B. NIH FY14 Budget and Legislation

The number of NIBIB RO1 andR21 applications with high-percentile-scores has increased by over 80 percent since Fiscal Year (FY) 2009. However, the NIBIB budget has not kept pace with this increase. Consequently, the RO1/R21 grant payline has substantially fallen.

C. NIH Activities Update

New Application Resubmission Policy

NIH will accept a new (AO) application following an unsuccessful resubmission (A1) application, but the subsequent new application no longer needs to demonstrate substantial changes in scientific direction compared with previously reviewed submissions. A new (AO) application also can be submitted following an unsuccessful AO application, without an intervening resubmission (A1) application.

BRAIN Initiative Update

The goal of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is to map the function of all neurons to revolutionize understanding, treatment, and prevention of brain disorders. The 15-member Advisory Committee to the NIH Director (ACD) Working Group created a plan to achieve the BRAIN Initiative's goals, and, most recently, released an interim report identifying nine recommendations that address high-priority research areas. Each recommendation requires development or refinement of investigative tools or technologies to achieve the BRAIN Initiative's goals. The ACD BRAIN Working Group will submit its final report on June 5, 2014.

President Obama's FY2015 Budget proposes to double the level of federal funding for the BRAIN Initiative from about $100 million in FY2014 to approximately $250 million in FY2015 across three federal agencies. Four Institutes currently are supporting the BRAIN Initiative at NIH. In FY2015, this number is expected to increase to ten Institutes.

Bill & Melinda Gates Foundation Requested Meeting

NIH has had considerable discussions with the Bill & Melinda Gates Foundation (BMGF) about developing technologies to help BMGF achieve their goal of improving global health. These discussions will continue with the NIH Consultative Workshop on Global Health Research and Development (R&D) Strategies on July 8-9, 2014. The two-day workshop will focus on organizational overviews of global health R&D strategies and utilizing leapfrog technologies in global health.

New Common Fund Initiatives

The NIH Common Fund continues to support transformative and innovative research. Four new initiatives have been approved on bioelectronics medicine, 4D nucleome, glycoscience, and mechanisms underlying benefits from physical activity. The Bioelectronic Medicine program is a Defense Advanced Research Projects Agency (DARPA)-like program that establishes methods to stimulate the peripheral and autonomic nervous systems for treatment of diseases. The 4D Nucleome program is a study of nuclear architecture and relevance to gene expression over time. Tools and methods to conduct functional analysis

of sugar compounds and their attachment to proteins will be developed in the Glycoscience program. Mechanisms Underlying Benefits from Physical Activity will look at genetic, physiologic, and biochemical mechanisms in physical activity and health.

D. NIBIB Activities Update

Personnel Transitions

After serving for ten years as NIBIB deputy director, Dr. Belinda Seto is now deputy director of the National Eye Institute (NEI). An active search is being conducted for her replacement and is expected to conclude by early fall. Ms. Nancy Curling, director of the NIBIB Office of Grants Management (OGM), is retiring after 12 years of service with NIBIB and over 35 years with NIH. Ms. Holly Atherton will be the new OGM director. She has over 24 years of service with NIH, and previously served as deputy director of the grants office at the National Center for Research Resources/National Center for Advancing Translational Sciences for the past 6 years.

Design by Biomedical Undergraduate Teams Challenge

The application deadline for NIBIB's Design by Biomedical Undergraduate Teams (DEBUT) Challenge is May 29, 2014. Previously, this challenge awarded three $10,000 prizes, each in a different category. This year, the prize amounts have been changed to three awards of progressive amounts ($10,000, $15,000, and $20,000) for the most promising and effective technologies to address substantial healthcare challenges, without any categories. Additional changes include the allowance of foreign students to be members of a team and that students need not be full-time students for the full year. The latter change was made to allow work-study students to participate.

US.-Mexico Partnership for Management of Diabetes

Over 200 individuals attended the jointly sponsored workshop on managing diabetes in low-resource settings in Mexico City in March 2014. Arising from this workshop are plans to develop a joint initiative to stimulate the community to develop affordable technologies to address diagnosis, management, and complications of diabetes. NIH will conduct a single review of applications from both countries, although funding will be split; Mexico will fund Mexican researchers and NIH support will fund U.S. researchers.

Take Your Child to Work Day, National Science and Engineering Festival, Congressional Staff

On April25, 2014, NIBIB hosted 45 congressional staff to showcase the tools and technologies for which NIBIB is supporting development. Selected technologies included ultrasound guidance for needle procedures, a wireless brain-tongue-computer interface, the iChip microfluidic device, and a modular system for functional electrical stimulation.

Over 250 students participated in NIBIB's activities for Take Your Child to Work Day on April24, 2014. These students engaged in an iPad-based version of the "Who Wants to Be a Bioengineer?" game and a demonstration of near-infrared imaging. On April25-27, 2014, NIBIB participated **in** the USA Science and Engineering Festival. About 1,300 students participated in NIBIB's iPad-based game at the festival.

The Coalition for Imaging and Bioengineering Research (CIBR) held its 5th annual Medical Technology Showcase on Capitol Hill on April28-29, 2014. The Academy of Radiology Research, the umbrella organization for CIBR and the force behind legislation which led to the creation ofNIBIB, presented Senator Richard Burr and Congresswoman Anna Eshoo with an Imaging Research Advocacy Award. Burr and Eshoo have been supporters of research funding through NIH, and both spoke about the importance of innovative research in imaging science.

Spinal Cord Injury

Drs. Claudia Angeli and Reggie Edgerton, and colleagues, recently published the article "Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans" in the journal *Brain.* This publication received considerable press coverage, including a front-page story in *USA Today*, extensive interviews with Fox News, and an interview with National Public Radio on its "Science Friday" segment.

E. Science Highlights

iPSC: Practical Challenge

Making induced pluripotent stem cells (iPSCs) from adult (differentiated) cells is becoming routine but is still too inefficient for the desired applications. This inefficiency has been addressed by one of NIBIB's grantees, Dr. Song Li, as reported in his 2013 *Nature Materials* article, "Microgroove-grown iPSCs display epigenetic mechanomodulation." Dr. Li's research has shown that growing iPSCs on a grooved surface, as opposed to a flat surface, forces the cells growing in the grooves to elongate. The elongating process has a stimulating effect that accentuates the chemical changes that are required to go from an adult (differentiated) cell to a stem cell. Narrowing the grooves forces the cells toward greater elongation, and the number of stimulated stem cells per colony of adult cells increases.

Magnetic Field Correlation Imaging and Attention-Deficit Hyperactivity Disorder (ADHD)

A lack of objective biomarkers for ADHD makes the condition difficult to diagnose. Dr. Joe Helpern, Medical University of South Carolina, has developed a new magnetic resonance imaging (MRI) approach that is sensitive to iron in the brain and has the potential to help doctors diagnose ADHD more definitively. ADHD is treated with psychostimulants, which increase dopamine levels, and altered brain iron levels have been associated with cognitive and dopaminergic changes. Helpern's research has shown that patients on psychostimulants also increase their levels of iron in key regions of the brain involved in hyperactivity or impulse suppression. The levels of iron in these target regions are comparable to those in normal control patients and increase with the duration of psychostimulant treatment. MRI relaxation rates are sensitive to iron, but specificity limited, because they are also influenced by non-iron molecular relaxation mechanisms. MFC is insensitive to these non-iron mechanisms and thus is much more specific to brain iron.

Science Education

NIBIB's Science Education website (http://www.nibib.nih.gov/science-education/bionic-man) features "The Bionic Man" interactive tool, which allows viewers to browse a selection of technologies and interventions developed by NIBIB-supported researchers.

International Society for Magnetic Resonance in Medicine (ISMRM)

Dr. Karla Miller presented the NIBIB New Horizons Lecture, "MRI in an Era of Multiscale Neuroscience," at the 2014 annual ISMRM meeting.

III. NIBIB's Future Utilization of Resources

Dr. William Heetderks, Director, Extramural Science Programs, provided a synopsis of the earlier Council Working Group discussion on NIBIB's future utilization of resources. He outlined three key suggestions on how best to utilize limited research resources:

1. Fund investigator-initiated or design-driven projects (RO1s and R21s). Council input is needed on how to optimize typical RO1/R21 funding-funding soft versus hard paylines.
2. Fund goal-driven programs, such as the Quantum Grant program, where a long-term goal is identified and a program is developed to achieve that goal.
3. Fund people, putting less emphasis on the specific project aims. Provide sustained funding for established, proven investigators.

Dr. Heetderks reviewed suggestions on how to fund established investigators. A mechanism similar to the K award could be developed to provide a base level of support to established investigators. Eligibility for merit awards also could be expanded. Programs and project awards with built-in training could be created to support established investigators. There also has been discussion on goal-directed programs to help support established investigators.

Determining how to measure the success of supported research grants has been a challenge. Dr. Heetderks highlighted a paper by Dr. Michael Lauer of NHLBI that discusses percentile ranking and citation impact. No significant difference in number of citations was found between the percentile groups. Citations are

imperfect markers of individual success, and using the number of publications as an indicator of return on investment is an issue for all of NIH. Nevertheless, Lauer's paper could help fuel additional discussion on how to fund individual investigators. Dr. Heetderks highlighted recommendations from the article "Rescuing U.S. biomedical research from systematic flaws," including providing more stable support; sunsetting large grants; increasing awards that recognize high-risk, innovative research; and looking at individual laboratories that receive a great amount of funding.

Discussion

Dr. Mark Musen noted that NIBIB-funded investigators are developing algorithms and techniques and suggested looking at the adoption of algorithms and techniques as a measure of success.

Dr. Cato Laurencin commented that the public measures success of research based on its value to patients. He pointed out that the "Impact of NIH Research" webpage lists four areas of emphasis: health, economy, communities, and knowledge. These are important and reasonable metrics that should be used for future planning.

Dr. Nola Hylton stated that it will be difficult to identify mechanisms for reallocation of funding until metrics, criteria, and incentives are defined. If metrics are developed, the mechanisms then will fall into place. Good assessment models for important goals such as technology innovation and improved healthcare do not exist. These models must come before the design of new allocation mechanisms.

Dr. John Gore emphasized the importance of providing more stability-a sustainable career pathway for investigators-and for those investigators to take risks and be creative. He suggested developing a career pathway whereby, after a K award, investigators could be continually funded in five-year increments based on the impact of their research.

Dr. Thrall commented that the research community is destined to cycle between different funding philosophies. As the community becomes dissatisfied with the current funding situation, institutions will move toward a different approach. He suggested looking at lessons learned by the Department of Energy when looking at funding individuals. Often, the same individuals receive repeated funding, and it is hard for new investigators to obtain grants. Sustained funding would be great, but there must be accountability. The current funding system relies on input rather than output. Universities keep track of funding received, but no one is tracking output of that funding.

Dr. Raphael Lee suggested that since the decision-making process in making an award relies heavily on the peer review process, it is imperative that the peer-review process be more efficient and effective. As has been alluded to, parts of the review process may involve consideration of information that has nothing to do with the science, and reviewers may place more emphasis on the reputation of the investigator than the actual grant applications. The bottom line for the public in investing in research is better healthcare and impact on the economy.

Dr. Sheldon Weinbaum commented that only 39-40 percent ofPhDs in biomedical engineering are women, and women account for less than 20 percent of new faculty appointments. Many female bioengineers reveal that they leave academia because of funding issues. He suggested developing a funding mechanism for women to keep them in the field. Dr. Lee suggested looking at other research related to success rates of underrepresented minorities in the grant process.

Dr. Bruce Tromberg stated that other Institutes are addressing the issue of limited resources by reverting to past approaches. He suggested that NIBIB establish an internal task force with external input to look at the available data and develop solutions. The prior Council Working Group meeting and the current discussion will generate some insight, but this issue requires deeper analysis.

Dr. Hunter Peckham recommended identifying funding gaps before trying to solve the issue of limited resources.

Dr. Laurencin suggested changing the maximum percentage of salary that can be obtained via NIH grant support. This would mean a change in how universities finance their research faculty. The funding situation at the National Science Foundation (NSF) is similar in that they also are receiving more high-quality

applications without an increase in funding. Dr. Sohi Rastegar reported that the NSF set the maximum limit at two months of summer salary.

Dr. Rastegar stated that he understands the concern about reducing the size of grants so that promising young scientists entering the field, particularly women and underrepresented minorities, are not lost. However, success should not be punished. Well-funded investigators may have an innovative idea that would not be funded because of these limits. He suggested having more tiers of awards that would keep more investigators in the pipeline-an increased number of smaller awards to keep more investigators involved without punishing the successful individuals.

Dr. Gore stated that, under the current funding model, investigators who receive one ROl grant need a second RO1 to survive financially in most private medical centers. If investigators could survive on a career award and other minor funds to conduct their research, funds could be divided more appropriately to other, new investigators.

Dr. Pettigrew recognized that this is a challenging multiparametric problem that will not be solved easily in a two-hour discussion. Given the current economic climate, funding levels are not expected to change substantially. Competing influences must be balanced in order to address stability, risk-taking, and getting more investigators into the system. NIBIB hopes to gain more individual and collective perspectives on these issues. The growth in number of high-scoring grant applications reflects that the field is growing and reviewers appreciate convergence of disciplines in addressing major challenges. NIBIB would like to have more cutting-edge grants that are far-reaching and, if successful, would be more transformative, but study sections tend to be more conservative. Funding stability has been discussed internally (i.e., increasing length of awards), but that comes at a cost of funding new projects.

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

Dr. Demsey welcomed visitors and members of the science press and scientific society constituencies. He noted for the record that a quorum was present for this Council meeting. Council member Dr. Mike Yaszemski and *ex officio* member Dr. James Smirniotopoulos were unable to attend. Dr. Demsey thanked Ms. Pam Glikman and Ms. Alisha Hopkins for planning the meeting.

A. Council Regulations, Policies, and Procedures

Dr. Demsey reviewed conflict-of-interest, confidentiality, and lobbying guidelines.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for Tuesday, September 16, 2014. Dr. Demsey noted that a Council member dinner will be planned for the night before the meeting. He asked Council members to inform him about conflicts with any of the upcoming meeting dates listed at the bottom of the agenda.

C. Approval of the January 22,2014, NACBffi Meeting Minutes

A motion to approve minutes of the January 22, 2014, NACBIB meeting was forwarded, seconded, and approved unanimously.

V. Uncovering New Strategies to Regain Voluntary Control of Movement After Complete Paralysis: Dr. Reggie Edgerton

Dr. Edgerton presented his research on novel ways to restore voluntary control of movement in patients after complete paralysis. The overall objective of his research is to develop, test, and deliver neuromodulatory tools--electrical, pharmacological, and sensory-that can improve sensory motor and autonomic function in paralyzed patients.

Dr. Edgerton's work takes advantage of automaticity in sensory-motor interactions. Sensory information is sent to the spinal cord from receptors in the muscles, tendons, and skin, but the brain is not aware of this information. In most cases after a spinal cord injury, the network below the lesion is still relatively intact. If signals can be amplified, these networks can reengage and relearn how to control movement. This can be accomplished pharmacologically and via electrical neuromodulation combined with training.

Animal experiments have shown that it is possible to take advantage of the automaticity of the network below the lesion. For example, after a spinal transection, rats injected with a pharmacological agonist could walk backward and sideways on a treadmill. This demonstrates that sensory information going through the spinal cord is capable of controlling an effective motion.

Automaticity in humans was demonstrated some years ago. Vibrators were placed on the quadriceps of normal subjects who were told not to step; however, after a few minutes of stimulation, the legs began to step on their own.

A new technique developed by Dr. Edgerton's colleagues uses a vibration boot on an uninjured subject. The boot applies pressure to the heel and then the toe. If cyclic sensory information is provided, the sensory system responds, sending information back to the spinal cord, which the spinal cord translates to locomotor action. Another technique stimulates the spinal circuitry through the skin. Placing electrodes at certain points over the spinal cord induces similar types of cyclic activity. Consistent stimulation of different spinal segments produces different patterns of activation in the patient. These observations raise an important research question: To what extent can these techniques be used with injured patients to get them to a point where they can step and support more weight independently?

Dr. Edgerton described how these techniques are being used in completely paralyzed patients. A stimulator was placed in a subject who had an injury at the mid-low cervical region of the spine; after six to seven months, the subject reported that he could move his toes. This result was unexpected. In the next three subjects, this movement occurred much sooner-too soon to be the result of axon growth. This indicates how much independence is built into the spinal circuitry. This neuromodulation has since been observed in six other subjects studied by Edgerton's team at UCLA.

Neuromodulation does not make a person move; rather, it enables the person to move. The spinal cord is used as a source of control. After an injury, there may be some activation, but there is no way to detect it. Adding modulation via epidural stimulation provides the activation required to cross the motor threshold and induce movement in the injured individual. Edgerton's data show that what happens at the sub-threshold is a very important factor in motor control and the way movement is controlled. Models are being created to help determine how stimuli are being translated from sensory information to motor information. These models will be extremely important for working with individual patients at each stage of their rehabilitation.

Dr. Edgerton concluded by explaining why this work requires a sustained group of researchers over a long period of time. The work requires a systems approach because posture, locomotion, hand control, blood pressure, bladder and bowel control, temperature control, sensation, sexual function, and well-being are all interconnected. Training is key to rehabilitate each patient effectively, and training four subjects for 18 months is expensive. In addition, it takes a long time to translate technology effectively in this field.

VI. Altering Spinal Cord Excitability Enables Voluntary Movements After Chronic Complete Paralysis in Humans: Dr. Claudia Angeli

Dr. Angeli presented her research on altering spinal excitability in humans to enable voluntary movements after paralysis. Epidural stimulation was combined with stand-and-step training to see whether the same results seen in Dr. Edgerton's animal models could be achieved in humans. The team hypothesized that tonic epidural spinal cord stimulation could modulate the human spinal circuitry into a physiological state that enables sensory input, derived from standing and stepping movements, to serve as the source of neural control to perform these tasks.

A mapping experiment was conducted using a 16-electrode array at different voltages. When the first patient was successful in moving toes, the team drew up a new experimental assessment to address this surprising result. The full research protocol was conducted with this first patient to confirm that it worked and to determine how to modify it for the next patient. The first paper to result from this research, which focused on this first human subject, was published in 2011 in *Lancet.*

In April2014, "Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans" was published in the journal *Brain.* Prior to implantation of the epidural stimulator,

patients received 80 sessions of locomotive training on the treadmill to see if their motor patterns changed with locomotive activity alone. If significant function was regained, those patients were not implanted.

Four patients were part ofthe study: two with Grade A injuries (one active and one quiet) on the ASIA Impairment scale and two with Grade B injuries (one active and one quiet). The first patient has a quiet Grade B spinal injury at the C7 level but presents T2 neurologically. He has full control of his arms and did not have electromyographic (EMG) activity resulting from sensory activity (stepping on the treadmill). The second patient has a quiet Grade A spinal injury, meaning he has complete lack of motor and sensory function below his T4 level of injury. His pattern on the treadmill was similar to the first subject's-very little EMG activity resulting from sensory input. The third patient has an active C7 Grade B injury, meaning there is some sensation below the level of injury. Although the level of injury is similar to that of the first patient, the third subject had EMG activity when stepping on the treadmill. The fourth subject has an active Grade A spinal injury. He showed a lot ofEMG activity with sensory input on the treadmill.

When subjects were asked to move without stimulation, no EMG activity was detected. With stimulation enabled, all of the subjects were able to move. The toe muscles and ankles were active. The subjects were initially stimulated at very low levels. They had to have the intent to move-the voluntary action necessary to come above the motor threshold. With each subject, the research team optimized the configuration of the stimulation to result in movement. Dr. Angeli tested the ability to modulate the amount of force and the range of motion generated in the subjects. Three ofthe four subjects could consistently modulate force.

Researchers also looked at how long the subjects could sustain a contraction. All of these indicators improved with training. Once it was determined that the subjects could move, they took the stimulator home to practice how to move their legs in order to reduce the voltage needed for the movement.

Reciprocal activity between extensors and flexors is controlled in order for subjects to move properly. Prior to training, subjects could perform four to five oscillations (over one minute of up-and-down leg activity) before stopping. Dr. Angeli and colleagues are using different analysis techniques to characterize muscle and neurological fatigue in order to determine what makes the subjects stop moving. They also are working to improve the timing of stimulation when flexion is needed.

All four original subjects showed changes in bladder and bowel function, temperature regulation, and sexual function. These changes persisted for short periods even when stimulation was off. Further study is needed to determine whether these changes persist when the stimulator is turned off for prolonged periods of time.

The research protocol conducted with these four patients will be repeated in four more patients. In addition to locomotive activity, researchers will look at cardiovascular function and other secondary quality-of-life issues that have more immediate impact on the subjects.

Discussion

Dr. Edgerton noted that it is surprising how much has been learned from comprehensive study of just a few patients. Secondary changes, such as bladder control, may not have been recognized if the researchers had studied hundreds of patients superficially. These secondary changes have great impact on patient quality of life. For example, improved bladder control makes travel much easier for a paralyzed patient. Dr. Angeli noted that patients want to be able to walk, but having bladder control is a more immediate need for them.

Dr. Tromberg asked about the role of focus and attention when the subjects are asked to move. Dr. Angeli responded that focus and attention are key, especially with the Grade A subjects. When optimizing configurations, a mirror is placed so that patients can see whether they are getting results from the attempt. The team has not conducted brain imaging to determine what is happening in the brain with these movements. Dr. Edgerton stated that there must be an amazing synergistic reorganization of the brain and spinal cord, considering how few fibers are making a new connection to provide movement.

Dr. Musen commented that the patients did not look spastic making these movements and asked how movement is kept under control. Dr. Angeli explained that movement prior to injury was coordinated. Raising excitability helps the spinal cord remember the coordinated movement. Rat experiments show that with training, neurons reform their own connections for better control.

Dr. Pettigrew asked what results the researchers had initially expected to see with stimulation in the first patient. Dr. Edgerton explained that they had hoped that the patient could stand bearing his full weight and step in a manner similar to that observed in the rat studies.

VII. Adjournment

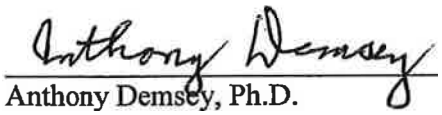
The open session of the NACBIB meeting was adjourned at 12:33 p.m.

VIII. Closed Session

The grant application review portion of the meeting was closed to the public in accordance with 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 3:00 p.m.

Certification:

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



Anthony Demsey, Ph.D.
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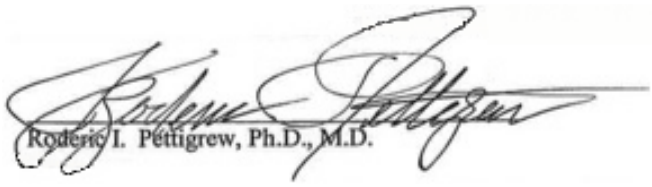

Roderic I. Pettigrew, Ph.D., M.D.
Chairperson,
National Advisory Council for Biomedical Imaging and Bioengineering
Director,
National Institute of Biomedical Imaging and Bioengineering

[2] These minutes will be approved formally by the Council at the next meeting on September 16, 2014, and corrections or notations will be stated in the minutes of that meeting.