National Center for Medical Rehabilitation Research (NCMRR) 20th Anniversary Scientific Symposium:

Advancing Research to Improve The Lives of Individuals With Disabilities

December 12-13, 2011

Eunice Kennedy Shriver National Institute of Child Health and Human Development

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Cover photo of male with prosthetic arms.
Credit: Rehabilitation Institute of Chicago (RIC)

To our friends and colleagues in celebration of the 20th anniversary of the National Center for Medical Rehabilitation Research (NCMRR):

NCMRR has had a fabulous 20 years of accomplishment. This publication represents a record of the presentations given by leaders and researchers on the NCMRR's history and development, as well as its promise of future research that will improve the health and quality of life of children and adults with disabilities.

One of the things that many of us at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) have been involved in over the last year is a scientific Visioning process. It is important to underscore that the one item that came up most frequently in conversations about the scientific opportunities of the next 10 years and beyond was the importance of transdisciplinary science—having people from different perspectives working together on the same problem. For more than 2 decades, the NCMRR has been a pioneer, not only in rehabilitation research, but in transdisciplinary science—and that is an important contribution to the culture of science.

The fact that many different kinds of professionals see the NCMRR as their home at the National Institutes of Health (NIH) is a reflection of the Center's *modus operandi* and a compelling reason for its success. The NCMRR supports a diverse research portfolio—including basic studies to learn about underlying mechanisms of repair, behavioral studies to improve adaptation to functional issues, clinical studies to examine comparative effectiveness of different therapies, investigations in the environmental and social impacts on injury and rehabilitation, applications of bioengineering, and much, much more. Each of these studies is directed by researchers from very different perspectives collaborating together for the common good.

One of the things that we do best at the NIH, often with the help of the Foundation for the NIH, is to convene diverse groups of people to address a common problem. It is important that these conversations continue, for rehabilitation research is critical to helping us understand and improve overall functioning, as well as the quality of life of individuals with disabilities and their families. This is central to NICHD's mission and to NIH's.

Many people over the years have debated whether the NICHD is the appropriate home for the NCMRR. I would argue that one of the reasons why the NCMRR is well-placed within the NICHD is that the Center was founded on some of the same principles that the NICHD was founded upon nearly 30 years earlier, and which it still holds dear—and both still share the goals of helping to improve the health and quality of life of those with disabilities.

It's admirable to get up in the morning determined to change the face of science; striving toward that single objective would be enough to have a great life and a useful career. But colleagues in rehabilitation research are focused not only on advancing science, but also in doing work that changes some of the core values of our society. That's a real accomplishment, and that's part of what we celebrate when we think about the 20 years of the NCMRR.

So, I commend the NCMRR for being a major part of this effort over the last 20 years, and I can promise you that in the next 20 years, we will see all kinds of great advances, both scientific and social, realized by the NCMRR.

Sincerely,

Alan E. Guttmacher, M.D.
Director, NICHD

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Chapter 1: Introduction

In recognition of the 20th anniversary of the National Center for Medical Rehabilitation Research (NCMRR), the Foundation for the National Institutes of Health (NIH) hosted a scientific symposium on December 12–13, 2011, to discuss the Center's major contributions to rehabilitation research and ongoing research activities. This publication includes presentations from the symposium, including:

- Remarks by Dr. Lawrence A. Tabak, Dr. Alan E. Guttmacher, and Dr. Yvonne T. Maddox describing the significance and accomplishments of the NCMRR during its first 20 years
- Historical reviews and observations by Mr. Richard E. Verville, historian of federal programs for people with disabilities; Dr. David B. Gray, the first administrator of the NCMRR; Dr. Marcus J. Fuhrer, Director of the NCMRR from 1992 to 1998; and Dr. Margaret G. Stineman, former chair, National Advisory Board for Medical Rehabilitation Research (NABMRR)
- A review of the contributions of the NABMRR to the growth and development of the NCMRR by Ralph Nitkin, Deputy Director
- Lectures from seven researchers describing current, cutting-edge research efforts in the rehabilitation of individuals with physical disabilities
- A summary of the scientific presentations and concluding remarks by NCMRR Director, Dr. Michael Weinrich

This publication is intended for researchers, clinicians, policymakers, public health experts, and a broad spectrum of professionals with an interest in medical rehabilitation and persons with disabilities. It documents important contributions in the field as well as the groundwork needed for moving forward.

Chapter 2: The NCMRR History and Development

The NCMRR: An Overview of Its Early History and Development

On November 16, 1990, Congress passed an amendment to the Public Health Service Act (known as Public Law 101-613) stating that there "shall be a National Center for Medical Rehabilitation Research (NCMRR) placed within the National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH)."[1] Its purpose was to conduct and support research and research training (including research on the development of orthotic and prosthetic devices) in medical rehabilitation and disseminate health information and other programs with respect to the rehabilitation of individuals with physical disabilities resulting from diseases or disorders of the neurological, musculoskeletal, cardiovascular, pulmonary, or any other physiological system (hereafter referred to as "medical rehabilitation").

In carrying out the mission of the NCMRR, the Act noted that its Director "may (a) provide for clinical trials regarding medical rehabilitation; (b) provide for research regarding model systems of medical rehabilitation; (c) coordinate the activities of the Center with similar activities of other agencies of the federal government, including the other agencies of the NIH, and with similar activities of other public entities and of private entities; (d) support multidisciplinary medical rehabilitation research conducted or supported by more than one such agency; and (e) in consultation with the advisory council for the NICHD and with the approval of the director of NIH, establish technical and scientific peer-review groups in addition to those appointed NIH and support medical rehabilitation research and training centers."

Since its auspicious beginning 20 years ago, the NCMRR has established a record of outstanding accomplishments in supporting cutting-edge research that has improved the health, independence, productivity, and quality of life of individuals with disabilities. The Center has become the primary entity for medical rehabilitation research within the NIH and the federal government.

Congress's purpose in placing the NCMRR within the family of Institutes and Centers at the NIH was its confidence that NIH leadership would provide the support for the NCMRR, allowing it to expand the medical rehabilitation field and coordinate rehabilitation research across federal agencies. In addition to creating the Center, Congress established the National Advisory Board on Medical Rehabilitation Research (NABMRR), which is charged with advising the Directors of the NIH, the NICHD, and the NCMRR on issues related to NCMRR programs and research.

The NCMRR became operational in January 1991 with its first deputy director, David Gray, Ph.D. The first meeting of the NABMRR was held in May 1991. From 1993 to 1998, the Director of the NCMRR was Marcus Fuhrer, Ph.D., whose tenure was followed by Yvonne Maddox, Ph.D., who served as Acting Director from 1998 to 2000. In February 2000, Michael Weinrich, M.D., assumed the directorship of the Center.

Current NCMRR Program Activities

Since its establishment, the NCMRR has actively supported research, trained investigators, and advanced the field of medical rehabilitation. The Center's administration comprises the NCMRR Director, Michael Weinrich, M.D., and five branch directors representing five multidisciplinary research programs described below.

[1] In December 2007, an Act of Congress renamed the NICHD as the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Behavioral Sciences and Rehabilitation Technologies (BSRT) Program Branch
Director: Louis Quatrano, Ph.D.

The behavioral science aspect of this program conceptualizes, initiates, and supports scientific efforts designed to advance knowledge relevant to the role of behavior of individuals with physical disabilities. A major focus of the program is to support research that informs the development or redevelopment of emotional, cognitive, and physical attributes. The program supports clinical studies of interventions that promote development and basic behavioral studies on factors such as plasticity. Other work focuses on identifying individuals with disabilities and measuring their abilities as a way to investigate the effects of disabilities on the individual and the family.

The rehabilitative engineering portion of this program develops and supports the application of engineering and bioengineering principles to study the habilitation of individuals with disabilities. A major focus of the Center's mission is to support research for developing assistive technology aimed at helping individuals with disabilities perform daily activities, and the rehabilitation engineering technologies portion of this program is the lead on such tasks.

Biological Sciences and Career Development (BSCD) Program Branch
Director (Deputy Director of the NCMRR): Ralph M. Nitkin, Ph.D.

The "biological sciences" aspect of this program promotes basic research to elucidate the scientific underpinnings of clinical rehabilitation and to understand the mechanisms of recovery and adaptation. This research may include studies of neuroplasticity, activity-mediated processes, cell and tissue engineering, brain imaging, muscle and bone function, secondary conditions, and even genomic influences. To further facilitate rehabilitation research, the Center supports access to state-of-the-art research facilities, mentorship, pilot grants, and other collaborative opportunities with expertise in areas such as bioengineering and robotics, cognitive rehabilitation, neurorehabilitation and regeneration, genetics and genomics, and muscle physiology.

In addition, this program provides support for the training and career development of rehabilitation professionals and for attracting established researchers from allied fields to focus on rehabilitative questions. The Center supports a unique program of individual career development awards (http://grants.nih.gov/training/careerdevelopmentawards.htm), national career-development networks for physiatrists (http://www.physiatry.org/?page=programs_rmstp), and networks for allied health professionals (http://www.corrt.pitt.edu/index.asp).

Pediatric Critical Care and Rehabilitation (PCCR) Program Branch
Director: Carol Nicholson, M.D.

This program focuses on developing research that links PCCR medicine and science to the epidemiology, prevention, and treatment of childhood disabilities. The effort sponsors competitive research on all aspects of PCCR—including critical analyses of outcomes for children who are survivors of trauma, congenital anomalies, neonatal asphyxia, infectious processes, septic shock, and many other less common, but still devastating childhood processes.

The PCCR program also provides support for the Pediatric Critical Care Scientist Development Program, a national faculty training and career development program that develops successful pediatric critical care physician scientists conducting research to enhance the scientific understanding, clinical management, and rehabilitation of pediatric critical illness. Through this program, the NCMRR supports the Collaborative Pediatric Critical Care Research Network, which serves as a national resource for studying the scientific bases of pediatric critical care medicine.

Spinal Cord and Musculoskeletal Disorders and Assistive Devices (SMAD) Program Branch
Director: Nancy Shinowara, Ph.D.

Musculoskeletal disorders include a variety of conditions, such as multiple sclerosis, arthritis, osteoporosis, and systemic lupus erythematosus. Certain aspects of cerebral palsy and muscular dystrophy may also fall into this program area. In addition, this program area also addresses research on mobility limitations that result from a variety of causes, including amputation and burns.

Like the BSRT program, a large portion of this program's activities focus on developing and supporting the application of devices to improve the human-environment interface and to restore or enhance an individual's capacity to function in his or her environment. This type of applied research and rehabilitation technology includes, but is not limited to, prosthetics, wheelchairs, biomechanical modeling, and other topics that aim to enhance mobility, communication, cognition, and environmental control.

Traumatic Brain Injury (TBI) and Stroke Rehabilitation (TSR) Program Branch
Director: Beth Ansel, Ph.D., CCC-SLP

This program supports research to understand all aspects of TBI and stroke, including their underlying mechanisms, and to develop and assess medical rehabilitation therapies and interventions related to improving function, quality of life, and outcomes for TBI and stroke patients. In addition, the program supports efforts related to secondary conditions of TBI and stroke, such as muscle atrophy, speech and language problems, pain, and the psychological and psychosocial effects of these conditions.

Research Training Programs for Career Development

The NCMRR leads and takes part in multiple national career-development efforts, including:

- Comprehensive Opportunities in Rehabilitation Research Training for Physical and Occupational Therapists
- Pediatric Critical Care Scientist Development Program
- Rehabilitation Medicine Scientist Training Program for Physiatrists
- Rehabilitation Research Career Development Program for Physical and Occupational Therapists

For further details, visit http://www.nichd.nih.gov/about/org/ncmrr/Pages/training.aspx.

Future Perspectives

The NCMRR's first 20 years of work in medical rehabilitation research has realized substantial accomplishments. With one in five Americans affected by some type of disability, with an aging U.S. population, and with wounded warriors returning from Iraq and Afghanistan, basic, clinical, and translational research in rehabilitation is an area of critical need in America.[2]

Because of the Center's outstanding staff and work in supporting and coordinating essential research and in training the next generation of investigators, the NCMRR will continue to contribute to our understanding of disability and the processes of recovery and to develop more effective interventions that improve the function and quality of life of individuals with disabilities.

[2] U.S. Department of Health and Human Services. Office on Disability. (n.d.). *What is disability and who is affected by disability?* Retrieved on November 12, 2012, from http://www.hhs.gov/od/about/fact_sheets/whatisdisability.html.

A Brief History of Rehabilitation Research and the NCMRR: In Celebration of Its 20th Anniversary

Richard E. Verville, J.D.

Principal, Powers Pyles Sutter & Verville P.C.
Washington, D.C.

We need to celebrate the NIH in Washington, D.C., for including and supporting the NCMRR and the people who made it happen between 1988 and its initial establishment. NIH is probably the finest biomedical research institution in the world. Any field of medical care thrives on research to establish improved methods of providing care, and medical rehabilitation is no different. Having established a home in the NIH and being fully supported by the professions and the U.S. Congress, the NCMRR has been very important to the growth and legitimacy of medical rehabilitation.

Therefore, we celebrate the creation of the NCMRR and those who were leaders in the effort to create it: Senator Weicker; Senator Kennedy *in absentia*; Senator Graham of Florida; Senator Harkin and Senator Specter; Congressman Pepper *in absentia*; Congressmen Dingell, Waxman, Walgren, and Porter; Bill Raub, former NIH Deputy Director and Acting Director; Duane Alexander, former NICHD Director; Yvonne Maddox, NICHD Deputy Director; David Gray, initial NCMRR Acting Deputy Director; Marcus Fuhrer, first NCMRR Director; and the many professional societies and disability organizations that advocated for the NCMRR: American Academy for Physical Medicine and Rehabilitation, American Congress of Rehabilitation Medicine, Association of Academic Physiatrists, the prosthetics and orthotics professions, American Physical Therapy Association, American Occupational Therapy Association, and consumer organizations, such as the Paralyzed Veterans of America, National Multiple Sclerosis Society, and the Amputee Coalition.

The Development of Medical Rehabilitation and Medical Rehabilitation Research

Medical rehabilitation first developed between about 1917 and 1950 largely as a result of programs developed in World War I and World War II, the latter under Dr. Henry Kessler and Dr. Howard Rusk. These two pioneers each went on in civilian life to develop institutes for care, research, and training in medical rehabilitation. Research was always an essential ingredient of the field's development, but early on, support was hard to find. Although the NIH was receiving substantial funding from Congress at this time, it was not interested in establishing a medical rehabilitation research program despite Rusk and Kessler approaching its leadership about such an initiative.

In 1943, the prestigious Baruch Committee, established as a private organization by statesman and philanthropist, Bernard Baruch, recommended academic centers in rehabilitation medicine focusing on research and training. It also recommended individual training programs for the rehabilitation professions, and rehabilitation programs for veterans administered by the Veterans Administration (VA). The VA recommendation was later developed and implemented by Dr. Paul Magnusson, who was its Medical Director. His concept of VA hospitals being affiliated with teaching hospitals was the foundation for the current system. Establishing medical rehabilitation services and training programs was a priority for Dr. Magnusson, an orthopedist who later founded the Rehabilitation Institute of Chicago, which is affiliated with Northwestern University. Rehabilitation research was also a focus of the VA, although its research was limited to VA-affiliated researchers, and its patients limited to U.S. veterans.

In 1950, Mary Switzer, an experienced Public Health Service employee became the Director of the Rehabilitation Services Administration or the RSA (then named the Office of Vocational Rehabilitation) within the Federal Security Agency. The Federal Security Agency became the core of the new Department of Health, Education, and Welfare (HEW). Director Mary Switzer promptly expanded research activities, training programs for rehabilitation professions, and facility construction. Research and Training Centers were funded during the 1960s, and there were 19 by 1970. Some $20 million was spent on rehabilitation research at this time, of which a large share was medical rehabilitation research.

Early Years of Leadership in Rehabilitation from Congress and the Disability Movement

Mary Switzer retired in 1970, but research and training programs received good congressional support throughout the decade. Congressional and disability movement leadership produced the 1973 Rehabilitation Act, which included civil rights provisions for persons with disabilities prohibiting discrimination in programs receiving federal assistance (education, social services, transportation, and housing), and the White House Conference on Disability, which in 1977 recommended many actions including expanded civil rights. In 1978, the Independent Living Program was enacted, and the National Council on the Handicapped, which reported to the President, was established. The Council developed and recommended to the President and Congress the Americans with Disabilities Act in 1986, which was enacted in 1990.

Also in 1978, the Institute for Rehabilitation Research (now the National Institute for Disability and Rehabilitation Research, [NIDRR]) was created within the HEW, and about $35 million was allocated for research. Dr. William Spencer of Baylor and the Institute for Rehabilitation and Research, a renowned pediatrician and rehabilitationist, effectively directed the Institute for its initial years. But in 1980, Congress, at the request of the Carter Administration, created the Department of Education (ED), and the RSA and the NIDRR were transferred out of the HEW to the ED.

Although the NIDRR has continued to date, and health and function projects are supported, the priority for research in the 1980s shifted appropriately from health-related matters to education, vocational rehabilitation, and community participation. At this point, the field began exploring opportunities for rehabilitation research and leadership at the NIH. Grants in medical rehabilitation were being funded by the NIH, but they were spread among 11 of the Institutes with no dedicated program leadership within any one of them.

The NIH and Congressional Interest in Medical Rehabilitation Research

In the mid-1980s, the field of medical rehabilitation research was supported by the NIH leadership; Dr. Raub, Deputy Director; and the Directors of the National Institute of Neurological Disorders and Stroke, National Institute on Aging (NIA), NICHD, National Institute of Arthritis and Musculoskeletal and Skin Diseases, and congressional committee staff. Efforts were made to expand research activity in the NIH and to place medical rehabilitation researchers on appropriate NIH peer-review committees. In 1987, legislation was developed for the purpose of creating the NCMRR, which would report to the Director of the NIH. The Center would have grant-making authority and a mission to plan and support trans-NIH medical rehabilitation research.

In 1988, Congressman Douglas Walgren introduced a bill with 16 cosponsors creating the NCMRR within the NIH and with its Director reporting to the Director of the NIH. Senators Weicker and Kennedy introduced the NIH Reauthorization Bill S. 2222, which had an NCMRR provision in it similar to the Walgren bill. The U.S. House of Representatives passed the Pepper, Dingell, and Waxman NIH Reauthorization Bill H.R. 3661, which included the Walgren bill. S. 2222 was not brought to the floor of the U.S. Senate, and the 100th Congress ended. In the 101st Congress, Senator Kennedy introduced another NIH Reauthorization Bill, which was the same as S. 2222. In 1990, that bill was reported from Senate committee as S. 2857 and passed by the Senate with an amendment.

Before Senate passage of S. 2857, the NIH, led by Acting Director Bill Raub, had created a Panel on Medical Rehabilitation Research to advise the Director on an environment in the NIH to foster and improve rehabilitation sciences. The Panel was chaired by Dr. Edward Brandt, former Assistant Secretary of Health and included 17 other prominent individuals most of whom were leaders in the field of medical rehabilitation research. On the Panel were Dr. Henry Betts, Dr. John Ditunno, and Dr. Dorothy Gordon, each of whom had been president of a major rehabilitation medicine organization. The Panel recommended a Center either in an Institute or as an independent agency reporting to the NIH Director to support research training and research grants, with an emphasis on grants in areas not covered by other NIH research projects. Joint funding with other NIH agencies was authorized and encouraged, and planning for NIH-wide medical rehabilitation research was required in their recommendations. Most of

these provisions were in the Weicker, Kennedy, Dingell, and Waxman bills of 1988 and 1989. Those bills established the NCMRR as an independent Center whose Director reported to the Director of the NIH.

In 1990, Congressman Walgren reintroduced his NCMRR bill, but with the NCMRR as part of the NICHD. The Senate then reported and passed its NIH Reauthorization Bill with the NCMRR as an independent agency reporting to the Director of the NIH. The House reported its NIH Reauthorization Bill, H.R. 5661, with the new Walgren provision, but it did not reach the floor of the House for a vote. Republicans on the Committee opposed H.R. 5661 because it micro-managed the NIH with new provisions on ethics in research, animals in research, and new programs in fertility research. At the end of the session and of the 101st Congress, Congress and the NIH reached an agreement that at least the NCMRR provision would be passed as long as the NCMRR was not independent. The House then passed H.R. 5661, the 1990 NIH Amendments with the NCMRR provision, and one other. The Senate accepted the House bill, and the bill was sent to the President to sign.

How Was the NCMRR Enacted in Light of a Stalemate on Reauthorization? Why Was It Placed in an Institute, and Why the NICHD?

Three factors caused the NCMRR provision to be passed: (1) the tenacity of the members of Congress who supported it; (2) the impact of the disability movement, and the education that members of Congress received during the passage and enactment of the Americans with Disabilities Act (ADA); and (3) the support by NIH leadership for a medical rehabilitation program.

Why is it in an Institute, and perhaps more thought provoking, why the NICHD? At that time, the NIH opposed independent agencies reporting to the Director and continues to feel that way—a feeling largely shared by Congress today.

Also, the NCMRR was inaugurated without any budget and staff. Given these limitations, it was felt that an established and interested NIH Institute could furnish the support system with the expectation that the NIH Director would provide some initial funding.

But why the NICHD? When surveying the NIH landscape, it appeared that no single Institute was a clear fit for medical rehabilitation research which spans all ages (children, adults, and the elderly) and involves most body systems, such as the nervous system, the musculoskeletal system, and the cardiovascular system. But the mission of the NICHD was, and had always been, inclusive of human development throughout the lifespan. For example, geriatric research had been in the NICHD from its inception until 1976 when the NIA was created. Also, the NICHD had a clinical research focus and supported studies in applied science and policy, which many of the other NIH Institutes did not have. Finally, Dr. Alexander and Dr. Maddox were very supportive. That reception was not found in other Institutes and was key in negotiating this 20-year partnership.

The Initial Years

David Gray, Ph.D., was appointed Deputy Director of the NCMRR in 1991. Funding was provided by the NICHD and the NIH Office of the Director. Staff for grants administration and the budget from the NICHD assisted the NCMRR in 1991 and 1992. The first appropriation for the NCMRR was in 1993 at $8 million. It was advocated for by Congressman John Porter of Illinois and supported by Congressmen Natcher and Hoyer and Senators Harkin and Specter. The $8 million amount was earmarked to the NCMRR and grew in later years: in 2000, the allocation was $45 to 48 million; by 2005, $75 million. NCMRR funding has declined between 2005 and 2011.

The first Director, Marcus Fuhrer, Ph.D., was appointed in 1993, and Dr. Gray was appointed Deputy Director. Research training was a priority for funding throughout the initial years of the NCMRR. Also in 1993, a research plan was developed by the Director and the NABMRR based on a conference funded by NIH in 1990, and led by Ted Cole, M.D., and V. Reginald Edgerton, Ph.D.

Where Are We at Year End 2011?

The training grants have been successful, and the field now has many researchers whose grant applications are very competitive. Centers for capacity-building have been established, which have further developed research capacity in medical rehabilitation, research, and clinical trials. Program projects that have been funded have been very successful and resulted in new and exciting advances to improve the health of individuals with physical disabilities.

The interest and support from the NIH Office of the Director have not been as generous and robust as they were in the early years, and funding for interagency-wide collaboration has not occurred with much frequency. The initial comprehensive plan for medical rehabilitation research has not been subject to major review and revision and has never become a tool for trans-NIH program planning and funding, a disappointment to those who recognized the significance of a coordinated plan of action for rehabilitation research at the NIH.

As in the beginning of the medical rehabilitation movement some 60-plus years ago, the key to success has been leadership from the agencies—the VA, RSA, NIDRR, and the NCMRR at the NIH—Congress, the professions, and consumer organizations. It remains so. Moving organizational boxes can create a good or better environment for research, but energetic, well-placed leadership is necessary to make fields grow, particularly when times are difficult for budgets as they are today.

Thank you.

Looking to the Past and to the Future: The Creation of the NCMRR

David B. Gray, Ph.D.

First Deputy Director of the NCMRR (1991)
Associate Professor of Neurology and Occupational Therapy, Washington University School of Medicine
St. Louis, Missouri

I thank the Foundation for the NIH very much for inviting me to the celebration of the 20th anniversary of the NCMRR. I am both pleased and honored. You have heard some of the history of the NCMRR from two of the key people involved in making the Center a possibility, Dick Verville and Governor Lowell Weicker. The NCMRR research plans provide a detailed sequence of events that transpired after President George H.W. Bush signed the Center's enabling legislation (Public Health Service Extension Act, Public Law 101-613) on November 17, 1990.

Personal Interest in Medical Rehabilitation

My personal interest in medical rehabilitation research began much earlier than 1990. Perhaps the only unique perspectives I can offer on why the NCMRR was such an important and much needed addition to the magnificent existing scientific organization at the NIH is to relate to you my personal journey from academia, to rehabilitation, to health science administration, and back to academia.

I received a doctorate in behavior genetics at Minnesota in 1974. My research interests were in evolution and the contributions of environmental and genetic factors to individual differences in behavior. My mentors were well-respected leaders in measurement: Paul Meehl, genetics of schizophrenia; Irving Gottesman, manic depression; Leonard Heston, mental retardation; Sheldon Reed, behavioral genetics; David Merrell, ecological genetics; and, most significantly for my career, Travis Thompson, NICHD-funded scientist in psychopharmacology and behavior analysis intervention for individuals with developmental disabilities.

My plans for conducting research to investigate these mysterious interactive forces were rudely interrupted when on July 14, 1976, I had a rapid onset of interest in medical rehabilitation. I fell from my roof that morning and spent 1 year at St. Mary's Hospital in Rochester, Minnesota. During that year, I learned that most of the medical interventions and all of the psychosocial therapies I received were based on traditions passed on from generation to generation. After several years of adapting to my new diminished physical ability levels, in 1981, my mentor, Travis Thompson, arranged an interview for me at the NICHD. I joined the NICHD for a trial year. Every Friday during that year I attended orientation courses on NIH basics and the funding process, and met people from other Institutes and Centers with different responsibilities, including Deputy Directors of Institutes, scientific review administrators, policy administrators who wrote reports to Congress, program officers, intramural scientists, grants and contracts personnel, and budget administrators. The contacts I made and the understanding I gained on the basic mechanism used at the NIH to fund the best medical research guided many of my decisions when I was the Director of the NIDRR and when I worked on the team at the NICHD that put together the NCMRR.

Events Leading Up to the Creation of the NCMRR

When the opportunity came to build the NCMRR, I was ready for the administrative challenges, but equally important was my training in the world of disability advocacy and policy. This educational opportunity began when I was asked to apply for the position of Director of the NIDRR. I was invited to meet almost every leader of a disability group who resided in Washington, D.C., and many others who paid regular visits to the nation's capital: Lex Frieden, Executive Director of the National Council on Disability; Evan Kemp, Nader's Raiders; Justin Dart, father of the Americans with Disabilities Act; I. King Jordan, President of Gallaudet University; Judy Heumann, co-founder of the World Institute on Disability; Peter Axelson, Rehabilitation Engineering and Assistive Technology Society of North America; Marilyn Spivak, National Head Injury Foundation; Harlan Hahn and Irv Zola, leaders in the academic social policy; and many more.

At the NIDRR, I met the leaders of the medical rehabilitation field, from Henry Betts in Chicago to Herbert Schaumberg in New York City, Ted Cole at University of Michigan, Carl Granger from Buffalo, and many others who became advocates of forming the NCMRR at the NIH. Immensely helpful to me learning how to be a Director were Peg Giannini (first NIDRR Director), Doug Fenderson (second NIDRR director), Richard Leclaire (Deputy Director of the NIDRR), Betty Jo Berland (research advisor at the NIDRR), and my colleagues at the NICHD. On the political front, I became acquainted with Richard Verville; Senators Dole, Kennedy, and Durenberger; then-VicePresident George H.W. Bush; and President Reagan. They not only advocated for better treatment of people with disabilities but supported the need for more and better rehabilitation research.

In preparation for this meeting, I ran a search for NIDRR-funded researchers who had received NIH funds during the past 5 years. Only three names appeared. I rolled into Dr. Wyngaarden's office feeling well prepared to answer his questions. To my surprise, he asked me if I was the son of Dr. Fred Gray of Grand Rapids, Michigan. I replied that yes my father was an obstetrician/gynecologist who practiced in Grand Rapids, but he had passed away in 1973. Dr. Wyngaarden expressed his sorrow and explained that he had trained with my father at Butterworth Hospital in the late 1940s. The rest of the meeting went very well.

In late 1987, I returned to the NICHD. I was more convinced than even in my days in rehabilitation at St. Mary's that medical rehabilitation research that could examine the biological, individual, and social aspects of disability needed a home both at the NIH *and* at the Department of Education. The medical rehabilitation and advocacy communities agreed and led the efforts to have legislation introduced to create such a home. Peter Thomas was a key player in the efforts to create and fund the NCMRR. As we all are aware, the NIH stance on establishing new Centers and Institutes has been to discourage the seemingly endless attempts to create more and more Centers and Institutes. Thus, I was not surprised when I was told that the NIH Director, James Wyngaarden, wanted a briefing on why the NIH should consider a separate entity for medical rehabilitation research.

Dr. Wyngaarden formed a working group from his staff to conduct further investigations into the issues that might be addressed by a scientific approach to medical rehabilitation that fit the NIH standards.

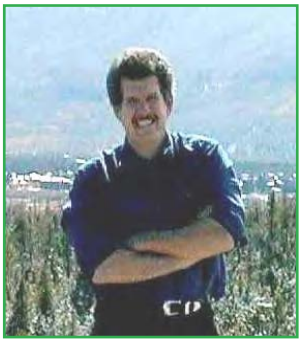
A very large conference followed at Hunt Valley, outside Baltimore, where advocates, scientists, practitioners, and policy makers developed a wide variety of topics that could be addressed by the NIH. After Dr. Wyngaarden left the NIH in 1989, I feared that all our efforts would not come to fruition. I was mistaken. Dr. Raub was named as Acting Director. He took up the challenge with vigor. A Director's advisory board meeting was called to hear the case for and against the formation of some entity at the NIH to house medical rehabilitation research. The discussion became heated. One side maintained that the NIH had rehabilitation within each of the existing Institutes and showed the projects and dollars that had been listed by each Institute. The other side won the day by pointing out that if medical rehabilitation was everywhere, then it was nowhere (thank you, Dr. Henry Betts!). The next months followed with another listing of projects and dollars from the NIH Institutes that counted as rehabilitation research. The numbers and amounts shrunk to amazingly low levels! Perhaps the history of taking research projects in the area of a new Institute's mission taught people to minimize their counts in a defensive move to keep them.

The Public Health Service Extension Act (Public Law 101-613)

In July 1990, President George H.W. Bush signed the Americans with Disabilities Act and in November 1990, the Public Health Service Extension Act (Public Law 101-613), which included the establishment of a medical rehabilitation research entity at the NIH. But before agreeing to sign the Extension Act, he asked his bridge partner and leading disability advocate, Evan Kemp, if he knew anything about the need for such a rehabilitation center at the NIH. Evan had been a volunteer worker when I was the Director of the NIDRR. His experience at the NIDRR had convinced him that the NIDRR should be moved out of the Department

of Education to a place in government where the management procedures were more conducive to fostering both good science and problem-oriented projects that were directed at issues faced by people with disabilities every day.

President Bush signed the legislation on November 17, 1990. In February 1991, Duane Alexander, Director of the NICHD, asked me to join an Institute team to put together a functioning center. Among the key members were Laurance Johnston, Director of Scientific Review; Don Clark, Director of the Office of Grants and Contracts; George Gaines of the policy office; and several other NICHD administrators.



The Early Years of the NCMRR

The legislation mandated the formation of an advisory board and a written research plan for the NCMRR. We held many meetings to review candidates for the advisory board. We were able to recruit leaders in medical rehabilitation research, rehabilitation practitioners, and disability advocates with national reputations for advocating for civil rights or for their contribution to assistive technologies for use by people with disabilities.

The NABMRR met and quickly took on the responsibility for providing guidance to the fledgling NCMRR. At the first meeting, Ted Cole held a closed session (closed to NCMRR and NICHD staff). The NABMRR met four times during the next 12 months, held three national meetings to get comments from people living in several locations, and produced the Research Plan for the NCMRR.

Top row: Peter Frommer, M.D., National Heart, Lung, and Blood Institute; Carolyn Baum, Washington University (occupational therapy); Robert Cooke, M.D., SUNY at Buffalo (pediatrics); George A. Zitnay, National Head Injury Foundation; Suzanne Campbell, Ph.D., University of Illinois at Chicago (physical therapy); Peter W. Thomas, Esq., American State of the Art Prosthetic Association; and Steve Hausman, Ph.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Second row: John Bowker, M.D., University of Miami (orthopedics and rehabilitation); Roberta B. Trieschmann, Ph.D., RBT Associates, Inc.; Theodore Cole, M.D., University of Michigan; Dorothy L. Gordon, D.N.Sc., School of Nursing, Johns Hopkins University; Carol Bennett, M.D., Rancho Los Amigos Medical Center (urology); Edmund Y.S. Chao, Ph.D., Mayo Clinic; and Duane Alexander, M.D., NICHD.

Front row: David Gray, Ph.D., Acting Deputy Director, NCMRR; Rebecca Ogle, Spina Bifida Association of America; Peter Axelson, Beneficial Design, Inc.; Henry Betts, M.D., Rehabilitation Institute of Chicago (physical medicine and rehabilitation); Judith Heumann, World Institute on Disability; Lex Frieden, The Institute for Rehabilitation Research, and Chair of the NABMRR.

Advisory board members not present for the photograph: Carl Granger, M.D., SUNY Buffalo (rehabilitation medicine); and Herbert Schaumberg, M.D., Albert Einstein College of Medicine (neurology).

In March 1991, Dr. Alexander asked me to recruit scientific and secretarial staff for the NCMRR. With some difficulty, we persuaded Louis Quatrano, a longtime member of the Division of Scientific Review at the NIH, to join us. Lou's early training in rehabilitation and his many experiences in reviewing assistive technologies were invaluable contributions to the NCMRR. Cheryl Chanaud, who was the Paralyzed Veterans of America Director of Research, provided a necessary link to the rehabilitation research community. Our first secretary, Shana Malone (now Anderson), was one of those accidental personnel recruitment miracles. She had had a spinal cord injury from a car accident and was trying to find work outside her former field of modeling. After she was hired, I discovered that her father, Dr. Tom Malone, had been Deputy Director of the NIH for many years. For the next 5 years, I received a constant stream of phone calls telling me how much the caller appreciated Shana's help on information for people with disability issues, ranging from where to look for grant announcements, where they could find information on announcements, to where they could find information on their impairment in and outside of the NIH.

Our team searched the NIH databases for areas of medical rehabilitation that were unexplored and that were described in the Hunt Valley meeting as topics that were amenable to scientific study. After Dr. Alexander reviewed our ideas, we presented the general idea to the NABMRR. If the Board approved the general idea, then we sponsored scientific conferences on the topics to get a detailed analysis of what could and could not be done. The next step was to issue a request for applications. Upon receiving grant applications, Laurance Johnston asked Anne Krey, an outstanding member of his review team, to form a study section to review the merits of the proposed research. Eventually, the NICHD funded many research projects in unique areas of medical rehabilitation.

Of course, this process took time, a long time. In the meantime we had a budget, albeit small, to distribute in some area of high need. One of the most frequent recommendations made at the Hunt Valley meeting was the need for training a new cohort of medical rehabilitation research scientists. We made the requisite announcements and held meetings with institutional training-grant principal investigators from a variety of fields to learn what they valued in their NIH-funded training programs. In the first year, the NCMRR funded 10 institutional training centers. This emphasis on training has continued for the past 20 years with exceptional results.

Medical Rehabilitation Today

Many of the early initiatives have formed a solid foundation for building the evidence base for medical rehabilitation. I will go out on a limb and say that we, the disabled, are better off now than we were 20 years ago. Going a bit further, I think that the field has seen significant growth in both the basic and applied aspects of rehabilitation. We may not have solved many of the problems that create impairments or found interventions to resolve disability at the cellular, system, or total body levels, but as Winston Churchill said in his last commencement address, "NEVER GIVE UP, NEVER!"

Thank you for your attention.

The NCMRR After 20 Years: Three Persistent Frustrations To Fulfilling Its Mission

Marcus J. Fuhrer, Ph.D.

Former Director of the NCMRR (1993 to 1998) and Scientist Emeritus at the NIH

It is a delight being part of this symposium celebrating the 2-decade existence of the NCMRR, just as it was a delight joining the Center in 1993. Having been a medical rehabilitation researcher for the preceding 30 years, as well as a member of the cadre championing for an organizational presence for the field within the NIH, the invitation to become the NCMRR's first Director was utterly compelling.

The Early Years

I assumed the position alight with high expectations. The Center already had considerable momentum. Thanks to the hands-on involvement of Duane Alexander, Director of the NICHD, and the yeoman efforts of the Center's original staff members, an advisory council had been appointed and a long-range plan had been drafted. The challenges before us were to engage the research community in exploiting the Center as a funding source for its most promising research, to grow the field's research capacity, and to establish the Center as the NIH's focus of medical rehabilitation science.

By the time of my retirement in 1998, the NCMRR had scored a number of worthwhile achievements.[3] They included, among other things, establishing a discrete treatment effectiveness research program, issuing requests for applications in the earlier years in several high-priority problem areas, and beyond the norm for the NIH, devoting as much as 15 percent of the annual budget to research training of various kinds. At the same time, there were the inevitable frustrations. I want to briefly discuss three of them that I believe are still concerns some 13 years later.

Three Frustrations

The first and foremost frustration regarded the Center's funding. It was simply miniscule in relation to the goal of providing a body of systematic research to support the evidence-based practice of medical rehabilitation. That frustration was mitigated to a degree by the beyond-the-norm annual budget increases that the Center enjoyed, increases that continued throughout much of the 1999 to 2003 period during which Congress doubled the aggregate NIH appropriation. It was obvious, however, that accelerated budget growth of this kind could not continue indefinitely in the context of the zero-sum game that is the NICHD's overall budget. The evidence of more recent years suggests this is the case. Between fiscal years 2007 and 2011, the overall expenditure of the NICHD's other three Centers increased by 6.6 percent, while the NCMRR's expenditure decreased by 7.3 percent. This occurred even while the Center's funding, $66.1 million in 2011, remained at a level akin to it being a Branch of one of the other Centers, rather than to being one of their peers. Indeed, at least five of the other Centers' 12 branches had 2011 expenditures exceeding the NCMRR's. The overall picture is one in which the Center's earlier pattern of marked annual budget increases is nowhere to be seen, even while its level of funding is wholly inconsistent with the scope and importance of its mission.

The second frustration regarded the Coordinating Committee for Medical Rehabilitation Research. The coordination of rehabilitation-related research being funded NIH-wide is a pregnant concern in view of the total amount of that expenditure and the number of organizational components dispensing it. In 2010, for example, 16 NIH Institutes or Centers expended a reported $458 million in such research (a supporting reference is available from the author upon request). Although the Coordinating Committee's reason for being is heralded by its name, the legislative language specifying its purposes is vague, if not downright confusing. It merely states, "The Coordinating Committee shall make recommendations to the Director of

[3] Fuhrer, M. J. (1998). The National Center for Medical Rehabilitation Research: Beyond infancy, looking toward maturity. *American Journal of Physical Medicine and Rehabilitation, 77*(5), 437-443.

the Institute and the Director of the Center with respect to the content of the Research Plan and with respect to the other agencies of the National Institutes of Health and with other agencies of the Federal Government."[4] Say what? No mention is made of coordination, either directly or indirectly. Thus set adrift, the Committee began meeting regularly in 1994, becoming little more than a forum for exchanging information. We would have been hard-pressed to demonstrate that its proceedings had any influence on the planning or decision making of any of its participating organizations. The Committee is unlikely to perform a meaningful coordinating role until its charge is more sharply delineated in future legislation.

The third frustration concerned our difficulty to adequately support a full spectrum of research spanning both the few problem areas that already had considerable momentum and the many more areas that were manifestly under-researched. A pervasive NICHD funding doctrine called for devoting the preponderance of the Center's annual budget to high-cost, high-impact, investigator-initiated R01-funded projects. These grants averaged approximately $275,000 annually for a period as long as 5 years and were in competition with all similar grants made by the NICHD. Accordingly, the studies were typically based on an appreciable amount of prior research establishing their empirical and theoretical foundations, the credibility of their hypotheses, and the adequacy of their methodology. The difficulty was that numerous problem areas lacked the research development necessary to undergird such studies. We were not devoting enough support to smaller-scale, building-block kinds of studies whose findings could lay the groundwork for major studies to advance the field.

The needed formative projects might take various forms. Included were analyses of extant databases to establish the epidemiological parameters of a clinical issue, studies to enhance the technical properties of outcome measures, investigations of the natural history of heretofore neglected disabling conditions, or early feasibility studies of novel rehabilitative interventions. Included as well were exploratory translational studies that take principles or mechanisms established by previous research and apply them to clinical questions. When cogently framed within an explicit, overall investigative strategy aimed at well-delineated research goals, these various kinds of studies can be essential contributions to what Whyte, Gordon, and Rothi term as a "systematic, phased, developmental approach" to addressing significant rehabilitation questions.[5] While those authors focus on developing effective rehabilitation treatments, their analysis generalizes readily to research with other aims—for example, regarding diagnostic, etiologic, or prognostic issues.

Some formative projects like those that have been described were eligible for support by either R03 or R21 grants. However, most failed to conform to the requirements of these mechanisms, either because they necessitated more funding or longer funding periods than could be provided by R03 grants, or their aims lacked the novelty and degree of risk that characterize R21-supported studies.

The request for applications (RFA) was—and continues to be—a particularly attractive means of supporting component studies in an overarching research plan. It involves setting aside funds for multiple research projects, with each one addressing a different aim. The aims can be organized in such a way that when jointly pursued, they constitute a systematic approach to answering a particular research question. Notwithstanding the advantages of RFAs for jumpstarting advances in strategically targeted research areas, none were issued during the latter years of my tenure at the NCMRR because of a ceiling on the Center's annual expenditures. Nor has an RFA been issued in recent years, probably for the same reason.

The Future

Fortunately, promising proposals are not lacking for improving the NCMRR's effectiveness. We have the guidance contained in the Institute of Medicine's two reports, *Enabling America: Assessing the Role of*

[4] Public Law 101-613, November 16, 1990. National Institutes of Health Amendments of 1990.
[5] Whyte, J., Gordon, W., & Rothi, L. J. (2009). A phased developmental approach to neurorehabilitation research: The science of knowledge building. *Archives of Physical Medicine & Rehabilitation, 90*(11), S3-10.

Rehabilitation Science and Engineering[6], and the more recent *The Future of Disability in America*[7]; the recommendations of the *Rehabilitation Medicine Summit: Building Research Capacity*[8]; as well those being advocated vigorously by the Disability and Rehabilitation Research Coalition (http://www.aapmr.org/advocacy/health-policy/DRRC/Pages/Disability-and-Rehabilitation-Research-Coalition.aspx). Now we eagerly await the views of the Blue Ribbon Medical Rehabilitation Research Panel (http://www.nichd.nih.gov/news/releases/090111-blue-ribbon-panel.cfm). No one wishes more than I that implementation of its recommendations will result in strengthening the foundation of an NCMRR whose achievements we will continue celebrating throughout the years.

Acknowledgments

I am grateful for the assistance of staff members of the NICHD Office of Science Policy, Analysis, and Communication who developed much of the fiscal data cited in these remarks.

[6] Brandt, E. N., & Pope, A. M. (Eds.). (1997). *Enabling America: Assessing the role of rehabilitation science and engineering*. Washington, DC: National Academy Press.
[7] Field, M. J., & Jette, A. M. (Eds.). (2007). *The future of disability in America*. Washington, DC: National Academies Press.
[8] Frontera, W. R., Fuhrer, M. J., Jette, A. M., Chan, L., Cooper, R. A., Duncan, P. W., Kemp, J. D., (2005). Rehabilitation medicine summit: Building research capacity. *American Journal of Physical Medicine and Rehabilitation 84*(12), 913-917.

Seeking Validity and Meaning in Science: A Quarter for Your Thoughts?

Margaret G. Stineman, M.D.

Professor of Physical Medicine and Rehabilitation, Perelman School of Medicine, University of Pennsylvania
Philadelphia, Pennsylvania

Many people speak about the translational pipeline, which goes from ideas, science, special interests, politics, legislation, and at the center of this thing is health care (Figure 1). And I think that it was very interesting that that's already come up in terms of Dr. Rymer's talk. Technology has moved faster than our ability as clinicians to provide the technology. Part of that is legislation, part of that is politics, part of that is dollars. And so, there needs to be a balance in terms of our ideas that stimulate science, and all of this is kind of linked together in terms of how we can help people.

So there is the idea, but then there are special interests (Figures 2-3). There are people with disabilities, but then there are the dollars that are available to take care of them, which are limited.

Politics

What mandates and shapes priorities? This is what I think. Why I think the NABMRR is so great because it can deal with many of these issues. What interest groups dominate? How can special interest and dollars be balanced? How are scientific principles maintained (Figure 4)?

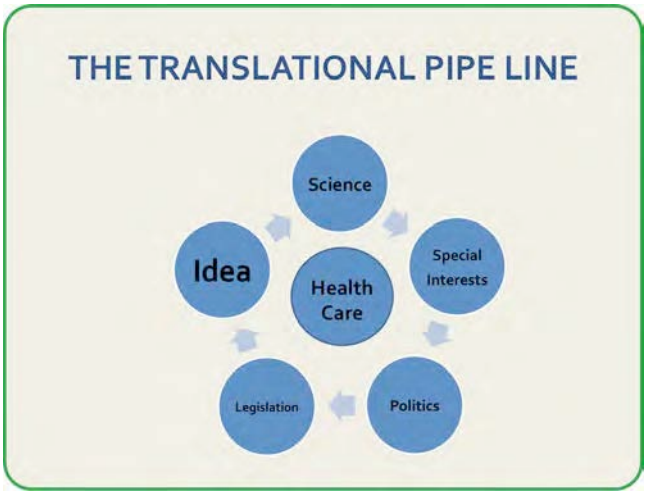


Figure 1.

Figure 2.

Figure 3.

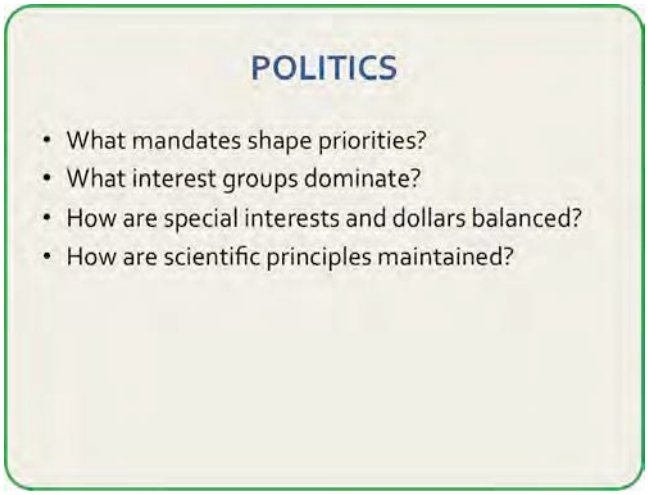


Figure 4.

Pay Lines

We might as well face it, pay lines determine research (Figure 5). The Board attempts to navigate all of these challenges, and I think it's very exciting because it includes both consumers as well as scientists (Figure 6). And as Dr. Nitkin said, I served on the Board first as a consumer advocate, and then I became a scientist and served again on the Council.

Scientists

This is my dad's old brass microscope (Figure 7). Scientists are sometimes forced to be opportunists because we have to really basically look at what can get funded. Something might be very important, but if it's not measurable, we can't necessarily study it. What is currently considered innovative? And there's always a potential disconnect between need and what one can do. So scientists are always well intentioned, but often, we are naïve in terms of what consumers might value the most. So with regard to scientists on the Board, there's often a disconnect (Figure 8).

Figure 5.

Figure 6.

Figure 7.

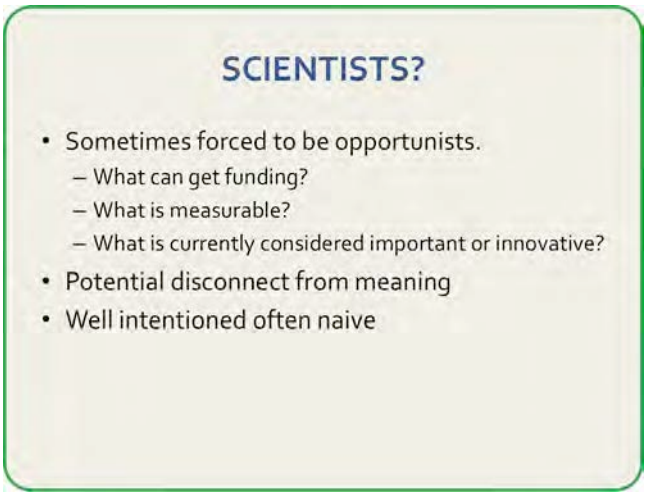


Figure 8.

Consumers With Disabilities and Advocates on the Board

Sometimes society and its barriers force consumers with disabilities to become radical activists. It's the only way they can survive. They may become myopic to their own circumstances in that if you have a visual limitation, your needs are different from a person who has a mobility restriction. Desires are highly meaningful and valid, but they may not necessarily be something that can be measured or created. Consumers' ideas might be very, very valuable, very, very meaningful, but not necessarily practical.

So there's a creative tension often on the board between the scientists and the consumers. Again, consumers are well intentioned, but they may be naïve (Figure 9).

People with disabilities on the Board frequently face challenges. There were a number of folks who could not really come to the meetings because of their disabilities, and this highlighted issues of those of us who attended, and continue to attend. Sometimes we are challenged. The hotels are always selected carefully so that they are accessible. However, even in this hotel, I can't physically open the door to get out of my room. So I would be trapped in there if there was a fire.

And sometimes accessible vans never come, and that's not the NIH's fault; it's just life. And it's something that I think I want to say to the NIH: you are courageous and wonderful to have us. It's beautiful, and I appreciate it (Figure 10).

Here is a painting I did to show inaccessibility of the environment conceptually based on distortion (Figure 11). Now I'm going to go right to the quarter story (Figure 12).

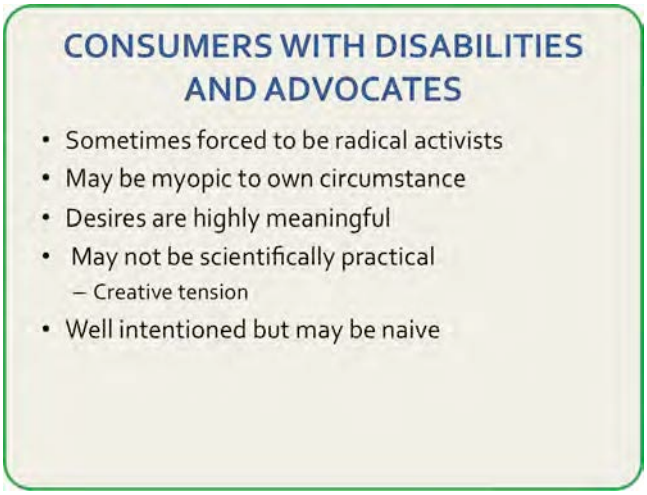


Figure 9.

Figure 10

Figure 11.

Figure 12.

The Quarter Story

Years and years ago, there was a meeting of the Board at the Natcher Conference Center, and it was right after the Natcher Center opened. It was very beautiful. After the meeting, all of the able-bodied people left in taxis. There was supposed to be an accessible taxi that would come and pick me up as well as another person with a disability, who was more disabled than I am, but the taxi never came.

And so, we were locked in the Natcher Conference Center. If you know the Natcher Center, it's a big beautiful building, there's a big kind of a lobby area that's all glass and there were plants around. Well, we were locked in this glass room, and even the telephone area was locked away from us as well as the bathroom. It was getting dark. I thought I heard the sound of somebody cleaning inside the area that was locked where I knew the telephones were. So I knocked on the door. The guy comes over to the door and he goes motioning with his hands for me to go away. And I knocked again, and he comes over and motions his hands again to me to go away. He couldn't speak English.

So I knocked again. This time, he opened a little bit and he said, "Go away!" I put my arm through the door so he couldn't close the door, and I said, "I've got a quarter; I need to make a phone call." This was before cell phones. So he kind of looked at me and he looked at my colleague, and he kind of scratched his head, so we went in. Now we could use the bathroom, thank God, because we had to go, and also make one phone call.

So this is the issue that came up, and the issue was what do we do with the quarter? My advocate friend, who is much more radical than I am, decided that we should really make this into a "happening" and call the press. Now, me, I wanted to get home and I knew the press did not have accessible vans. So I said, "No, we're going to call the cab company that has accessible vans." So I called the cab company. Much to her disgust, and basically, another hour later, it was all dark. The cab came. There was only one place in the cab for a wheelchair, so one of us had to stay in the Natcher Center all alone in the dark. Guess who did it?

So here I am; I'm sitting all alone. It's dark, the light is on, I felt like a fish in a fishbowl. I started thinking: what if it doesn't come back? Where am I going to sleep? Shall I leave the building and try to get help? If I leave the building, well, I won't be able to get in again because the door will lock. So I decided I'll just stay. I got out of my wheelchair and I sat on the floor, and I had a peak experience, and this is what happened.

I sat in this building all alone and I thought, think of all the science that's going to happen in the future, and all of the science that's happening now. How extraordinary, I'm breathing the air of all of these people who have some of the greatest minds in the world. And I said, some day, I would like to be one.

Diverse Perspectives Enhance Depth of Understanding

Now, I'm not going to tell you the end of the story. Diverse perspectives, heads, and hands enhance depth of understanding, scientists and consumers together struggling, are gears that turn the innovation machine—the past, the present, the future (Figures 13-14). And I'm going to move fast!

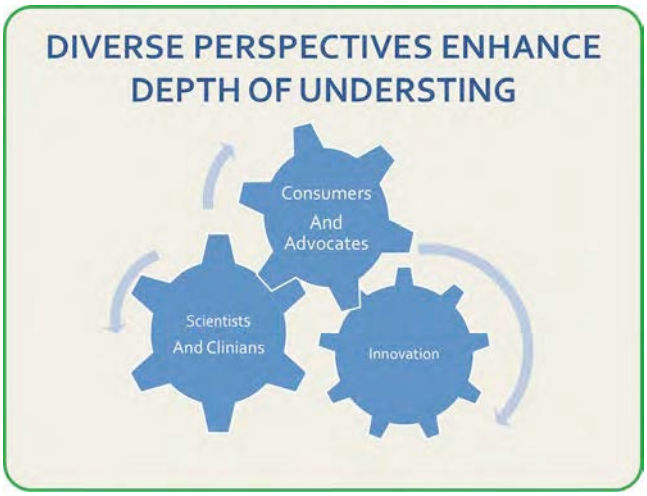


Figure 13.

Figure 14.

I will say one of the tweets from one of our old Boards was "Progress in research is not linear; often there is a lag time." Only about 10 percent of the research that's done hits the mark and becomes used (Figures 15-16). What a tragedy that is.

Figure 15.

Figure 16.

Well, I moved my office a few years ago and all of my beautifully kept, careful project books from the first decade of my career got recycled. So there they are on the floor of my office after they've been dumped out of my cabinets. On the left-hand side of this screen, there is a pack, a stack (Figure 17). Those are all the project books and manuscript drafts that went into the Function Related Groups (FRGs), which now are basically paying for rehab services throughout the country. That research got used. The rest of it is still stewing. So all the rest of it, I don't know whether it's going to have any meaning or not. It may not (Figures 18-19).

Figure 17.

Figure 18.

Figure 19.

Shift in Paradigm

So how can we increase the value per dollar spent? And I've got to make this go fast. I do want to talk about a shift in paradigm (Figure 20). This shift in paradigm, really I think, is critical because when I was on Council, the NIH moved dramatically toward a cure focus. Cure is very important. It's fantastic. It's where science should go. However, the more we advance science and advance towards cures, the more there are going to be new residual impairments, new disabilities, new symptoms that are going to emerge. So I believe very strongly that we have an ethical mandate, an imperative to help people maximize their function and to empower them when they can't be cured, or perhaps until the day they can be cured.

So rehabilitation is function focused. It happens when cure fails. And so, I think that it's important to recognize that there is always going to be a need and a place. And so, here is an expanded model. There's the person on one side, the environment on the other (Figure 21). And so many people, Dr. Whyte, Dr. Gray, so many people in this audience, Dr. Jette, all of you, Dr. Florence Clark, we have all talked about expanding models to include the environment, and how you have to consider the person as well as the environment in which they live.

Figure 20.

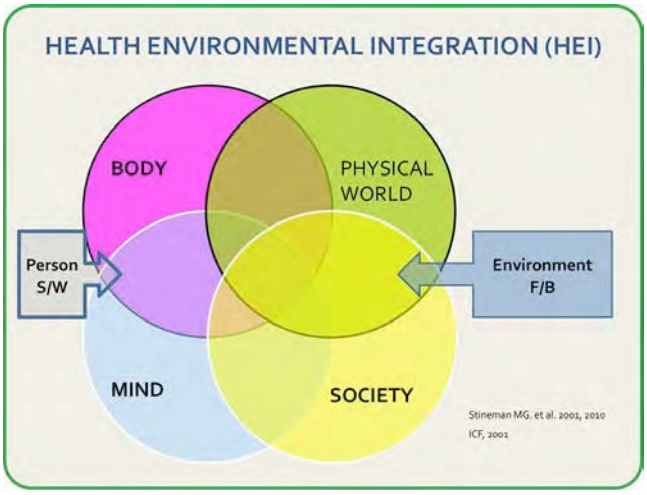
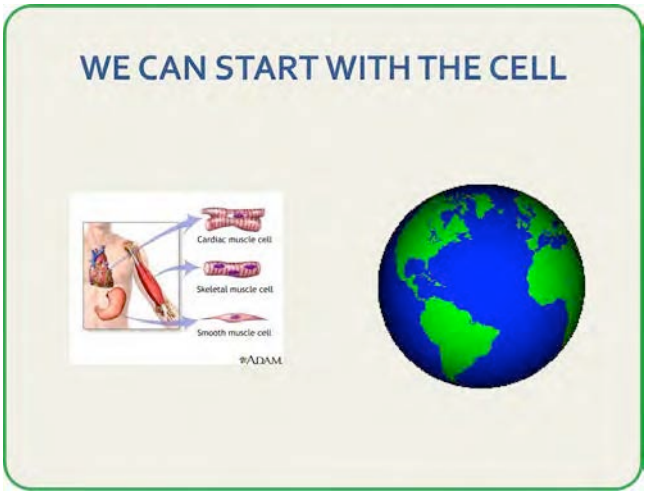


Figure 21.

We can start with the cell, and through working with cellular mechanics and mechanisms such as we heard this morning, increase people's access to the world (Figure 22). So targeted muscle reinnervation is an example. You can take an electromyography (EMG) signal, which is physiologic, and run a prosthesis (Figure 23). Similarly, brain-environment interfaces: we've heard about that, also (Figure 24). We're starting with physiology, basic science, translating it. We can also start with the world and change the world so as to allow the person with disabilities to enter it (Figure 25).



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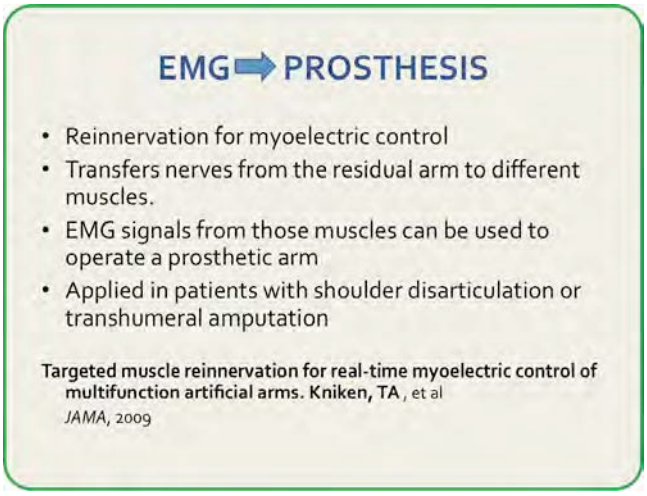

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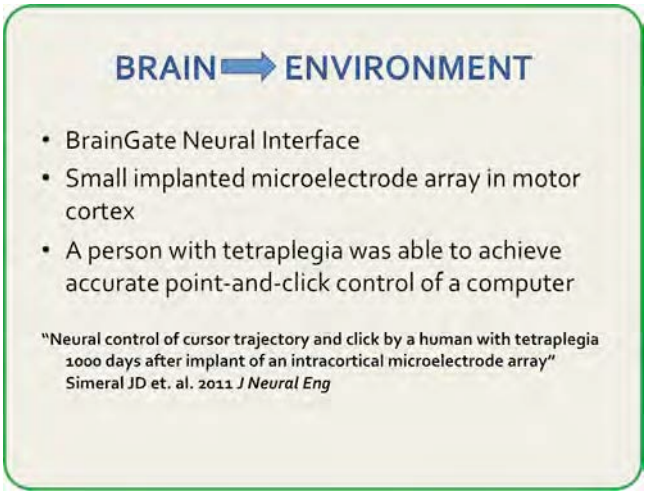

Figure 24.

Figure 25.

This is the work of one of our T32 fellows, and it uses a staging system we're developing for basic disability function. As the stage increases, disability increases, and you can see some rather fascinating startling things that we found in his work. As you increase the stage of disability, the risk of falling increases dramatically up until the last stage, which is the most profound level of disability, and then the risk drops (Figure 26).

Well, it turns out that the few people with the most profound disabilities, who fall, fall multiple times, and we believe that that is probably the environment. Once you get to a point where you can no longer do basic activities of daily living (ADL) self-care tasks, you don't have as much opportunity to fall, so the falling risk goes down, but then if you do fall, you fall many times, multiple times because you are in an environment that is not supporting you (Figure 27).

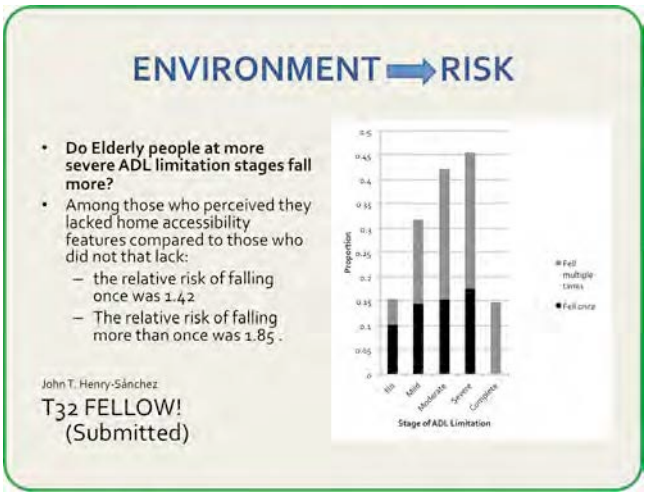

Figure 26.

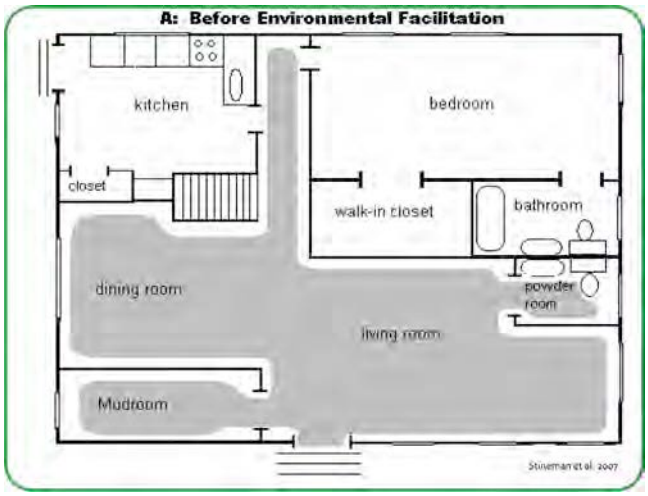

Figure 27.

This approach to environmental mapping was inspired actually by David Gray's work. It's an environmental diagram and it illustrates how, if we change the environment, you can increase access (Figure 28).

The Future

T32 submitted. This guy just put his first paper in; I am proud of him. They are the future, and that's all I'm going to say about the future (Figure 29).

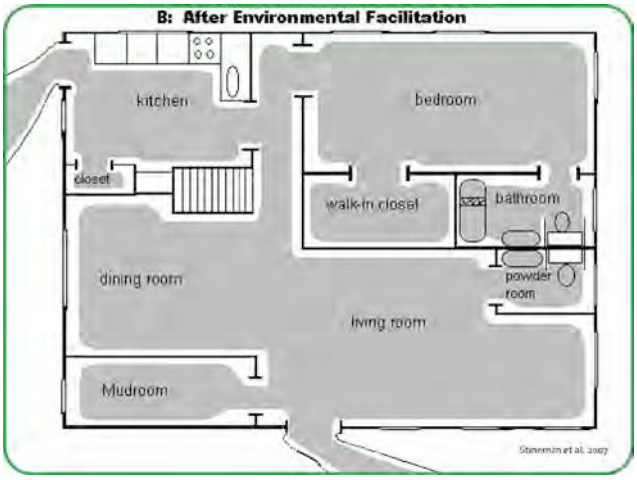

Figure 28.

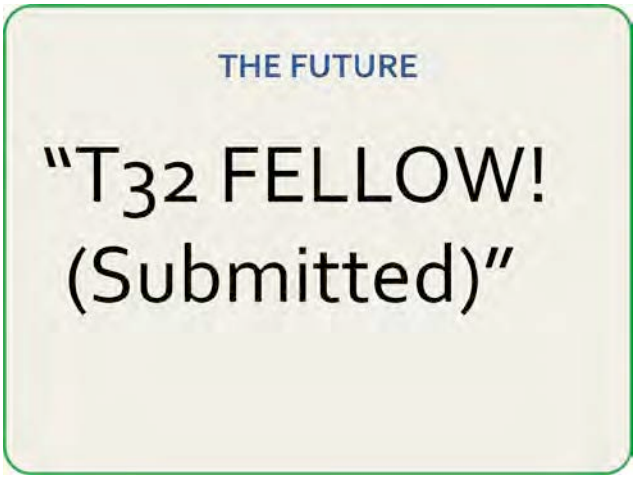

Figure 29.

Final Thought

My final thought for you: a quarter for your thoughts (Figure 30). There has been inflation. It used to be a penny; now it's a quarter. So final questions: if you were locked in the Natcher lobby at night, what would you do with your quarter? As a society, we need to make similar choices at the level of supporting science. If we have a quarter of a million, or a quarter of a billion, how should we spend our quarter? (Figure 31)

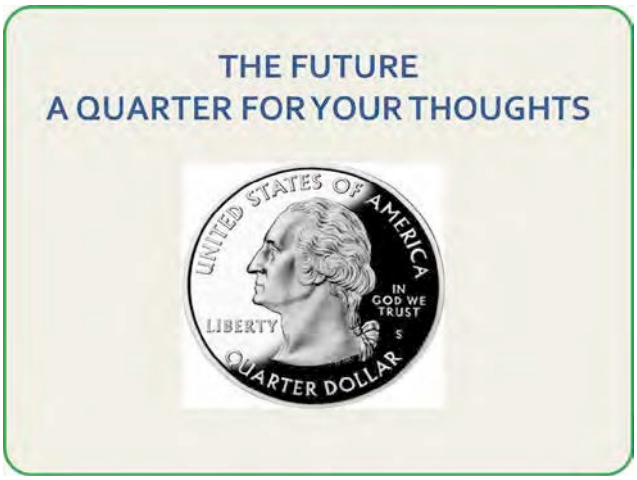

Figure 30.

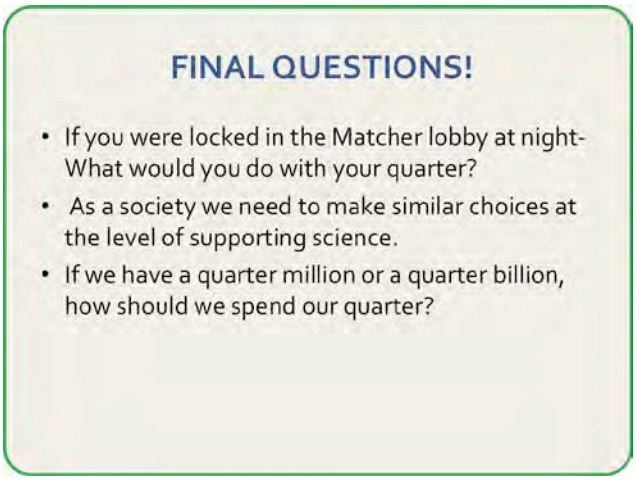

Figure 31.

In closing, thank you for being there for us, NCMRR staff and NICHD staff (Figure 32). And that is my end.

Figure 32.

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Chapter 3: The Role of the NIH in Rehabilitation Research

The following presentations are by three NIH leaders—Dr. Lawrence Tabak, Dr. Alan Guttmacher, and Dr. Yvonne Maddox—who provided their comments on the mission and contributions of the NCMRR over the past 20 years. Dr. Tabak extolls the Center's contribution to the mission of the NIH as perceived by the Office of the Director. Dr. Guttmacher and Dr. Maddox recognize the Center's record of accomplishments as an integral part of the NICHD family, not only realizing substantial accomplishments in rehabilitation research but also enhancing the research of other programs throughout the NICHD.

20 Years of Turning Discovery Into Healing and Recovery

Lawrence A. Tabak, D.D.S., Ph.D.

Deputy Director, NIH

First, let me thank Alan Guttmacher for personally inviting me to celebrate this special occasion with you. I can honestly tell you that the invite came directly from Alan himself because he actually used the terms "Protocol, shmotocol" in his note to me. Who else would do that? The difficulties involved in trying to spell "shmotocol" alone probably would have prevented most other people from composing the note. I accepted the offer immediately, too—and with just as much formality.

I'm also here on behalf of Dr. Francis Collins, Director of the NIH. He'd already committed to another event, but I know he's sorry to miss this celebration. I also know him well enough to know he'd take this as an excellent opportunity to do something all of us at the NIH have been trying to do a bit more often recently and that is publicly recognize the enormous benefits of medical research.

Two Decades of Progress

I know we're thinking especially about 2 decades of scientific progress by the NCMRR. However, the NCMRR's triumphs can certainly be used to illustrate the NIH's—and medical research's—larger story. The NIH is known for "turning discovery into health." Here, we acknowledge that for the last 20 years, the NCMRR has led the charge to turn discovery into healing—and recovery. You'll hear a lot more about the actual science the Center supports and conducts during this symposium. And you'll hear much more about the Center's history.

The Big Picture

My job, however, is to talk to you for just a few moments about why rehabilitation research is so important now, and in the near future. Additionally, I want to stress how important we believe such research is to the broader future of the NIH and medical research in general.

We're here in the thick of holiday rush, that time of year that is naturally chock-full of festivities, gatherings, and parties. Of course, celebrating the 20th anniversary of the NCMRR is different. It's special—because of its mission, certainly, but also because of the climate we're in these days.

The truth is we're delighted to trumpet NIH scientific accomplishments and achievements at any time, but particularly right now. I don't need to point out that this has been a tough economic year for everyone, and medical research has certainly felt the pinch. So, it's an especially good time to be able to take a couple of days to tout some good news—to recognize a vision realized. That's what this event is about—acknowledging what can be accomplished in the space of 20 years, a generation.

We recognize that the NCMRR has made an enormous impact on an entire generation. Over the course of that time, we've made many biomedical advances that save lives. Rehabilitation research, though, looks beyond that to helping improve quality of life and functioning.

Perspective

Let's all think back to 1991. It was considered the last year of the Cold War and the first year of the Gulf War. That April, the Dow Jones Industrial Average closed above 3,000 for the first time. The NIH welcomed its first female Director, Dr. Bernadine Healy, and treated cancer patients with human gene therapy for the first time.

Also, 1991 was the year Gopher was created. Does anyone even remember Gopher, the first user-friendly Internet interface? With a smartphone in every hand nowadays, the Gopher trend truly seems like a lifetime ago, doesn't it? But that's the climate in which the NCMRR began to make a difference in people's lives.

Today, new trends make us all the more aware of the importance of rehabilitation research. The aging baby boomer generation—with higher life expectancies—is placing new demands on the health care system.

Let's consider the facts. Today in the United States:

- 21 million people have their mobility limited in some way due to arthritis.[9]
- 10 million adults age 50 and older have osteoarthritis of the hip, with nearly 37 million more at risk for the disorder.[10]
- An estimated 3.6 million people in the United States are affected by traumatic brain injury, spinal cord injury, or loss of limb.[11]
- Annually, almost 800,000 people have a stroke.[12]
- Countless others suffer from such chronic disorders as muscular dystrophy, cerebral palsy, and multiple sclerosis.
- Many of our veterans are returning from war with serious injuries (loss of limbs, traumatic brain injury, *et cetera*).

The NCMRR brings light to these issues and other important health problems affecting people with disabilities. In doing so, the Center plays a central coordinating role in rehabilitation research at the NIH and in the broader scientific community.

The Impact of Rehabilitation Research

Let's applaud the tremendous impact rehabilitation research has made in just its first 2 decades. We can't put a dollar figure on what we've learned in the past 20 years of the NCMRR. How can we put a price tag on the new insights we've gained about the nervous system or on the progress in prostheses, for example?

We haven't even mentioned the hundreds of investigators who have been trained via NCMRR-supported education mechanisms. Or how about the impact of the countless researchers and related professionals who are now pursuing careers in medical rehabilitation research?

Perhaps we can't know exactly how big a return we've gotten on the nation's investment in the NCMRR. One thing we can say with certainty, though, is that an entire generation of lives has been significantly improved. Lives nearly destroyed by illness or injury have been healed, abilities restored, and functions recovered—due in no small measure to the enormous commitment and competence of the NCMRR.

Congratulations, NCMRR, for 20 years of contributions to medical rehabilitation research and for making just the most recent powerful case for medical research and its benefits to the public. Every time we celebrate a milestone like this, we help the public appreciate a bit more the importance of supporting and promoting medical science and research. Here's to the NCMRR's next 20 years of finding better ways to help people heal and recover!

Thank you.

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[9] Cheng, Y. J., Hootman, J. M., Murphy, L. B., Langmaid, G. A., & Helmick, C. G. (2010). Prevalence of doctor diagnosed arthritis and arthritis-attributable activity limitation—United States, 2007–2009. *Morbidity and Mortality Weekly Report, 59*(39), 1261-1265. Retrieved on November 12, 2012, from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5939a1.htm?s_cid=mm5939a1_w.

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[12] Centers for Disease Control and Prevention. (2012, July). *Stroke.* Retrieved on November 12, 2012, from http://www.cdc.gov/stroke.

In Commemoration of the 20th Anniversary of the NCMRR

Alan E. Guttmacher, M.D.

Director, NICHD

It is a pleasure for me to join you and the staff of the NCMRR in celebration of its 20th anniversary and to acknowledge its major contributions in rehabilitation research.

During the last 2 decades, the NCMRR has made possible numerous scientific advances that have had a tremendous impact in the field of rehabilitation research—and on people's lives. Because of time constraints, I'll share just a few highlights.

Sophisticated neuroimaging techniques employed by NCMRR-funded researchers have pinpointed which parts of the brain control various functions and allowed monitoring of the effectiveness of different therapies in patients with traumatic brain injury. This information allows rehabilitation specialists to design more effective and targeted interventions to improve function in specific areas.

Studies in animal models have yielded promising results that may lead to effective therapies for people. In a study in rats, for instance, researchers found that folate promoted regrowth in damaged spinal cord tissue by triggering DNA methylation. These results suggest that a greater understanding of the chemical sequences associated with folate metabolism and DNA methylation could lead to new techniques to promote healing of damaged spinal cords and other nervous system injuries.

Other researchers developed a successful treatment for dogs with the canine version of Duchenne muscular dystrophy by employing a novel genetic technology that compensates for genetic errors. That technology, known as "exon skipping," uses tailor-made snippets of DNA-like molecules as molecular "patches" to cover up mutant DNA sequences, allowing the dogs to make imperfect—but serviceable—muscle proteins and significantly improving their muscle functioning.

The NCMRR has also supported some of the first randomized controlled trials in rehabilitation science, which have led to important findings on the value of a number of therapies. One study in stroke patients showed the comparative effectiveness of a new technique in improving motor function. While traditional therapies focused only on improving function of patients' unimpaired limbs, constraint-induced movement therapy compels patients to practice using their impaired limbs instead, gradually leading to improved function and the development of new brain pathways.

Through its small business innovation research program, the NCMRR has made significant advances in bioengineering as well—resulting in new developments and improvements of assistive technologies that benefit people with disabilities. Wheelchair designs have come a long way in the last 20 years, due in part to support from the NCMRR. Today, wheelchairs are available that allow users to ascend hilly terrain or steep ramps without rolling backward, to adjust their seats to varying heights for different activities, and to maneuver more easily in tight spaces.

Other technologies supported by the NCMRR have helped restore physical functioning. Robotic Upper Extremity Repetitive Therapy (RUPERT) helps patients perform repetitive exercises specially tailored to the individual to improve flexibility and strength. As a supplement to traditional therapies with rehabilitation specialists, RUPERT has the potential to save costs while helping individuals regain function.

NCMRR-supported research in prosthetics has led to advances such as improved sockets that automatically adjust throughout the day to maintain a precise fit, improving quality of life for amputees—and, more recently, to state-of-the-art prosthetic arms that offer increased control and even "feeling," using severed nerves from the residual arm re-implanted into the chest wall.

Another noteworthy scientific advance is the BrainGate™ system, which provides paralyzed patients with the ability to control a computer cursor with their thoughts. New research building on this technology aims to allow individuals with severe disabilities to control other objects in their external environment as well.

Future Directions

As we reflect on the NCMRR's accomplishments of its first 20 years, we see how far we have come—and how far we have yet to go.

This year, the NICHD has been engaged in a Visioning process to identify the most promising scientific opportunities of the next decade, which should be an unparalleled era in biomedical research. The aim of this process is to inspire the NICHD, our many partners, and the research community to achieve critical scientific goals and meet pressing health needs. The Visioning process entailed conversations with many hundreds of stakeholders, from a broad range of backgrounds, and was successful, I think, in generating excitement about future research directions.

During these conversations, rehabilitation research emerged as a strong theme and an area ripe for continued exploration, with many important questions still in need of answers. For example:

- What are the underlying mechanisms of plasticity?
- How might we manipulate certain factors to influence plasticity and speed repair?
- And what are the roles of environmental and social factors in recovery from disease or injury and rehabilitation?

As we move into the next era of biomedical research, advanced technologies such as robotics, brain stimulation, and the virtual environment provide exciting opportunities to test interventions and allow more precise outcome measurements. Exploring the genetics of drug action may help us better understand individual variation in patients' responses to rehabilitation. And there remains much work to be done on concussive injuries—to determine the magnitude of risk and long-term impact of these injuries and to design effective preventions and treatments for them.

Throughout the scientific Visioning process, one thing was underscored again and again, and that was the value of transdisciplinary research and collaboration. The NCMRR already knows this well and has worked hard over the years to establish a research community that represents a range of scientific and technological disciplines and backgrounds and to strengthen collaborations with multiple partners. Today, the Center is participating in a trans-NIH committee on sleep research to learn more about the effects of sleep on recovery and rehabilitation. The NCMRR is also involved in an interagency coordinating committee to advance pain research and is in talks with the Departments of Defense and Veterans Affairs to address rehabilitation needs of our troops injured in combat. Similarly, it is exploring with a number of potential partners from the public and private spheres how best to advance concussion research. The Center also continues its longstanding support of a national research network to improve care of critically ill and injured children.

I have no doubt that the NCMRR will continue to be a major player in the field of rehabilitation research in the years ahead. With the experience it has gathered from past research accomplishments and the momentum derived from new scientific opportunities, the NCMRR is poised to make significant contributions in the next 20 years and beyond. But what makes me most confident in the NCMRR's future success is its people:

- Individuals here today whose vision helped establish this Center
- Researchers who bring curiosity, innovation, and commitment to their work everyday
- Advisory Board members who provide valuable insights in guiding the Center's efforts
- Dedicated staff members who work tirelessly to coordinate research activities and make good use of our resources

- Advocates who promote the value of investments in rehabilitation science
- And most of all, the innumerable patients and their families who count on our continued progress and are irreplaceable partners in it.

Thank you.

The NCMRR: Making a Difference in the Lives of Children and Adults with Disabilities

Yvonne T. Maddox, Ph.D.

Deputy Director, NICHD

It is a distinct pleasure for me to be a part of the program today and to share in this recognition of the NCMRR for its 20 years of contributions to the field of medical rehabilitation research. Many of you here today may subscribe to the philosophy that whenever you listen to someone, you would like for them to tell you something you didn't know. Well, in the spirit of that philosophy, let me say that it is fortuitous that the Foundation for the NIH, which helped us to organize this 20-year celebration, and the NCMRR were both established by Congress under the same amendment, the NIH Amendments of 1990 (Public Law 101-613, November 16, 1990).

In another spirit of "Tell me something I didn't know," if you attended the Hunt Valley, Maryland, meeting of June 28 to June 29, 1990, and had a chance to review the Report of the Task Force on Medical Rehabilitation Research, you would soon recognize that research in medical rehabilitation has come a great distance since then, and you would see that the Center has been the locomotion both pulling and pushing the field ahead.

The Incidence and Impact of Disability

While disability is not a new health issue, its incidence and general impact have increased. Every day, expectant couples agonize over the small but real possibility that their newborn will have a birth defect. Older adults are aware that vulnerability to activity-limiting conditions increases with age. Drivers of motor vehicles, workers in hazardous occupations, and residents of crime-ridden areas accept, or have little choice but to accept, an elevated injury risk that can result in lifelong physical or mental impairment.

Though often difficult to grasp in the abstract, these and other risks have a very concrete manifestation—the estimated 50 million people, or one in five Americans, who have a physical or mental disability.[13] It is no exaggeration to say that most people will experience disability, either directly or in a family member or close friend.

For example, I had no idea that I would spend the past 11 years of my life supporting and caring for my mother who had a stroke in 2000, a deep right hemorrhagic bleed, which left her paralyzed on the left side. There is a large amount of both emotion and strength associated with my story as with so many others, but the complete story—with its various components from speech to physical therapy, to grief management, to issues of mobility and accessibility—speaks to the total value of medical rehabilitation and its contributions to improving the quality of life for patients and their families.

Thus, the widespread nature of disability and the ubiquity of its risk factors are testimony to a need for a continuing and evolving scientific and social understanding of disability, and indeed, filling this need has been a major contribution of the NCMRR.

Contributions of the NCMRR

The NCMRR has increased the visibility of the field and helped to establish the field as a competitive and rigorous discipline for the study of disabilities in children and adults who have different abilities, or as those in the intellectual and developmental disabilities field would like to say, "differabilities."

I came to appreciate the importance of the Center long before I became the Deputy Director of the NICHD or the Acting Director of the Center, but in the mid-1980s when I was a health scientist administrator and Deputy Director of the Biophysics and Physiological Sciences Program of the National

[13] Centers for Disease Control and Prevention. (2011, December). Disability and Health. Retrieved on November 12, 2012, from http://www.cdc.gov/ncbddd/disabilityandhealth/data.html.

Institute of General Medical Sciences. In this role, I managed the trauma and burn injury portfolio, another congressionally mandated program and one in dire need of a focal point at the NIH. This field required a central, facilitating, and coordinating trans-NIH entity to focus on setting a research agenda around traumatic injury. This entity would also be responsible for making the goals of the *Injury in America Report* a reality by following through on the report's recommendation that there be strategic planning and coordination of injury research across the agency. The creation of the NCMRR and the associated Medical Rehabilitation Coordinating Committee served as a response to the *Injury in America Call to Action.*

When Michael Weinrich, M.D., Director of the NCMRR, was interviewed several months ago for the Center's newsletter and asked his views on the NCMRR and its establishment, he remarked, "The NCMRR has not only solidified medical rehabilitation as a scientifically robust and innovative field, but has also helped to advance the understanding and management of various physical disabilities and conditions throughout the lifespan." I would add to those remarks and say that the NCMRR has raised the visibility of physical disability as a health condition and has promoted and enhanced participation of persons with disabilities in society.

The aim of medical rehabilitation research is to promote recovery, adaptation, and functioning for patients with disabilities resulting from stroke, spinal cord injury or brain injury, developmental or degenerative disorders, or other persistent physical conditions.

This goal has been realized by the work of the Center as its areas of research have extended across the entire spectrum, from basic to clinical, and involved many disciplines and professionals: physical therapists, social workers, speech therapists, surgeons, neurologists, engineers, and many others, a true multidisciplinary team.

Innovations in Assisted Devices

The seven areas that the NCMRR uses to guide its research and research priorities have each had a role in advancing the lives of those living with disabilities (and so have the NCMRR staff). And these advances have ranged from the proverbial basic sciences, where a major emphasis has been on plasticity and adaptation. Understanding these two critical components of rehabilitation allows for developing more effective rehabilitation interventions, and we must understand how individuals adapt to particular disabilities in order for researchers to design effective devices and achieve a better perspective of the necessary community support systems that would hasten recovery.

There have been great achievements in improved wheelchair design through the application of basic engineering principles, coupled with the individual's needs and preferences. These principles have also governed the development of many other assistive devices.

For example, when we review the accomplishments that were made possible through NCMRR-supported research, there are the many improved prosthetic devices such as RUPERT. I know the name "Rupert" may bring many with that name to mind, but most of us in this audience know that I am speaking of R-U-P-E-R-T, Robotic Upper Extremity Repetitive Therapy, a portable robotic device that helps stroke patients retrain their muscles to perform basic tasks such as picking up a cup. As the patient's abilities improve, the robot's computer adjusts its assistance. RUPERT offers multiple degrees of arm movement for the shoulder, elbow, and wrist. Studies show that RUPERT is low cost, safe, and easy to use at home or in the clinic.

Clinical Trials

Then there is the work that the Center has supported in the clinical trials arena, including observational studies, pilot trials, and, of course, the gold standard—the randomized clinical trial. Here we think of EXCITE (Extremity Constraint-Induced Therapy Evaluation) trial, SCILT (Spinal Cord Injury Locomotor Trial), LEAPS (Locomotor Experience Applied Post-Stroke) trial, and CRISIS (Critical Illness Stress-Induced Immune Suppression) trial.

Software Tools

With names like BrainGate2™, HIT (Head Impact Telemetry) system, and Trailware[2.0], these software tools can store and analyze data on trial characteristics (such as grade, cross slopes, surface, and width) and create a report on the queried characteristics. They allow trails to be maintained and can assist in proper signage so that those who are in wheelchairs or have other assisted devices, even canes, can plan their trail travel appropriately. There is StepWatch™ (an activity monitor that provides a reliable means for obtaining data of a person's physical function in many areas of the medical rehabilitation field, also in health maintenance, behavioral research, and private practice); and then there is MagicWheels®, which I will mention a bit more about in a minute. I declare, the NCMRR has some of the most interesting acronyms and trade names found within the NICHD portfolio. But all jokes aside, these studies have meant more to the various publics than numerous publications in some of the best journals and impressive media coverage on the top-rated news magazine programs such as "60 Minutes" and others. These studies have changed people's lives.

The Two-Geared Wheelchair

I want you to meet Mary F., or perhaps I should say Mary and her sister, from Seattle, Washington. Mary is 58 years old, and she was diagnosed with spinal cord injury, T10, suffered as a pedestrian in a vehicle accident. You can imagine her clinical problems, but suffice it to say, she has back pain and immobility; she has neck and spinal fusion and a rod in her spine. Until 2008, Mary had used a manual wheelchair, with conventional wheels installed, to attempt to integrate into society with the help of her sister, who gave her transfer assistance and pushed her up hills when needed. In her testimonial, Mary talked about the severe shoulder pain she experienced and the feelings of dependency that she felt when it came to going up ramps and inclines, as she had been dependent on her sister since the accident. The research supported by the NCMRR to develop MagicWheels® has changed her life. MagicWheels® are wheelchair wheels with a geared hub that provides a 2-to-1 mechanical advantage and automatic "hill holder."

With Mary's new wheels, she now has minimal stress to her arms and shoulders, and she gets in and out of her van by herself. She loves her independence. She can negotiate the hills, the steep hills in Seattle, and the hill holder allows her to take a cell phone call. She can also encounter cobblestone streets. She had always loved to travel, and now she does so frequently.

When we talk about the NCMRR, we also know that a focus has been to study the need for rehabilitation following or with secondary conditions, such as obesity, pressure ulcers, bladder-bowel disorders, pain, and neurological disorders and diseases such as multiple sclerosis and cerebral palsy, to name some.

Robotic Therapy

Now I want you to meet Jenna, or let me say Jenna Culleeney and her mom. Cerebral palsy affects about 10,000 babies every year. More than 750,000 kids and adults in the United States are living with cerebral palsy.[14] Many kids have to rely on a wheelchair or walker to get around. Jenna was born 16 weeks early and weighed a pound and a half; she experienced a bleed in her brain at birth, which caused cerebral palsy. Her mother speaks about this in a strong testimony. She had surgery to break and reset her legs (several times, in fact), but Jenna still struggled to walk.

Thanks to research supported by the NCMRR and the investigators of the R24 infrastructure centers program, new robotic therapy is helping children with cerebral palsy walk. Mrs. Culleeney talks about this larger-than-life robot that the Shriners Hospital for Children in Chicago has, which has helped to improve Jenna's balance and gait and teach her the right way to walk. The legs of the robot are specially designed for children. Traditionally, two therapists would have to hold onto the child's legs on a treadmill, manually placing the feet in position. This allows for consistent movement in the child's legs and with lots of repetition, not something that two therapists could keep up with.

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[14] National Institute of Neurological Disorders and Stroke. (2012). Cerebral Palsy: Hope through Research. Retrieved on November 12, 2012, from http://www.ninds.nih.gov/disorders/cerebral_palsy/detail_cerebral_palsy.htm#211493104.

The machine allows children to consistently repeat the motion, strengthening muscles and increasing endurance. This technology was first used in adults with spinal cord injury, but through NICHD co-funding, this approach has been adapted for kids. After 6 months on the machine, Jenna was able to get more confidence in her own feet, and said, "My walking isn't going to be as good as other kids, but I'm doing very good."

When we think of the physical therapists who worked with Jenna, and the many other health professionals, we must also remember the training support that the NCMRR has provided to the medical rehabilitation field, through the K12 Career Development Awards program, fellowships, the Presidential Early Career Awards for Scientists and Engineers Program, and other research mechanisms.

Many of this symposium's speakers point to the significant accomplishments of the NCMRR over the last 20 years, notwithstanding, of course, that there is much still to be done. However, we end up with a positive gain, and I haven't mentioned the stem cell research, the bone density studies, and the wound healing and tissue regeneration investigations. But I have mentioned or described over 20 accomplishments and stories of discovery, and they translate to an average of over one a year, since the Center was established. I believe the NCMRR has been a worthwhile investment of taxpayers' dollars.

The research supported by the NCMRR has become visible because it has changed people's lives—the patients, their families—and has shaped the landscape of our society in general. This research has served to assist in integrating people with disabilities into the community, from the very young to the very old. Whether it is to improve the extra 5 years of a 75- or 80-year-old who has had a stroke or to give the 4-year-old with cerebral palsy a whole life, the NCMRR has given life to years.

Chapter 4: The National Advisory Board on Medical Rehabilitation Research (NABMRR)

Dr. Ralph M. Nitkin, Deputy Director of the NCMRR and Executive Director of the NABMRR, addresses the important role of the NABMRR as a nongovernmental group of experts whose purpose is to advise the NCMRR, the Director of the NICHD, and the Director of the NIH about issues of policy, mission, and short-term and long-term plans for rehabilitation research supported by the NCMRR. The NABMRR has attracted the "best and the brightest" national scholars, scientists, and researchers to advise and counsel NCMRR professional staff and leadership in the NICHD and the NIH.

The NABMRR: A Brief History of the Board and Its Interaction with NCMRR Staff

Ralph M. Nitkin, Ph.D.

Deputy Director, NCMRR

Public Law 101-613 established the formation of the NCMRR in 1990 and placed it within the NICHD. According to this legislation, the Center was charged with fostering the development of scientific knowledge needed to enhance the health, productivity, independence, and quality of life of persons with disabilities. The legislation also established the formation of a NABMRR to review and access federal research priorities, activities, and findings regarding medical rehabilitation research and to make recommendations to the director of the NCMRR and the director of the NICHD. The Board was also charged with identifying current rehabilitation research activities across the government, opportunities and needs for additional research, and recommendations for the coordination research activities.

The Board in Early Years

Although each Institute of the NIH has its own advisory council, the formation of an advisory board for a Center or Division with an NIH Institute is a little unusual, perhaps foreshadowing the intended growth of this newly formed research enterprise. Nonetheless, the NABMRR provided the NCMRR with a unique opportunity to interact with the research community and the larger advocacy community to keep the Center focused on the needs of people with disabilities and to reflect research findings back into the larger community.

According to the charter, the Board was to consist of 18 members from outside the federal government as well as 16 *ex officio* members from other relevant NIH Institutes and government agencies. The 18 charter members were to include representatives of health and scientific disciplines as well as individuals with disabilities and other rehabilitation advocates. Board members serve overlapping 4-year terms, and over the years this has included an impressive array of prominent researchers, clinicians, and disability advocates. Rehabilitation is a broad, interactive, multidisciplinary field, which includes basic neuroscientists and physiologists, rehabilitation clinicians, bioengineers, behavioral and psychosocial researchers, and health care advocates.

In the early years, the Board had a somewhat contentious but nonetheless productive interaction with the Center as the advocates came to grips with the fact that the NCMRR (and the NIH in general) was very good at biomedical *research*, but had a more limited role in the broader advocacy for health care support, improved access, and re-integration for people with disabilities and their families. The Board helped the NCMRR push the NIH to go beyond the traditional bounds of molecular and pathophysiological studies to consider the individual, as the focus expanded from pathophysiology to impairment, function, disability, and participation.

Board discussions helped NCMRR staff to identify key research needs and opportunities and to refine staff-proposed research initiatives. The Board actually initiated the idea for the formation of rehabilitation research networks to provide individual researchers with access to key research methodologies and collaborations that might be beyond their local reach. The Board also provided support for NCMRR training and career development initiatives to support rehabilitation clinicians going into research careers as well as attracting researchers from allied fields to pursue rehabilitation research issues.

The Board's Role in Promoting Research

Research initiatives from those early years included chronic pain, women with disabilities, health promotion, musculoskeletal issues, and prosthetics and orthotics. Later workshops and NCMRR research initiatives focused on building infrastructure: clinical trial design, career development networks, modeling of movement, and patient-centered outcomes. More recently, the Board has worked with the NCMRR to promote research on critical care and pediatric rehabilitation, advanced prosthetic design, neuroplasticity and stroke recovery, role of genomic factors, and multidrug combinational therapies for brain injury.

Advisory board meetings continue to be highly interactive and draw a decent number of other interested parties throughout the NIH, other government agencies, and other rehabilitation-related organizations—a subtle testament to the utility and quality of the discussions. And the NCMRR sees this as a two-way street: the Board members have the responsibility of promoting NIH research activities back in their respective academic, professional, and personal communities.

The NCMRR looks forward to continued constructive interaction with the NABMRR. Recently, the director of the NIH empowered a blue ribbon panel to evaluate the progress of the NCMRR, the scope of rehabilitation within the NICHD, and the coordination of rehabilitation research activities across the NIH. The Board will have a central role in helping the NCMRR respond to the blue ribbon panel report and operationalize its research recommendations. Further background on the Board, including minutes of past meetings and the current roster of Board members, can be found on the NICHD website at http://www.nichd.nih.gov/about/advisory/nabmrr/Pages/index.aspx.

Chapter 5: Symposium Presentations

Prior chapters were devoted to historical developments in the creation of the NCMRR, a review of its valuable record of accomplishments to date, and additional comments about its future contributions to the health and quality of life of all people with disabilities through outstanding rehabilitation research. A number of researchers and research programs supported by the NCMRR are conducting cutting-edge research to improve the lives of children and adults with disabilities. From this cadre of NCMRR-supported researchers, seven were selected to discuss their current research projects and their recommendations about needed future research at the symposium. These presentations represent a look at the future of rehabilitation research supported by the NCMRR.

Research Conducted by the NCMRR-DC Core Molecular and Functional Outcome Measures in Rehabilitation Medicine

Eric P. Hoffman, Ph.D.

Director, Research Center for Genetic Medicine, Children's National Medical Center Washington, D.C.

It is a great pleasure to represent the Children's National Medical Center Medical Rehabilitation Research Infrastructure Network (MRRIN) here in Washington, D.C., and to help celebrate the great accomplishments of the NCMRR on its anniversary.

I would also like to thank Ralph Nitkin, the Deputy Director of the NCMRR. I have had the great privilege of working with Ralph for many years, and we also share a research interest in the neuromuscular junction—the origin of quite a few disabling conditions.

The Role of the Children's National Medical Center MRRIN

As one of the NIH review officers mentioned to me in passing, "So you are the molecular guy!" Yes, our MRRIN Center in D.C., focuses on the fundamental origins of disability and rehabilitation—the molecular players in muscle and nerve. In that sense, we represent the "smallest folk" of the MRRIN network—helping medical rehabilitation research laboratories worldwide understand the molecular building blocks of health and disease.

In this slide, I briefly illustrate what our Center does (Figure 1). Studying the molecular players in health and disease is often given the moniker of "-omics," and we provide all sorts of -omics services: genomics, proteomics, epigenomics, all as applied to medical rehabilitation research. Since our initial support from the NCMRR in 2006, we have helped hundreds of laboratories nationally and internationally. We provide highly specialized expertise, equipment, and services on DNA, RNA, proteins, and functional outcome measures.

Our Center functions with a two-tiered system for providing assistance. The first tier is a fee-for-service model, where we provide access to expensive and specialized equipment to anyone doing medical rehabilitation research. For example, we are helping the military test thousands of basic training recruits, helping them understand who is experiencing muscle damage and the consequences of rehabilitation. In the first tier, anybody (in the United States and abroad) who wishes to carry out a rehabilitation project can ask for assistance with experimental design, bioinformatics, and generating data at our D.C. site. We request only that our Center be reimbursed for consumables (supplies), while all expertise, personnel time, and equipment is provided at no cost to the remote investigator.

The second tier is more restrictive and selective. For the few tier two projects each year, the NIH and our staff agree that these are particularly "high-impact" projects for medical rehabilitation research. With this special designation, we provide support for the project itself, inclusive of costs of consumables. Together with NIH Program Officers Dr. Ralph Nitkin and Dr. Naomi Kleitman, we enable these promising high-impact projects to obtain enough preliminary data to spin off to larger funded studies. To date, applicants applying for the tier two funding have shown a 25-percent success rate.

Presentation Overview

For the remainder of my presentation, I've selected two biomarker studies and a therapeutics development study as exemplars supported by our center (Figure 2). I was going to go over each one of the 100 or 200 projects in detail, but Ralph told me that wasn't permitted at this venue. The two biomarker projects include one on muscular dystrophy and one on spinal cord injury. The muscular dystrophy project was generated by a 24-site international clinical trial organization, spun off from the rehab support early in its evolution. The second biomarker project involves metagenomics (urinary microbiome) and was initiated by the National Rehabilitation Hospital (NRH) in downtown Washington, D.C.

Figure 1.

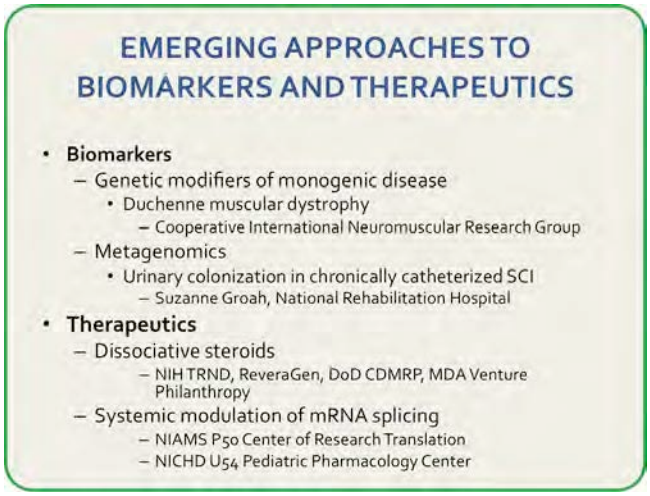


Figure 2.

After these biomarker projects, I'll describe an experimental therapeutics project on systemic modulation of RNA splicing. A clear goal of rehabilitation medicine is to prevent disabilities or to improve the quality of life of patients with disabilities, and certainly therapeutics is part of that. Dr. Guttmacher mentioned this project in his introductory remarks. I'll show a few slides on this therapeutics project and briefly describe two recent large NIH grants that were funded based on the preliminary data generated by the NCMRR.

Two of the topics I'll talk about focus on Duchenne muscular dystrophy (DMD) (Figure 3). DMD is the most common single-gene disorder, and many of us here are familiar with this disease.

Briefly, the disease is X-linked recessive, affects mostly males, involves both skeletal and cardiac tissues, and shows progressive weakness. Affected boys are largely asymptomatic in early years, but then begin to show onset of proximal muscle weakness at about 4 or 5 years of age (Figure 4).

It is possible to identify all DMD boys from birth using neonatal screening. However, screening is not currently adopted by state screening programs due to lack of therapeutic approaches for DMD patients.

Genetic Modifiers

The first project I'll speak about is a "genetic modifier" screen in DMD. While all DMD patients share the same primary biochemical defect (dystrophin deficiency secondary to mutations in the dystrophin gene), patients show variability in disease onset and progression. This variability is thought to be caused, at least in part, by "genetic modifiers." These are polymorphisms in genes (distinct from the dystrophin gene) that modulate disease expression. Much as genetic polymorphisms between us in this room modify our appearance, blood pressure, and other traits, some of these same polymorphisms may influence disease progression in DMD.

To identify genetic modifiers, it is necessary to have access to a large series of well-characterized DMD patients that can be studied. In our case, this involved 24 clinical recruitment sites distributed worldwide (Figure 5). Each site adopted the same standardized protocol for patient recruitment and phenotyping. The clinical network carrying out this study is the Cooperative International Neuromuscular Research Group (CINRG, pronounced "synergy"). CINRG is headquartered in Children's Hospital downtown, and I currently serve as the Scientific Director.

The CINRG is carrying out a 450 DMD patient longitudinal natural history study, where each patient is seen annually for 8 years. In the genetic modifier study presented here, we studied the initial 300 subjects that had been followed for 2 or more years. Craig McDonald of University of California, Davis, is the study chair, and the study obtains a large series of functional outcome measures, including strength, mobility relative to peers, pulmonary measures, and others.

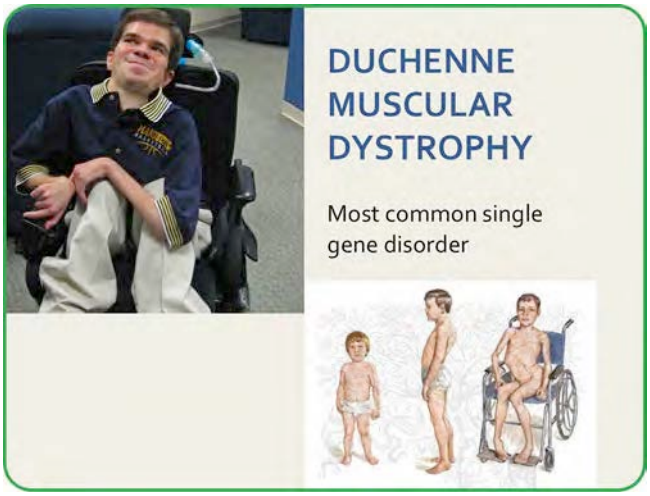


Figure 3.

Figure 4.

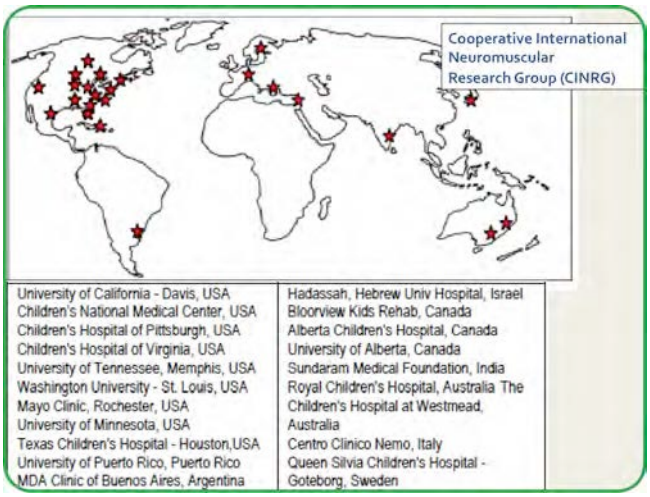


Figure 5.

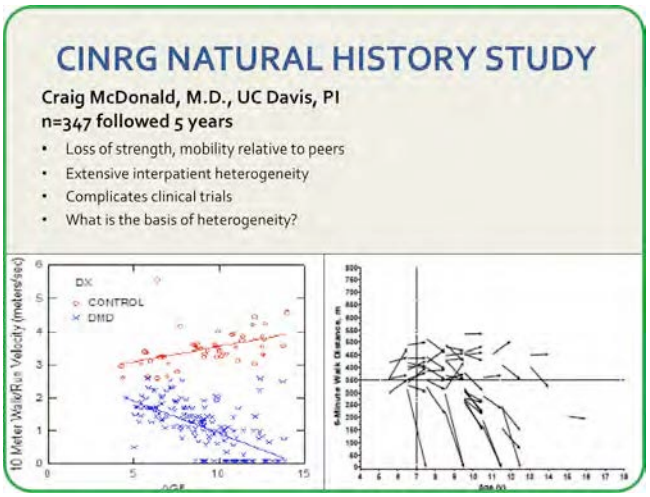


Figure 6.

In this slide, we see the 10-meter walk velocity in normal kids going from 5 to 15 years, with the expected increase in velocity as a function of age (Figure 6). In contrast, Duchenne muscular dystrophy kids show a steady decline in velocity over this same age range, leading to loss of ambulation by about 15 to 20 years. Importantly, observe the interpatient variability in the functional decline of the DMD patients; some kids decline rapidly, while some improve in speed. This heterogeneity complicates the conduct of a clinical trial, as it is challenging to power a trial appropriately with a "reasonable" number of DMD boys given such interpatient variability.

So what we started looking at was genetic modifiers. The goal is to find those key single-nucleotide polymorphisms (SNPs) that modulate severity. Once identified, it should be possible to build those into clinical trial design, functionally reducing interpatient heterogeneity by statistically modeling the known effects of genetic modifiers. This would provide a statistical mechanism for explaining clinical heterogeneity and controlling for this.

Here, we present data on the first validated genetic modifier of Duchenne muscular dystrophy. This work was a collaboration among the CINRG group and its natural history study, and a second natural history cohort followed by Elena Pegoraro in Padua, Italy (Figure 7). Elena and I utilized two different approaches to identify candidate genetic modifiers. My group studied previously characterized SNPs in muscle traits and metabolic syndrome in normal volunteers, whereas Dr. Pegoraro studied muscle biopsies from Duchenne muscular dystrophy patients that were outliers from the expected clinical course (particularly mild progression vs. particularly severe progression). We used a test cohort and validation cohort design, where Dr. Pegoraro's DMD natural history cohort in Padua could serve as the "test" and our CINRG cohort the "validation" cohort (Figure 8).

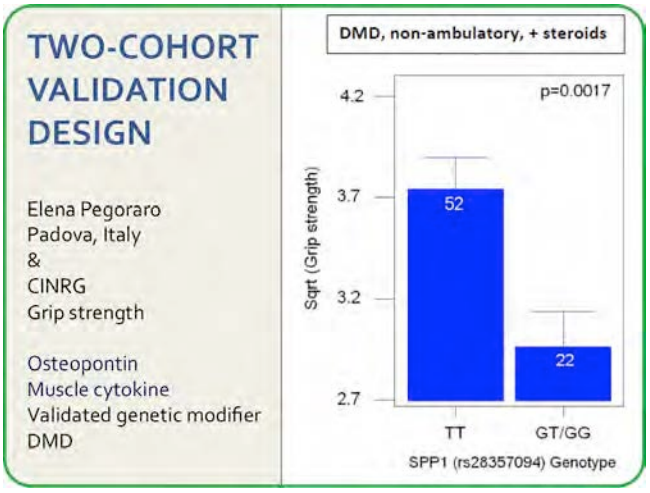


Figure 7.

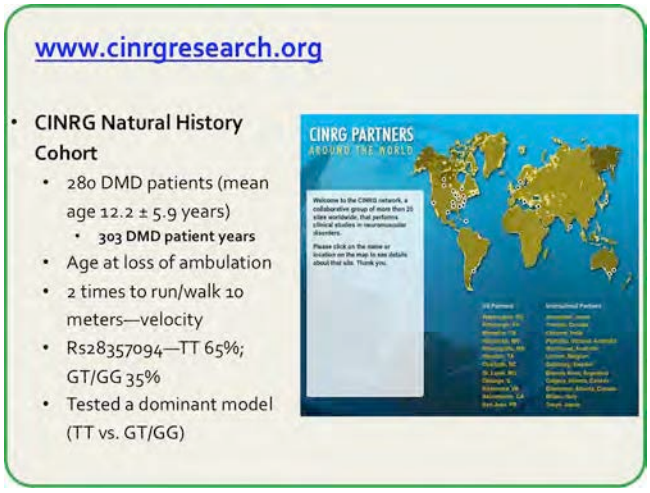


Figure 8.

Our initial study of 29 SNPs found an osteopontin SNP as the strongest validated genetic modifier of DMD. Shown is grip strength stratified by osteopontin genotype in the CINRG cohort (n=156 patients in cross-sectional study). Dr. Pegoraro found correlation of the same SNP with age at loss of ambulation (n=106).

This preliminary study was published about a year ago. In the next slide, I focus on data expanding the CINRG cohort data to 303 patient years of longitudinal data.

Here, we expanded the CINRG natural history data to include age at loss of ambulation, as well as velocity change in walking speed (10-meter timed walk) over 12-month windows (Figure 9). Note that about two-thirds of DMD patients show the common TT genotype, and one-third show the GT/GG genotype. Statistical analyses were done by Dr. Avital Cnaan and Dr. Heather Gordish-Dressman.

In this slide, we are looking at change in velocity over 12-month windows, with patients grouped by the age ranges given on the X axis. The Y axis is normalized to 0 change, so that data points above the red line represent increased walking speeds over the 12-month window, and data points below the red line are decreases in speed (Figure 10). What becomes clear is that the GT/GG genotype DMD patients show improvements in velocity over the 7- to 12-year-old time window. This contrasts to the TT genotype patients, where there is significant deterioration in speed over this same age range.

This slide shows the same data, but now the Y axis shows the velocity at each age, stratified by osteopontin genotype. This shows that the TT do indeed decline more rapidly in the 7- to 10-year-old range shown, but this also shows that this is in part because they started out at age 6 years, considerably faster than the GT/GG genotype DMD patients. In other words, the TT patients start stronger and faster, but then decline more rapidly.

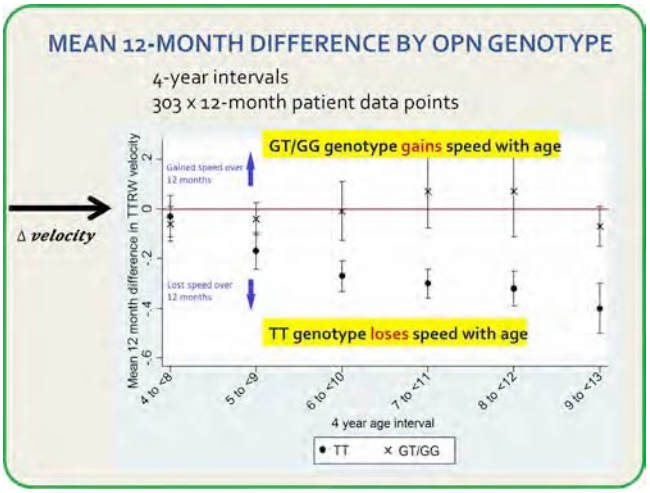


Figure 9.

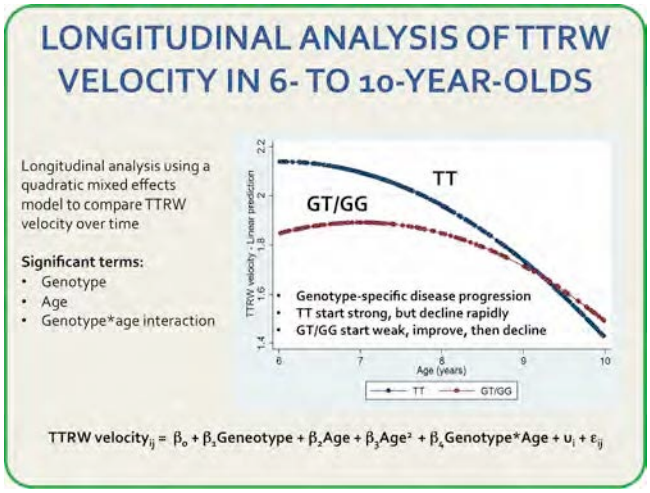


Figure 10.

These data have implications for clinical trials. Most clinical trials in DMD are focused on studying the effect of interventions (drugs) in preventing deterioration of functional outcome measures (timed walk). The stratification of DMD patients into genetic modifier genotype groups shows that this has a dramatic effect on the numbers of patients needed for clinical trials. This slide shows statistical power analyses, determining the number of DMD subjects needed in specific age ranges to see a significant effect of a drug in preventing deterioration of velocity (Figure 11). This shows that trial arm sizes of n=25 is sufficient for the TT genotype, whereas group sizes of nearly 1,000 patients are needed for the GT/GG genotype. This is because the TT genotype patients deteriorate rapidly, making it statistically more robust to see a drug effect.

Employing genetic modifiers in drug development can complicate drug approvals. This effectively stratifies your patient population and could require distinct drug development plans for different genotypes. For rare disorders, the regulatory hurdles may not be so challenging. Indeed, it is possible that drug approvals for one genotype group of a genetic modifier may lead to approval for the other genotypes as well.

We are optimistic that this NCMRR-supported research will facilitate clinical trials in DMD, reducing the numbers of patients required to conduct robust clinical trials.

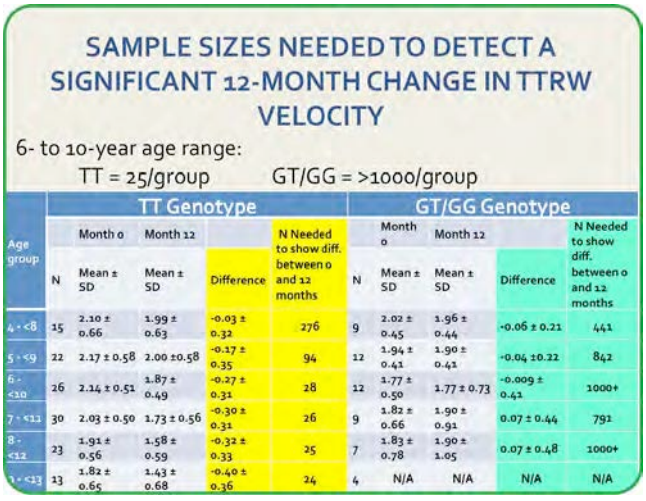
Metagenomics

Here we return to the outline of this presentation, and the second topic: metagenomics (Figure 12). This project is led by Dr. Suzanne Groah at the NRH here in downtown D.C. (next door to Children's Hospital). The goal of this project is to study bacterial colonization of the urinary tract in chronically catheterized spinal cord injury patients.

To provide a bit of a background to this project, the focus is on the microbiome—or the characterization of the types of bacteria—in a clinical sample. We've all grown up to feel that bacteria are generally bad. In infections, the traditional approach is to identify the offending bug by culture, and then hit it with appropriate antibiotics.

Knowledge of the complete population of bacteria that show a symbiotic relationships with all of our epithelial surfaces has begun to change the view to that of "symbiosis." Bacteria and our bodies are in a balance of good and bad, both internally (gut) and externally (skin). We can now identify all subtypes of bugs (not just those that grow in a Petri dish) using sequence analyses. Next-generation sequencing can then provide a window at the balance at any point in time in any biological sample and, hopefully, use that to define individualized balance in health and disease, targeting treatments in the individual and their balance (Figure 13).

Here, we provide a bit of a background on spinal cord injury (SCI) and catheterization (Figure 14). As many of you know, many SCI patients are chronically catheterized; chronic catheterization leads to chronic colonization, with recurrent urinary tract infections. SCI patients have a shortened lifespan, at least in part due to sepsis, and that sepsis likely originates from the urinary colonization.



Age group	TT Genotype					GT/GG Genotype				
		Month 0	Month 12		N Needed to show diff. between 0 and 12 months		Month 0	Month 12		N Needed to show diff. between 0 and 12 months
	N	Mean ± SD	Mean ± SD	Difference		N	Mean ± SD	Mean ± SD	Difference	
4 - <8	15	2.10 ± 0.66	1.99 ± 0.63	-0.03 ± 0.32	276	9	2.02 ± 0.45	1.96 ± 0.44	-0.06 ± 0.21	441
5 - <9	22	2.17 ± 0.58	2.00 ±0.58	-0.17 ± 0.35	94	12	1.94 ± 0.41	1.90 ± 0.41	-0.04 ±0.22	842
6 - <10	26	2.14 ± 0.51	1.87 ± 0.49	-0.27 ± 0.31	28	12	1.77 ± 0.50	1.77 ± 0.73	-0.009 ± 0.41	1000+
7 - <11	30	2.03 ± 0.50	1.73 ± 0.56	-0.30 ± 0.31	26	9	1.82 ± 0.66	1.90 ± 0.91	0.07 ± 0.44	791
8 - <12	23	1.91 ± 0.56	1.58 ± 0.59	-0.32 ± 0.33	25	7	1.83 ± 0.78	1.90 ± 1.05	0.07 ± 0.48	1000+
9 - <13	13	1.82 ± 0.65	1.43 ± 0.68	-0.40 ± 0.36	24	4	N/A	N/A	N/A	N/A

Figure 11.

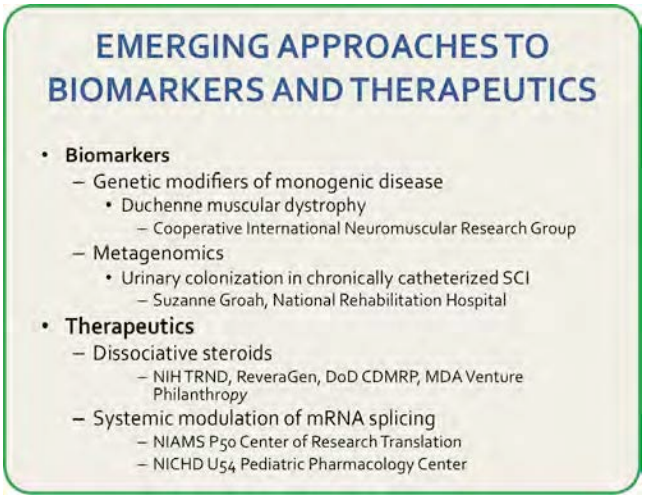


Figure 12.

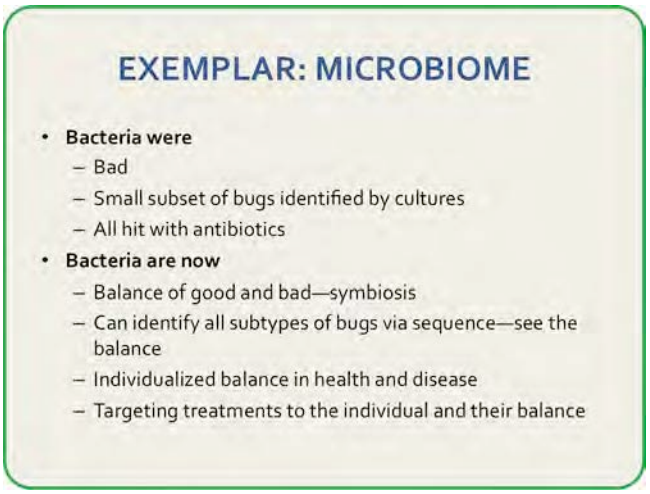


Figure 13.

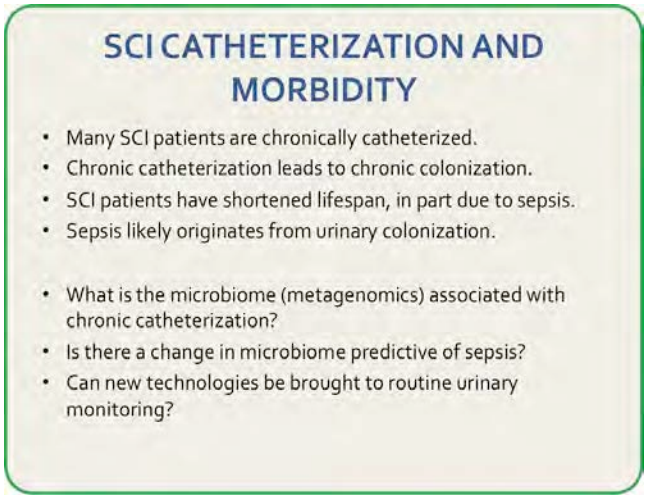


Figure 14.

Dr. Groah approached our NCMRR Center at Children's Hospital with a proposal to look at the urinary microbiome in SCI patients. She wanted to address the question: "Is there a specific microbiome signature associated with catheterization, and is there a change in microbiome predictive of sepsis?" Our NCMRR Center brought new technologies to bear on this project (next-generation sequencing).

Now, Dr. Groah named this project the "GENUSCIS Project" (Figure 15). Now, I think there should be laws against really stretching those names too far. And I think this is over the top, isn't it? I have to talk to her about this. So she is at the NRH, and it's a collaboration with Georgetown University, Children's National Medical Center, and the J. Craig Venter Institute.

Here we show the subject recruitment and study design (Figure 16). This pilot study involved 57 patients seen at NRH, stratified by spinal cord injury and catheter use. Urinalysis and urine culture were done as background, and metagenomics analysis included deep 16S ribosomal RNA sequencing. Amplicon-based sequence generation was done using a 454 Genome Sequencer FLX machine. Data analysis involved about 600,000 RNA sequence reads, with mapping of taxonomy of bacteria in each patient.

Shown here are our preliminary data (Figure 17). If you look at healthy non-SCI, lactobacillus is the predominant type of bacteria there. But if you look at SCI, one sees a completely different pattern, with enterobacteria predominant. These changes are seen in all SCI patients regardless of catheterization status, but the shifts in the catheterized patients are more dramatic.

With this pilot data in hand, we're now looking at longitudinal studies of outcome and developing a rapid and inexpensive test.

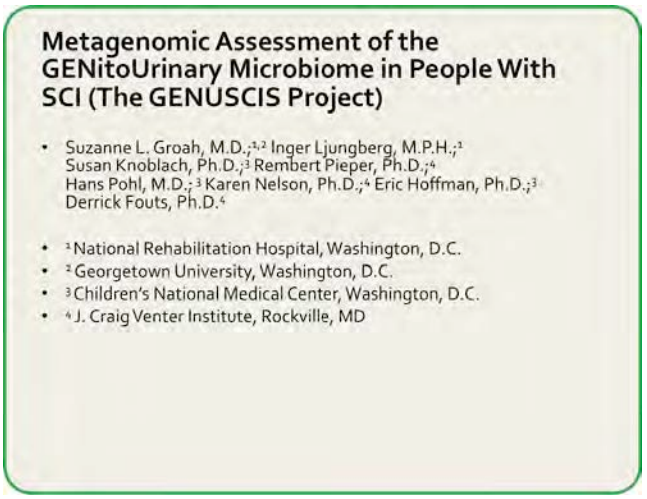


Figure 15.

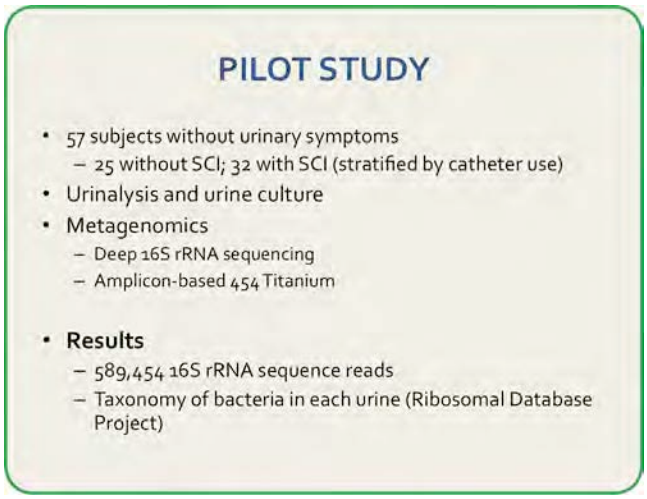


Figure 16.

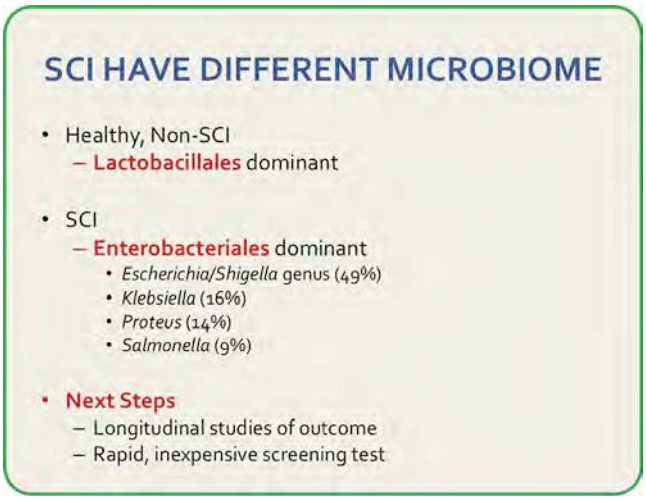


Figure 17.

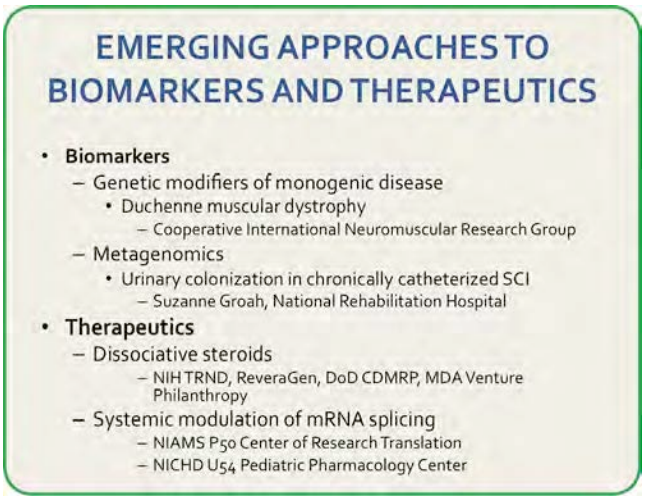


Figure 18.

Systemic Modulation of mRNA Splicing

Now I'll turn to the last rehab project—systemic modulation of mRNA splicing (Figure 18). Dr. Guttmacher mentioned this project in his remarks.

Here we turn back to Duchenne muscular dystrophy. Here we show images of muscle biopsies from a normal patient (normal dystrophin), and a Duchenne muscular dystrophy patient (absent dystrophin) (Figure 19). The goal of this last project is to "bring back" the missing dystrophin. In a way, this is the ultimate goal of "molecular rehab"—to bring back dystrophin where it is missing.

How are we going to accomplish this? In this slide, we show a key piece of background to the approach I'll describe (Figure 20). On the top of this slide, we see a schematic of the dystrophin gene, with its 79 component exons. Below this, each colored line represents a patient that has either deleted or duplicated the corresponding region of the dystrophin gene. You see that some of these deletions and duplications are quite large, covering 30 percent or so of the 79 exons. However, despite showing such large changes, all these patients have Becker muscular dystrophy (BMD), a clinically milder variant of Duchenne muscular dystrophy. Indeed, some of these patients can walk to quite an old age. The key thing is these mutations are still compatible with making some dystrophin protein, as shown in this lower panel of muscle biopsy dystrophin data. Here is normal dystrophin; here is Becker (smaller molecular weight) dystrophin. The Becker patients are able to put together what's left of their gene (in-frame mutation), while the Duchenne patients cannot (out-of-frame mutation).

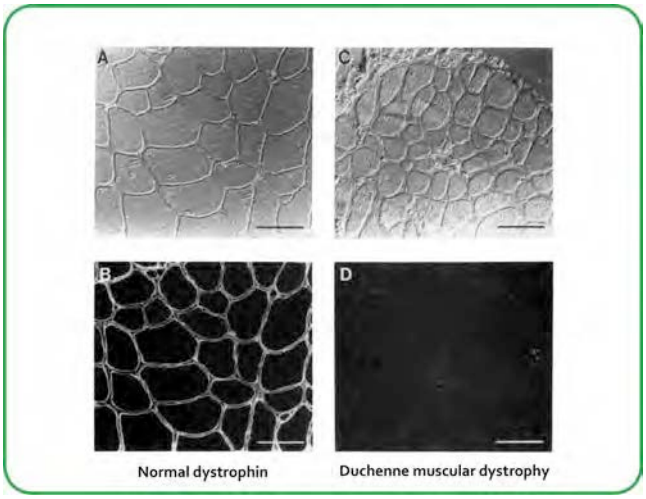


Figure 19.

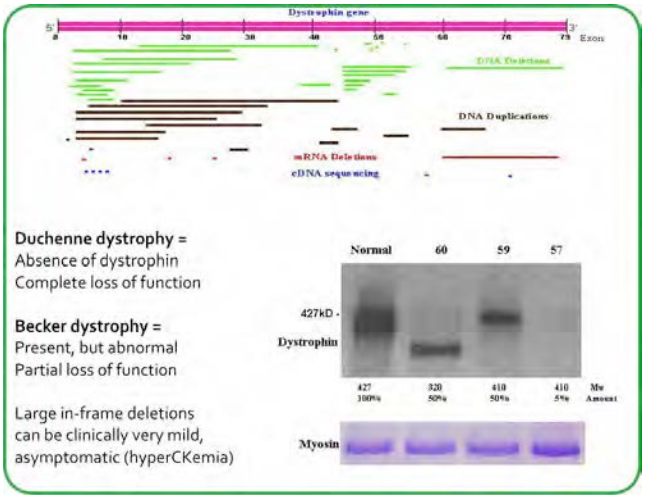


Figure 20.

This is a bit unusual in the protein biochemistry world. Most proteins are unable to retain their function with so much amino acid sequence deletion or duplication. However, dystrophin appears to function like a Tinker Toy™, where you have the center part and the functional ends that you plug together. Deletions or duplications of the center part are still compatible with protein function, as the "connector ends" are still intact. So we can really change the rod domain and still retain function of the protein.

The goal of systemic antisense (exon skipping) is to convert a Duchenne deletion mutation into an in-frame Becker deletion mutation. This involves using designer antisense drugs to remove additional exons to bring the remaining transcript back into frame. So the goal of this project is to turn Duchenne, with missing dystrophin, into Becker, with present but deleted semifunctional dystrophin.

The approach used to accomplish this is called exon skipping, and this is diagrammed schematically in this slide (Figure 21). In the left panel, you see a normal myofiber, with a part of the dystrophin gene diagrammed in the nucleus. The exons in the DNA are transcribed into mRNA, where the reading frames fit together precisely to be translated into dystrophin protein. The dystrophin protein then associates with the plasma membrane and stabilizes it (normal dystrophin function). In the central panel, we see the case of a DMD myofiber.

In this example, the patient has a deletion mutation of exon 50. The patient's gene is transcribed into mRNA, but you see that the exons do not fit precisely together. This creates a frame-shift, and dystrophin protein cannot be made. With no dystrophin made, the plasma membrane becomes unstable, and this initiates the disease process.

In the right panel, we see the goal of exon-skipping therapeutics. Small antisense drugs are designed and delivered so that they get into the nucleus of the myofibers and block exon 51. Exon 51 is now unable to be spliced into the mRNA, so this Duchenne patient is now splicing exon 49 to exon 52.

In this case, the new 49/52 exon/exon junction is in frame and compatible with dystrophin protein production. Semifunctional dystrophin (Becker-like) is produced, associates with the plasma membrane, and rescues muscle function.

So some of you in the audience might be thinking: well, antisense therapeutics has been around for about 20 years, and it has a very troubled history with no drugs actively marketed.

Indeed, this is quite accurate. If you look on http://www.ClinicalTrials.gov there have been 90 clinical trials of antisense therapy. Forty of these have been completed, with more than 2,000 patients treated with various antisense drug approaches, targeting cancer, inflammatory disease, and other indications. Only one drug has been approved and it's off the market, and that was for intraocular injection (Figure 22).

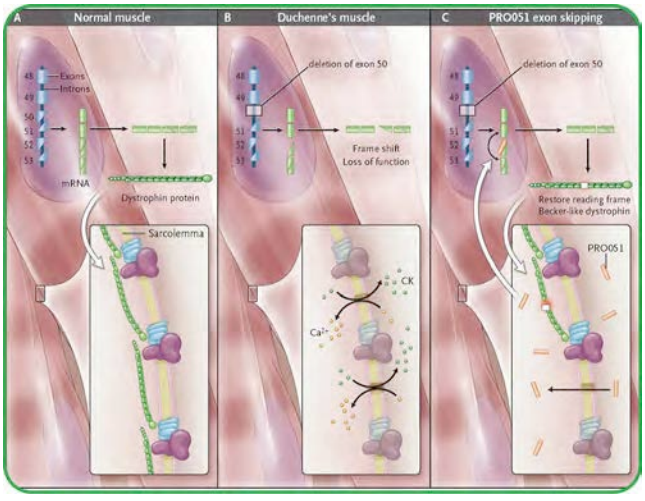


Figure 21.

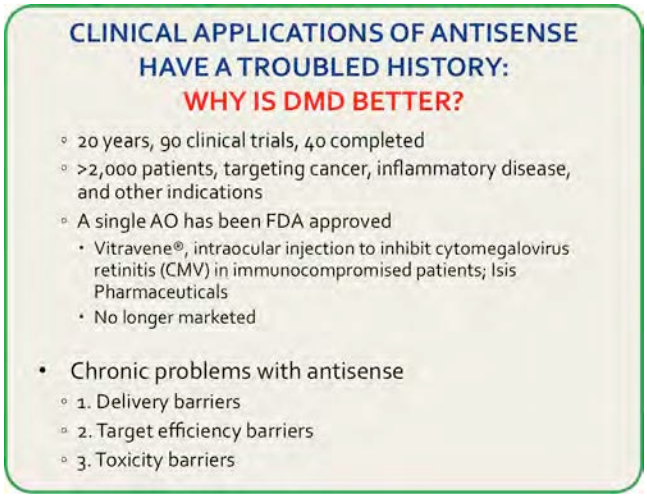


Figure 22.

So why do we think DMD might be a better indication for antisense? The key barriers to development of antisense therapies have been delivery barriers, target efficiency barriers, and toxicity barriers. Regarding delivery, it has been challenging to get antisense drugs across plasma membranes of cells, and at high enough effective concentrations within the target cells. In DMD, we seem to have a disease-specific delivery system: pre-existing holes in the plasma membranes of DMD myofibers.

Remember I showed you the holes in the cell that's part of the pathophysiology of Duchenne dystrophy? You're missing that protein, so the myofibers have overt breaches. We can just leak the drug through there in bulk flow. So all of the other indications had to get the drug across the plasma membrane and that's very hard. So they couldn't achieve efficient concentrations.

A second key issue has been therapeutic window (toxicity barriers) (Figure 23). This is coupled with delivery in many ways. Modifying antisense drug chemistries to make them more effective at delivery often make them more toxic. On the other hand, in DMD, we are relying only on overt breaches (holes) in the myofiber plasma membranes, so we can use uncharged (morpholino) chemistry that is inherently nontoxic.

Here we review some of the different chemistries used for antisense drug development (Figure 24). You'll notice that the morpholino chemistry is very different in structure, with the ribose ring replaced with a morpholino ring. This unique structure prevents metabolism by the body, yet it retains high affinity binding to DNA or RNA.

With the combination of improved delivery in dystrophin-deficient myofibers via unstable plasma membranes, the fact that we are rescuing the target (restoring reading frame) rather than knocking it down, and using more stable and less toxic morpholino chemistry, applications to DMD look more promising than most other indications for antisense to date.

As a proof of principle of the approach of systemic exon skipping to DMD, we turned to the DMD dog model in collaboration with Dr. Shin'ichi Takeda's group in the National Institute of Neuroscience, National Center of Neurology and Psychiatry in Japan. The dog model is a spontaneous mutation of the dystrophin gene causing a splice site change. To skip over this mutation, we required three morpholino antisense drugs delivered simultaneously—to skip two consecutive exons in the pre-RNA. This was delivered at very high doses (120 mg/kg per week, intravenous). The dogs have a progression of disease that is more rapid than human patients, with weakness and significant disability by 6 months.

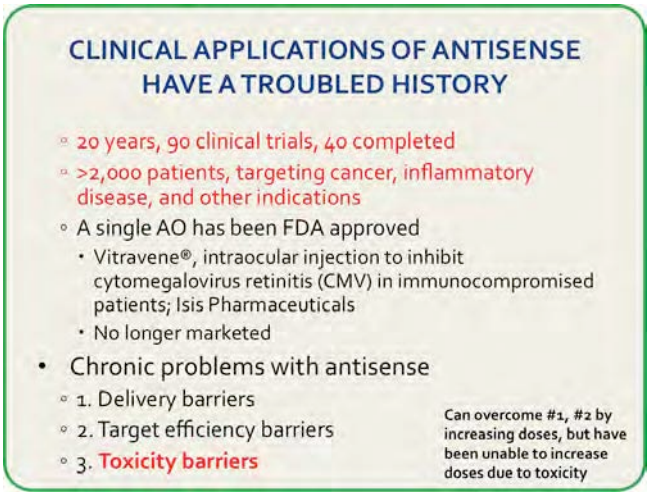


Figure 23.

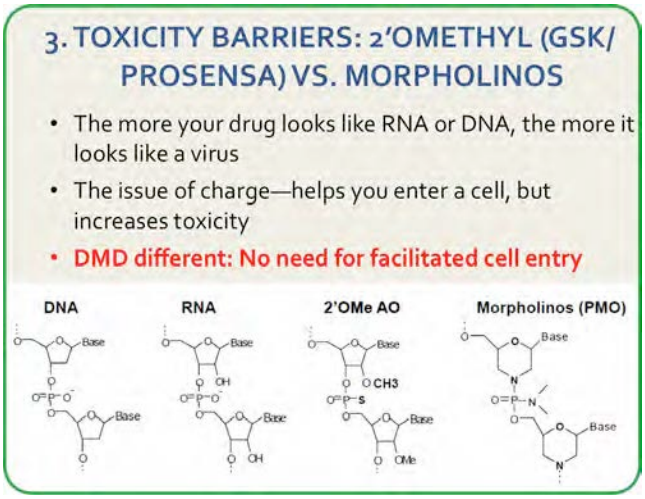


Figure 24.

In these videos, we show two littermates (Figure 25). The littermate on the left was untreated; the one on the right was given 11 weekly intravenous injections of morpholino drugs. As seen in the video, the untreated dog is unable to run and tires easily, while the treated dog is able to run easily. Many other tests of dystrophin protein production, histology, serum laboratory studies, and functional studies all pointed to significant benefit provided by the morpholino treatments.

We feel the dog is an important proof of principle for a number of reasons. First, the disease is considerably more aggressive than seen in human patients, and our ability to mitigate disease in the dog model bodes well for human studies. Second, the dog mutation was particularly difficult to skip by drugs, also suggesting that "easier" skips for human patient mutations may go well.

Finally, we were able to conduct many tests of multiple muscles in the dogs, providing robust support for biochemical and clinical efficacy. Here we show the drug-induced dystrophin production in multiple muscles of one of the treated dogs (Figure 26). Note that the *de novo* dystrophin production varied from muscle to muscle, and was not successful in heart.

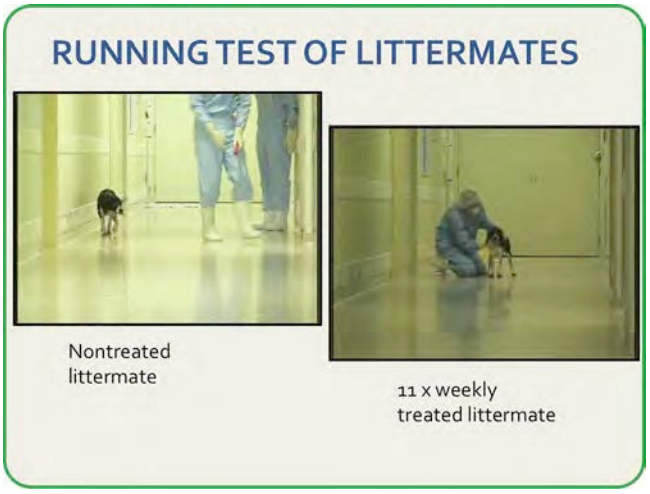


Figure 25.

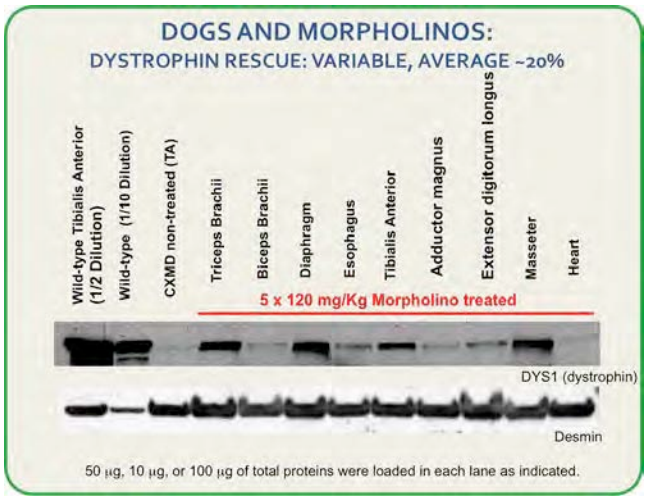


Figure 26.

So where do we stand with exon-skipping drug development, and what's the trajectory? Clinical trials are well under way in both 2'Omethyl (Prosensa and GlaxoSmithKline), and morpholino chemistries (AVI Biopharma). An exon 51-specific 2'Omethyl drug is in pivotal studies, and enrollment should be complete in 2012. An exon 51 morpholino drug has been in dose escalation studies in both England (Francesco Muntoni) and the United States (Jerry Mendell). There are also drug development programs under way for additional exons (Figure 27).

Now, there are challenges and unknowns (Figure 28). First, there are many different exonic targets: the dystrophin gene has 79 exons, and patients have gene mutations distributed throughout all exons. Thus, to treat the majority of DMD patients, many exon-specific drugs need to be developed (Figure 29). Exon skipping in DMD is viewed as one of the first personalized medicine drug development approaches, and this brings regulatory challenges as well as fiscal challenges in drug development. Second, we are not certain of the biochemical functionality of the different Becker-like (internally deleted) dystrophin proteins.

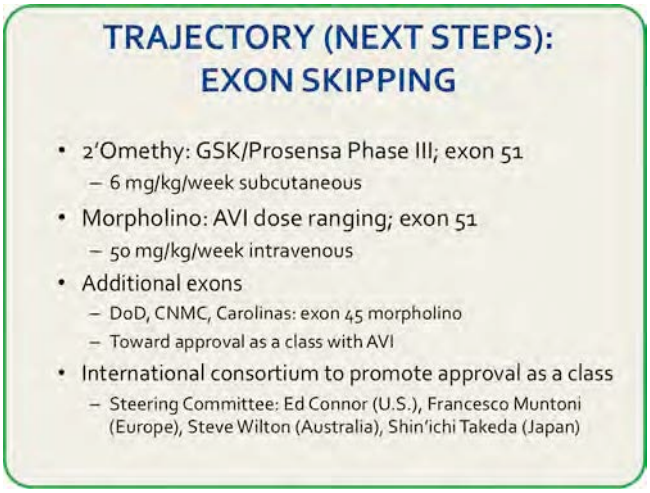
Finally, the doses required are very high: morpholino dosing is about 10 times higher than other antisense oligonucleotide trials. The long-term toxicity of repeated high dose oligonucleotides must be studied carefully.

To help address these questions and concerns, our NCMRR Center was successful in supporting these preliminary studies in exon skipping, and then spinning off two NIH Center grants.

Spinoff Studies

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) recently funded a Center of Research Translation (CORT) to address issues of multiple-exon drug development, functionality of internally deleted dystrophins, and the clinical correlates of specific mutations in Becker dystrophy (natural history trials).

The NICHD has funded a U54 Research in Pediatric Developmental Pharmacology Center at Children's National Medical Center focused on long-term safety of high-dose morpholino delivery and dose optimization (Figure 30).



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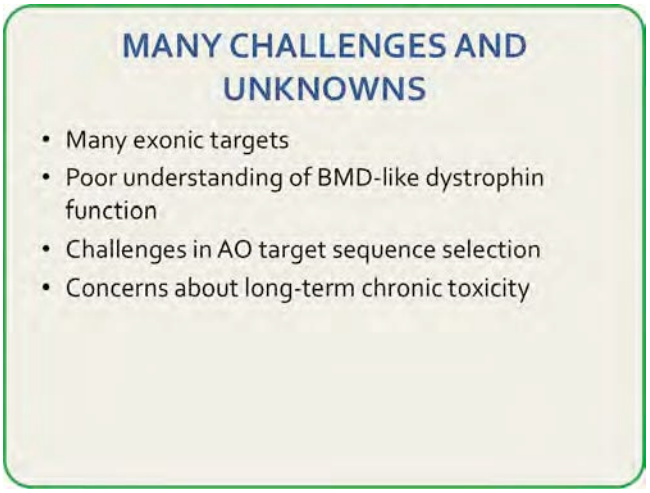

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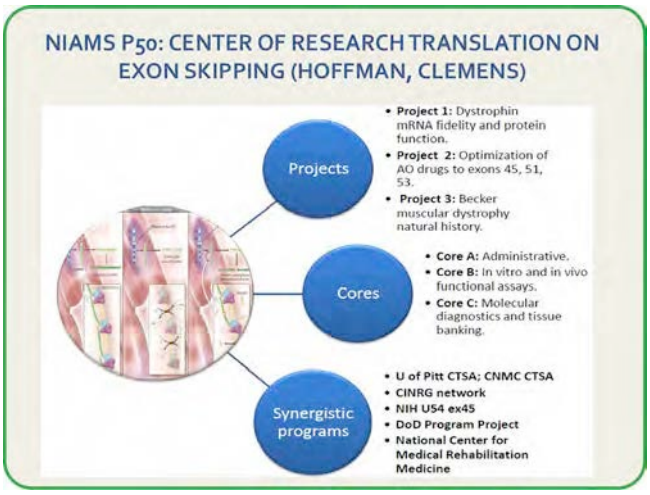


Figure 29.

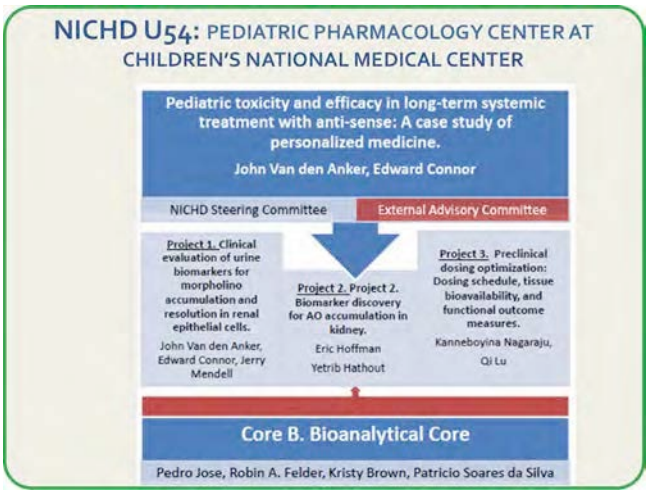


Figure 30.

I'd like to acknowledge the collaborators in the last project, particularly Shin'ichi Takeda in Japan; a T32 scholar, Toshifumi Yokota, did a lot of the dog work; and Terry Partridge. I'd also like to acknowledge Dr. Susan Knoblach at Children's National who helps me run the NCMRR MRRIN Center here in D.C. Finally, I gratefully acknowledge generous research support from the Congressionally Directed Medical Research Programs of the U.S. Department of Defense, the Foundation to Eradicate Duchenne, Crystal Ball – Muscular Dystrophy Association (Richmond), NIAMS U54 Wellstone, NICHD U54 Pediatric Developmental Pharmacology Center, NIAMS P50 CORT, and the Ministry of Health of Japan (Figure 31).

Thank you very much.

Figure 31.

Skeletal Muscle Research in Rehabilitation

Richard L. Lieber, Ph.D., and Samuel R. Ward, P.T., Ph.D.

Vice-Chair, Department of Orthopaedic Surgery, University of California, San Diego, and the Veterans Affairs Medical Center
La Jolla, California

It's a pleasure to be here, and I appreciate being part of this celebration. I do remember the creation of the NCMRR and have considered it a great privilege to be part of it. I'm here representing myself and Sam Ward. We're actually at University of California (UC), San Diego, but I was trained at UC, Davis, and we are going to present several types of patients with whom we interact and for whom muscle is a big deal.

Muscle Physiology

I was trained in muscle physiology. I love to show this picture of muscle as a composite tissue, and you can see here muscle at a variety of scales (Figure 1). And we think of it at a variety of scales because as physiologists and biophysicists, we understand a lot about muscle structure. I know you all learned about it in medical school and graduate school, but clinically, it's very tough to find good clinical correlations between structural changes in muscle and clinically relevant functional changes. That's what we're really interested in, and I'll elaborate on that.

In the background of this graph, you can see muscle sort of as a tissue, a composite. Muscle cells, embedded in connective tissue matrix, interface with the cardiovascular system, interface with the nervous system, interface with the endocrine system, and therefore, muscle health is very tightly associated with human health, which is part of the reason we love it. It's so functionally significant; if the muscles are in good shape, typically the person is in good shape.

The other nice thing about muscles is they have built-in structural markers, yet, here at the microscopic level, we will talk a lot about the sarcomere, sort of the functional unit of contraction of a skeletal muscle—this machine, which has myofilaments that interdigitate with one another and that generate the force in muscle. So we have developed several measuring tools to try to understand muscle structure and its functional correlation.

Just to remind you, skeletal muscle is often called striated muscle because of the striation pattern, and the striation pattern is a reflection of the myosin banding pattern within the skeletal muscle. This happens to be a light micrograph of my favorite muscle fiber, which is a frog muscle fiber, which is really where we learned all of our physiology and which largely applies to humans at the single-cell level (Figure 2).

If we look at one small portion of that fiber, and image the tissue by electromicroscopy, we see the familiar longitudinal micrograph that shows myosin bands in the middle of this tissue of the cell, the actin containing bands on the outside, and the Z band that makes the boundary of the sarcomere (Figure 3).

So the reason it's important to understand sarcomere properties is that because of the specific structure-function relationship between sarcomere length and muscle force production, if we measure sarcomere length in a patient or in an animal model, we can infer function, and that's really exciting for us to be able to do in humans.

Intraoperative Measurements

The first patient population I want to talk to you about is children with cerebral palsy (CP) (Figure 4). This is collaborative work I've done with Ann Nachemson, who was the Chief of Hand Surgery in Gothenburg, Sweden, and my colleague, Jan Fridén, who splits his time between Gothenburg and Neuchatel, Switzerland, as a tetraplegia surgeon. But the interesting thing about these contractures (as you know they are very severe), they can be painful, they're disabling, and the surgical treatment for contracture is literally release of the tendon intraoperatively.

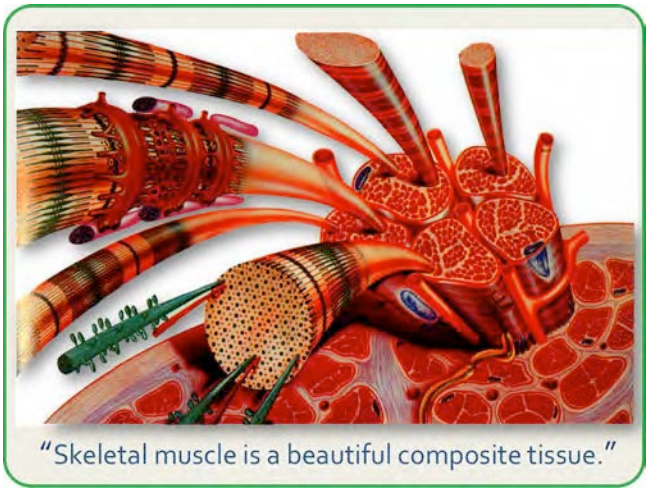
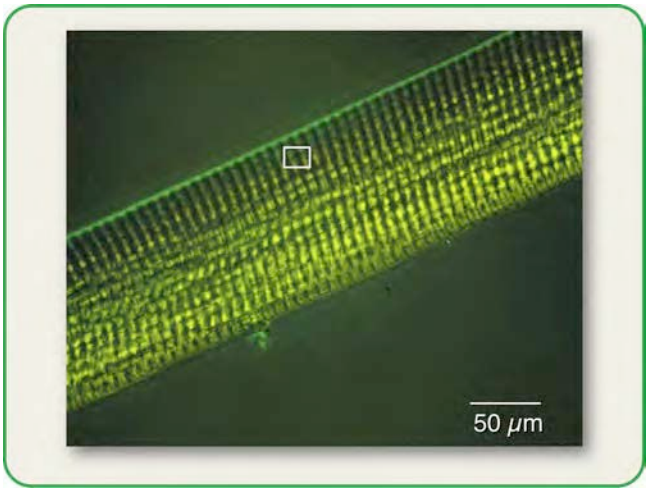


Figure 1.



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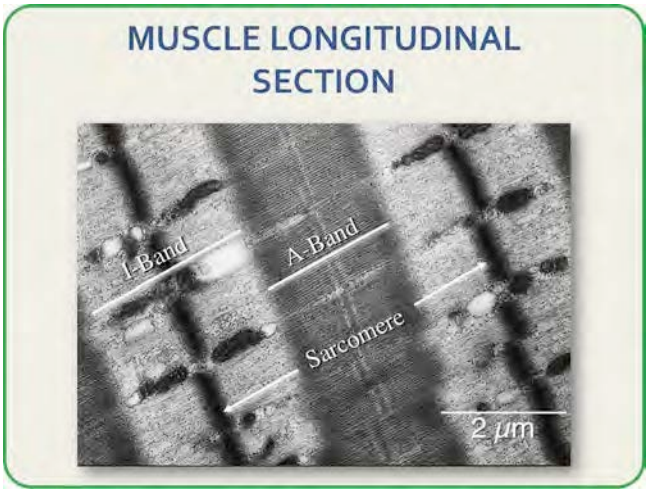


Figure 3.

Figure 4.

It's obvious in the operating room when you release the tendon that the muscle retracts, the muscles are clearly under a lot of tension. We were interested in the structural properties of these muscles, which are stretched tautly but are in a shortened position, especially in children with wrist flexion contractures. Part of the reason this is significant is we just wanted to understand the biology of muscle. But if we're trying to treat the contracture, and ultimately, we'd like to treat them nonsurgically with smart biological tools, we have to understand the structural changes.

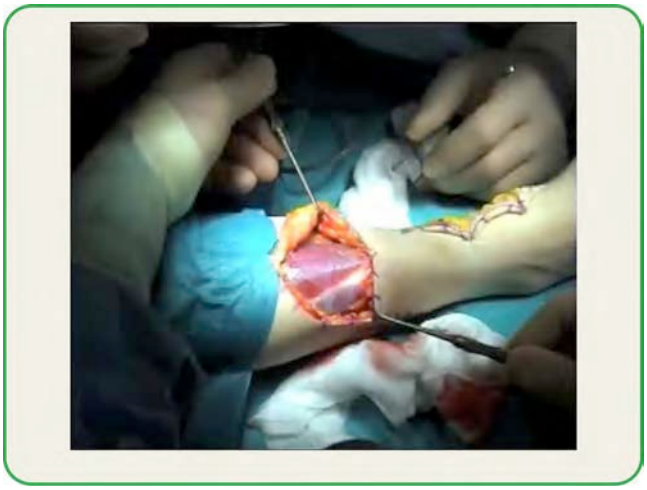


Figure 5.

So we developed a small tool that we can use intraoperatively. Here we're in the operating room already; the muscles are already exposed, and you can see a small bundle of muscle fibers that's being isolated by blunt dissection (Figure 5). This bundle, while it's relatively small, is still hundreds or thousands of muscle fibers, and in appropriate control experiments, these represent very nicely sarcomere lengths throughout the muscle.

Because the structure of the muscle is so regular, if we shine a laser into the muscle, you can see constructive interference between laser light and the microstructure of the muscle. So it's essentially like having the patient on the operating room table under a microscope to be able to look at their sarcomere structure. And I'll show you several applications, but the important point here is you have a window into the microscopic adaptation of the muscle tissue.

When we measured the sarcomere lengths in these kids, the shocking result was that even though the muscles were highly shortened in these wrist flexion contractures, the internal sarcomeres were actually highly stretched. This was actually a pretty small sample size (eight or nine), but you can see in the kids with spastic wrist flexion contractures, sarcomere lengths were about 3.6 µm, which is highly stretched, compared to normal, which is about 2.4 µm (Figure 6).

What that means is with these stretched sarcomeres, first of all, stretched sarcomeres are under a lot of passive tension, hence the significant retraction when you release them in the operating room. And the other thing is at these very long sarcomere lengths, muscles are relatively weak. As you know, one of the byproducts of CP is muscle weakness. So if you put these data into perspective, they would suggest that this kid with the wrist flexion contracture would generate maybe 20 percent of normal muscle forces.

The other thing I want to point out that really struck me because we'd look at sarcomere adaptation in a lot of animal models, is this type of adaptation is completely unprecedented in the animal kingdom. It's well known in animal models that you can chronically stretch or shorten a muscle and it will change its sarcomere number. That's what muscles do.

But what has never been documented in any animal system was shortening a muscle, which is happening here, and the internal sarcomere is actually getting longer. So we have studied the biology of these tissues and think we have some insights into why that muscle is adapting inappropriately. And again, because of the understanding of that adaptation, we think that provides a few therapeutic targets for affecting contractures.

Physiological Tests

We also do a lot of work at the muscle tissue level. So after we make these measurements in the operating room, we'll take a small piece of muscle back to the laboratory, and we can analyze it using physiological or biophysical tools. For example, here is a picture in the left portion of the slide of a single cell, which is attached to a force transducer motor. We can do complete physiological tests—active and passive mechanical tests on the muscle cells from the same human who is having surgery (Figure 7). And again, I like to point this out because we learn a lot from animal models, and my lab uses a lot of animal models, there are some things that I think are just not appropriate for animal studies. I don't think there is a good animal model of contracture, and that means we needed to develop some pretty cool tools to use in people.

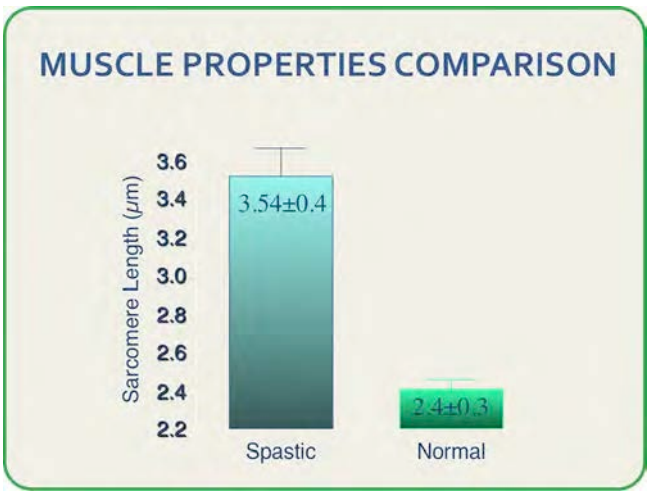


Figure 6.

Figure 7.

In addition to doing single-cell mechanics, we also look at small bundles of muscle fibers. And again, I am happy to send you papers, and we can have good discussions later. One thing we've learned that has again changed our paradigm for understanding human whole muscle function is that muscle fibers don't scale very well to muscle bundles, and muscle bundles don't scale very well to whole humans. This has been a little bit frustrating because a lot of us can measure very high-resolution things at the microscopic level from muscle biopsies. But again, it's very hard to come up with functional correlations.

So I'll just show you one example of that, and that is looking at the mechanical properties of single fibers and comparing that to bundles. And remember, bundles, as shown up here in the upper portion of the slide, are muscle fibers embedded in their connective tissue.

So if I just plot the modulus of the tissue that I'm looking at on the vertical axis and the specimen is either a muscle from a kid with a contracture or a muscle from a typically developing kid, you can see at the cellular level, there is a difference in stiffness, and it's roughly about twofold (left-hand side of slide) (Figure 8). And so, we were really excited about this early on because we know these contractures end up being stiffer, but it turns out the magnitude of the muscle fiber effect is small, at least in these muscles. These were upper extremity wrist flexors, and we don't have the same data for lower extremity muscles. In the lower extremity muscles, at the single cell level, they're about the same. The big difference in all muscles, whether it's upper extremity or lower extremity, tends to be at the muscle fiber bundle level, and the cartoon here shows that these are muscle cells embedded in the connective tissue matrix.

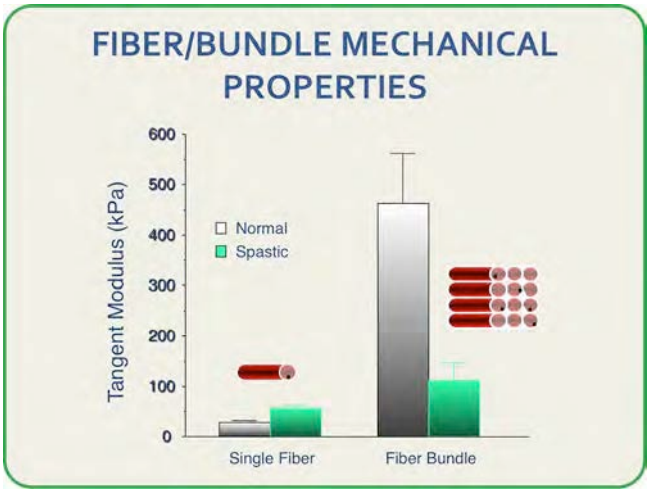
Extracellular Matrix Studies

So muscle bundles are always stiffer than muscle cells, and what that means is the extracellular matrix material is stiffer than the fibers themselves, and therefore, muscle is a true composite, sort of compliant muscle fibers in a stiffer extracellular matrix. What's really interesting when you quantify the magnitude of the difference and you have to do this knowing how much of the different tissues there are, it turns out that the extracellular matrix (ECM) in typically developing children or normal patients, is extremely stiff compared to the muscle fibers; whereas the matrix in kids with CP is only marginally stiffer (right-hand side of slide). It's sort of like in the normal muscle, you've got fairly compliant muscle in a stiff extracellular matrix with some very clever molecular connections between the two, and in kids with CP, that ECM is either deteriorated or it's responded to changes in stiffness of the muscle cell, or we don't know. But we do know it is more compliant.

Not only is it more compliant, there is more of it. So if this happens to be one stain of many we could use, this happens to be a laminen stain, which is an extracellular glue in the matrix. On the left side of the panel, E and G are normal tissue from typically developing kids (Figure 9). This is work that's done in collaboration with Hank Chambers who is a pediatric orthopedist in San Diego. The cool thing about working with Hank is he does a lot of anterior cruciate ligament reconstruction on teenagers, so we can sort of age-match maybe young teenagers with older kids who have CP and try to get rid of some of that age effect in this experiment.

On the top is the cross-section, on the bottom is a longitudinal section, left-hand typically developing right-hand CP, and you can just see more of that stuff in the extracellular matrix. It's thickened and in longitudinal section. You can really see it; it's less organized. And I'll tell you, as Sam and I were looking at these data, we were surprised at the magnitude of the effect, that is, how much ECM there is, and the change in material properties.

We thought what we would do is we'd go into the muscle literature and just look up connective tissue properties of muscle, the collagen types, all that stuff, and it's simply not there. So we have started doing studies because these data, the ECM data, are what correlate with either the magnitude of the contracture or the intraoperative stiffness or the decreased range of motion of the patient. The ECM data correlate; whereas the muscle fiber data don't.



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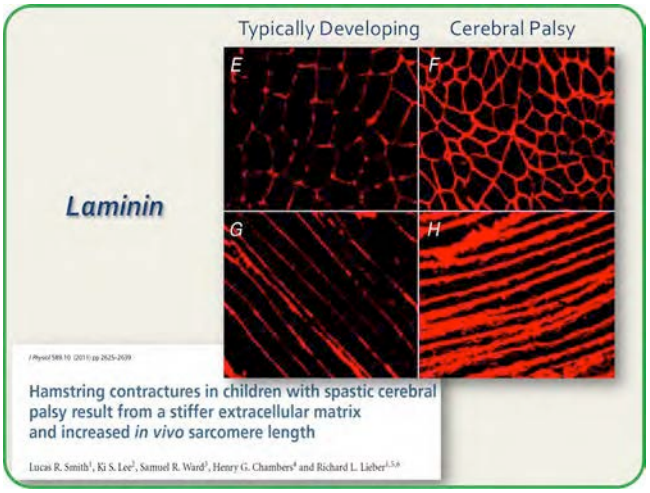


Figure 9.

We have started doing very detailed studies of the extracellular matrix of skeletal muscle, and in collaboration with my student, Allison Gillies, a Ph.D. student, and Mark Ellisman, a great microscopist at UC, San Diego, we've begun identifying the true structural feature differences between endomysium, perimysium, and epimysium (Figure 10). Again, we all teach it in medical school, but it's very hard to find real structural bases for these various tissues.

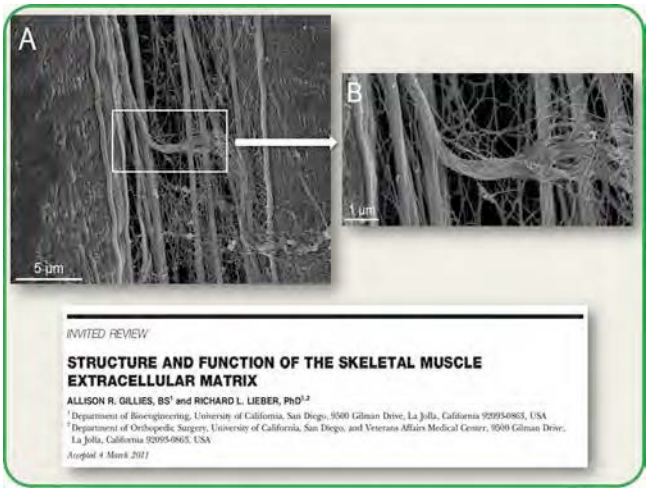
And what we're seeing is that perimysial connective tissue especially comes in these very well-defined bundles. This happens to be a stretched-out muscle fiber bundle, again, I refer you to a recent review in *Muscle and Nerve*, that's composed of collagen fibrils, and we have a variety of models where ECM adapts in ways that are again, I'd say unprecedented in the animal literature. We're just at the very beginning of our ECM journey, but we think there is going to be a lot of fruit there because it has such functional significance in terms of patient mobility and outcomes.

Applying Measurements to Tendon Transfer Procedures

Now, another area I wanted to talk to you about was the whole area of applying these structural measurements to tendon transfer procedures in tetraplegic patients. This work is in collaboration with Jan Fridén who really only does tetraplegia surgery now. Jan and I took this idea of laser diffraction and applied it to a pretty simple and dramatic patient population—C6, C7 tetraplegic patients who have lost elbow extension. They have no triceps. And of course, when you have no triceps, you can't use a manually powered wheelchair, you can't transfer, you can't reach up against gravity, you have tremendous loss of mobility, independence, self-esteem, *et cetera*.

And so, as you can do in Sweden, the highly organized country where everybody gets a number and everybody comes back for every follow-up visit, or else they're shamed, you can do hundreds of patients. And what we did is simply put little stainless steel markers in these patients as they were having surgery, and then followed them up over time. The basic clinical problem was even though you could do a tendon transfer and restore elbow extension, over time, elbow extension was lost. So you started with full extension and then you'd have a lag of 15 degrees, 20 degrees, or whatever. And we were trying to understand, is that the muscle becoming weaker? Is it sort of like a post-polio syndrome where it's an overused slip of a muscle? Is there a change in the mechanics of the repair?

And it turned out it was a fairly simple result. I won't show you the gross pictures, but intraoperatively, the proximal connection to the graft that connects posterior deltoid to triceps, is fairly loose. There's not a ton of connective tissue where the deltoid inserts on the humerus. And it turned out that the proximal deltoid was where the majority of this slippage occurred. So again, in Sweden, where it's possible to mandate a certain treatment protocol, if we simply required these patients to have an armrest on their wheelchair, which prevented active extension and gave them the proper healing time, this spot-weld of a healing would occur, and there was no extension deficit up to 2 years after the surgery (Figure 11).



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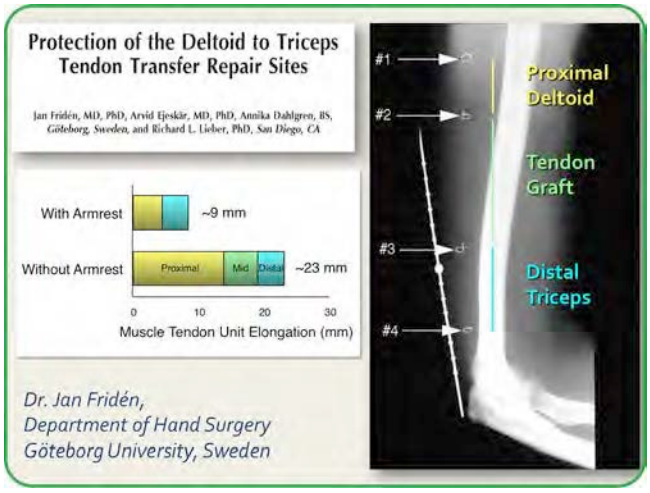


Figure 11.

So these are fairly simple biomechanical studies. They're a little bit of organizational stuff with clinical colleagues, but they changed the paradigm and therefore changed the effectiveness of how these patients can function.

This is just one example of a guy on one side (Figure 12). The patient had a deltoid-to-triceps extension tendon transfer. He didn't have it at this time on the other side; he has had it since. But you can see it's a tremendous change in the ability to perform. In fact, patients like I've shown here who have had bilateral tendon transfers can actually use a manual powered wheelchair against gravity (Figure 13).

And once you have independence in a regular wheelchair, again, this is life-changing. It's not real expensive; it takes a little bit of training for hand surgeons to learn this, but it's, we call this truly a dramatic outcome. I always say people study outcomes research and they have fancy experimental designs. The best outcomes data I can tell you is this guy got kicked out of his tetraplegia wheelchair league as a cheater because he came in with a manual wheelchair and people said, "You're a cheater, you're a liar, you're not C6. . . ! " and he said, "No, I just had tendon transfers," and that's probably the best advertising we can have.

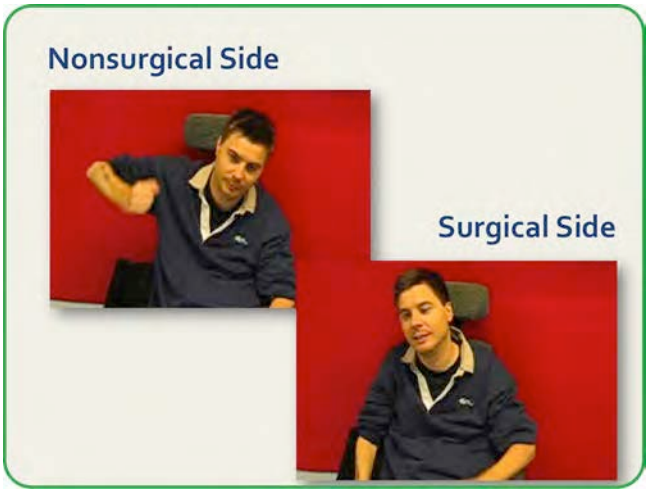


Figure 12.

Figure 13.

Okay, I'd like to show you another. Again, these are just clinical applications of some of this muscle-based clinical research. This is a common problem that you've probably heard of, the fracture in the growth plate resulting in a limb length discrepancy, and with Jenny Boakes, who is a pediatric orthopedist up in Sacramento, California, this Ilizarov procedure where a frame is put on the bone and the bone is slowly distracted, is used to restore leg length (Figure 14).

So she has surgery here at time 0 and then for 3 months, you've probably seen these kids, she clicks her clickers and she slowly elongates the bone. And we were trying to understand when she stretches her femur, is she stretching the bone and the muscle just stretches or is the muscle going to adapt? Because if it's just a stretched out muscle, you're sort of trading one thing for another, and contractures are a complication, a distraction in osteogenesis.

Here, we show that the fascicles themselves are stretched by almost 100 percent, and then during this 9-month period where the bone is healing, consolidation, we can still measure the fascicles (Figure 15). So we start out with fascicles of a certain length. I'm showing here sort of like a cartoon. But they get stretched about 100 percent, and the question is do they get stretched and just sit there in a stretched position, or maybe do some biomechanical stretch relaxation? Or is there a biological response where the muscle, sensing that it's overstretched, starts making new sarcomeres and ends up with sort of more or less normal sarcomere lengths? That's the question.

Figure 14.

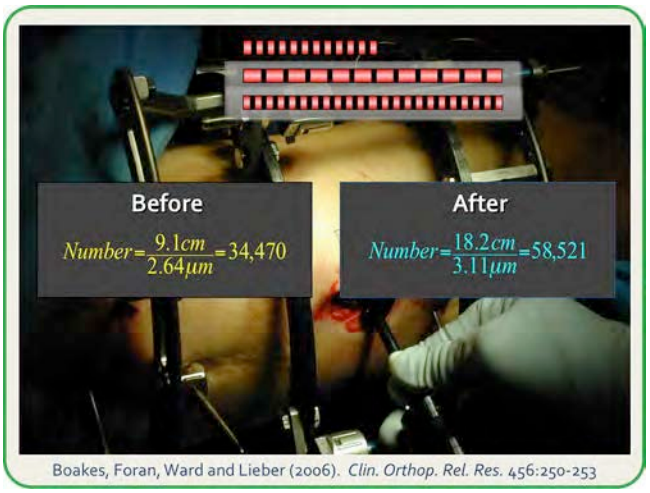


Figure 15.

You could never figure this out by ultrasound. I like the ultrasound measurements, but they only give you a fascicle length. So you have an end-to-end fascicle length with no indication of the microstructure, and the microstructure is where the action is when it comes to function. So if we just knew she had stressed fascicles, we wouldn't understand how the muscle had changed.

Because she's having a second surgery to remove the frame after a year, we can go back in, we can measure sarcomere length of the distracted muscle, and we can make simple calculations. We know how long her fascicles were and what her sarcomere lengths were, so we know she had at the initial frame placement about 34,000 sarcomeres in series. And then after, based on the new numbers, we know that she almost doubled that, about 58,000. In other words, she almost doubled her fascicle length, she almost doubled her sarcomere length; therefore, her muscle made thousands and thousands of sarcomeres over time. That's really good news.

Now, she has normal innervation of her muscle. I'm not saying this would be the same for a stroke patient or a head injury patient or a child with CP, but it's again to this point, we had zero data in the literature that show that human muscles would even change sarcomere number even though we know that's a fairly common finding in the pediatric world.

We would say in terms of the model choices at the top, we would say it's more likely one where she adds the number of sarcomeres, and then when you look at limb length after the surgery, of course, she ends up having the same limb length, which is also great (Figure 16).

Biomechanical Modeling

Now, the last thing I'm going to show is also relatively simple work, again, done with Jan Fridén, a couple of hand surgeons in Sweden, and Sam Ward in San Diego (Figure 17). It's the whole idea of rethinking the biomechanics of a lot of these surgical rehabilitation methods. I really do consider tendon transfer as a rehabilitation; it's a surgical rehabilitation. And of course, that's another thing we probably ought to all get our arms around is the interface between the surgeons and the rehab medicine people, but it's one that's crossable at least.

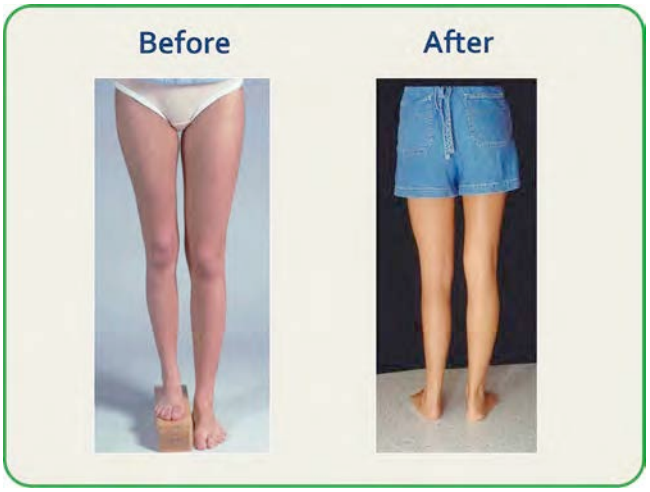


Figure 16.

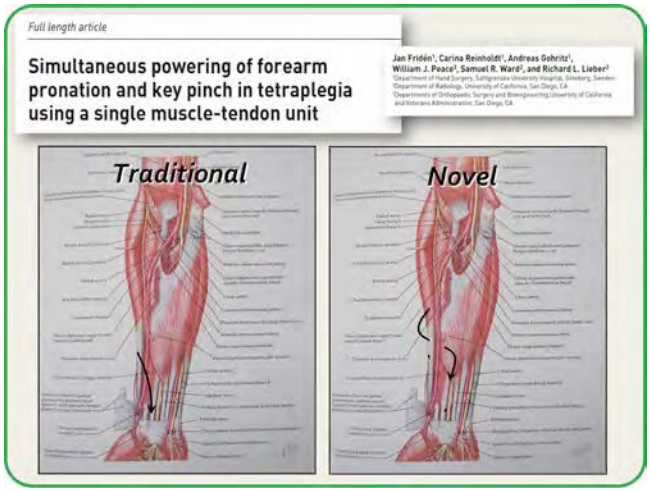


Figure 17.

And the basic idea was this: in the tendon transfer literature, the dogma has been "one muscle, one function." And the trick there is in tendon transfers: you don't always have a bunch of muscles available to restore function in the forearm. For example, if you have key pinch by restoring thumb flexion, you may not have forearm rotation, because you sometimes have to sacrifice a brachioradialis muscle, which is the forearm rotator to obtain the thumb flexion (Figure 18).

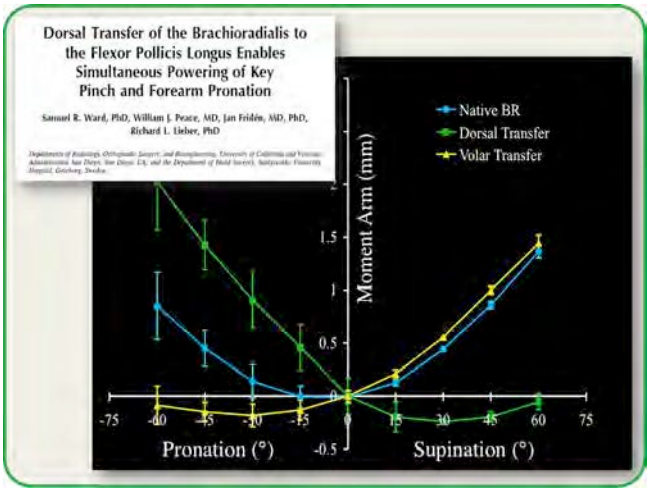


Figure 18.

And so, I'll show you here, this is just a cartoon of the anatomy of the forearm, and you can see here on the lateral aspect of the forearm the brachioradialis (BR), which is often transferred to flexor pollicis longus (FPL). So BR to FPL is used to restore thumb flexion, which when combined with elbow extension gives a patient a tremendous amount of function.

In fact, the funniest story I ever saw was a patient who came in—he had had his spinal cord injury 30-something years earlier and he decided on his 65th birthday he wanted to drink his own beer by himself, and that was his goal. So when Jan was talking to him about patient function, he said, "Well, how much function do you need?" And he answered, "Well, how much key pinch do I need to raise a beer?" So we did little pilot experiments to figure out sort of whether it was even reasonable and how full the glass would be, *et cetera*.

Okay, so restoring key pinch is tremendously functional, but the idea was maybe you don't have to go directly from brachioradialis to flexor pollicis longus. Maybe if you went around the radius, you could simultaneously give the patient key pinch and forearm rotation. This is better than sacrificing forearm rotation because even if you give them pinch, if they're stuck in supination, that's a much less functional position.

So Sam and his colleagues in San Diego did simple biomechanics where they measured the mechanical advantages of muscles in different conditions, either a native brachioradialis, one that was transferred dorsally, which is the novel method or one that used the traditional volar transfer. And again, I'm happy to talk to you about the data, but the bottom line of this graph is that the dorsal transfer, which was novel, more closely approximated the function of a normal brachioradialis, at least in terms of getting the pronation.

And no kidding, after we did the experiments in San Diego, Jan returned to Sweden and this is a videotape of the first surgical result of a patient who is simultaneously pinching and rotating his forearm. Here's the transferred brachioradialis (Figure 19). You can see it bulging out here. It's passed dorsally around the radius into the FPL, and this guy can both pinch and rotate his forearm. And this work just came out in the *Journal of Hand Surgery (European)*. These data just show that there is a tremendous range in the pronation side.

These are examples of the kinds of things that can be done with relatively straightforward biomechanical modeling, and I will also say we do have a tremendous basic science lab where we look at transgenic animals and muscles that have been modified. We use those basically as reality checks for the human models rather than the other way around.

But I did want to highlight this one study that was done in San Diego by Ju Chen in which a genetically modified animal died when it was very young (Figure 20). It was neonatal lethal, in other words. And a lot of the function of neonatal lethal mutations or genetic alterations is unstudiable because these are teeny tiny muscles. In the slide here, you can see this is about a 1 mm long muscle belly of a tibialis anterior attached to sort of jelly-like tendons. And again, using modern mechanical methods, we can make functional measurements on these that will enable us to understand how these genetic modifiers end up being functionally significant in the skeletal muscle.

So with that, I'll stop. I'll point you to our website (Figure 21). We have a lot of "regular old" muscle physiology you can study. We acknowledge the tremendous funding we've gotten not only from the NIH but from the Department of Veterans Affairs, where I also have a lab. And I know all of the R24 Center Directors are very grateful to the NICHD and especially Ralph who has been our cheerleader on the phone and keeps pushing us along to go in the right direction (Figure 22). Thank you very much.

Figure 19.

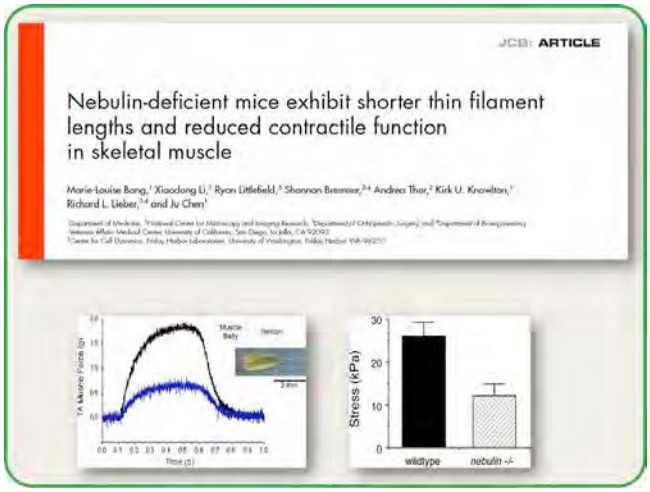


Figure 20.

Figure 21.

Figure 22.

Computer Simulations

Scott L. Delp, Ph.D.

Professor of Bioengineering, Mechanical Engineering, and Orthopaedic Surgery, Stanford University
Palo Alto, California

Well, hello, everybody. I'm really so thankful to be here, and I want to thank you guys for inviting me to participate. I feel like I grew up with the NCMRR. I started my faculty career 20 years ago. My department chair was Henry Betts at Northwestern University and the Rehab Institute of Chicago, and Zev Rymer was my mentor and boss. And I still remember the day that Zev walked into my office and told me about the formation, the official formation, of the Center and said, this is a great day for rehabilitation research. And he was right. So I'm just really happy to be here 20 years later and celebrate with all of you.

We're working to bring advanced computer simulations into rehabilitation research. When you think about it, almost every complex product or device or engineering system that is built today is first designed on a computer: cars, keyboards, kitchen cabinets. They're all produced by first generating a computational prototype, testing it out before we ever try it in real life. We almost never do that in rehabilitation research or in medicine in general. So our goal is to try to bring simulations into rehabilitation research. And we're motivated to do that because understanding human movement is extraordinarily complex.

If you take, for example, treatment of gait abnormalities in children with cerebral palsy (CP), it's quite complex. There are a number of potential causes simplified here: impaired motor control, for example, spasticity, weakness, muscle contractures, bone deformities (Figure 1). Some or all of these may be present in an individual who comes in the laboratory, and we're attempting to design the right surgical or rehabilitation program to better restore their locomotion.

When you think about what the possible treatments are, they may have orthopedic surgery to release tight muscles or to realign bones (Figure 2). They may have physical therapy to improve range of motion or strengthen particular muscle groups. They may have orthotics or assistive devices, neurosurgical procedures, for example, by selective dorsal rhizotomy to reduce spasticity or altering medications that can be taken orally or injected into muscle like Botox®. So it was pretty tricky to figure out what the cause is, which ones are dominant in an individual patient, which ones are compensations, and what the right package of treatment is going to be to best restore mobility.

And I can tell you I've reviewed hundreds of patients that have had quite remarkable outcomes, fantastic improvements in gait, for example, after a particular intervention. I've also reviewed from many different centers throughout the country outcomes that are not good, that the gait has changed but it's certainly not improved. It's not surprising that that happens. It's extraordinarily complex to try to figure out what's causing what in a complicated moving system.

Biomechanical Models

The question is: can biomechanical models help? Can we gain some additional insight that complements experimental approaches in treatment planning for both basic science questions and clinical care (Figure 3)?

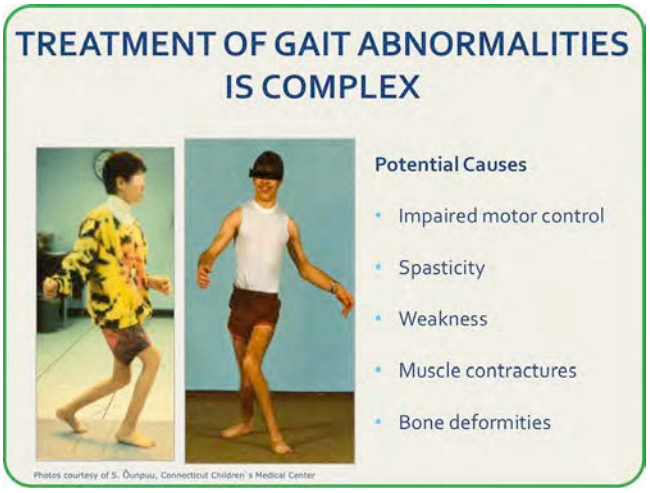


Figure 1.

Figure 2.

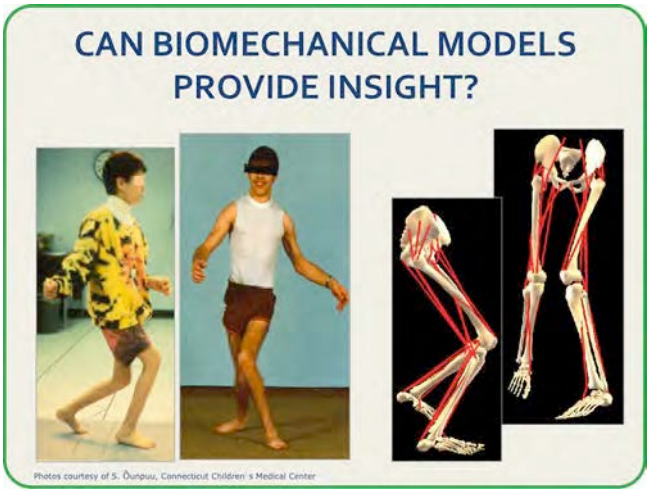
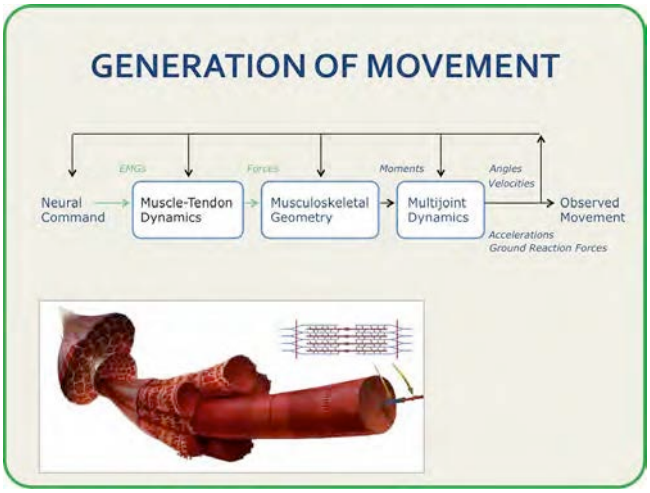


Figure 3.

When you think about whether a biomechanical model might help, first consider just the basic outline of events involved in the generation of movement (Figure 4). Of course, we begin with a neural command generated in the central nervous system. We then have muscle that turns our ideas into action-generating forces. Muscles act on the musculoskeletal system that has complicated geometry, so muscles generate force (Figure 5). They act at a distance from the joint, the moment arm, and those generate movement not with single muscles acting but with many muscles in concert in the face of gravity and external reaction forces. And that produces observed movement. It's not just forward, it's not just brain to motion, there is of course feedback from proprioceptors, and the system is highly complex and coupled (Figure 6).

So then, a bunch of things can go wrong. There may be, as I mentioned, impaired motor control, changes in muscle tendon dynamics that Rick, for example, just presented, or changes in CP where there may be cases of muscle contracture, muscle weakness. There are changes in musculoskeletal geometry because the skeleton is developing over time under the influence of abnormal forces. There is abnormal bony torsion of the tibia and the femur, and as a result, we have abnormal multijoint dynamics (Figure 7).

The challenge is that someone walks into a gait analysis laboratory, for example, and what can we do? We can measure the inputs, we can measure the electromyographic patterns of the muscles, and we can measure the output. So we can measure the angles and angular velocities and external forces, but we don't know what's causing what (Figure 8). We might see a pattern of abnormal excitation of a particular muscle, but we don't know what motion that muscle is causing. We also may see ten abnormal patterns of excitation and three or four abnormal motions, and we really can't sort out which muscle is causing what motion (Figure 9).



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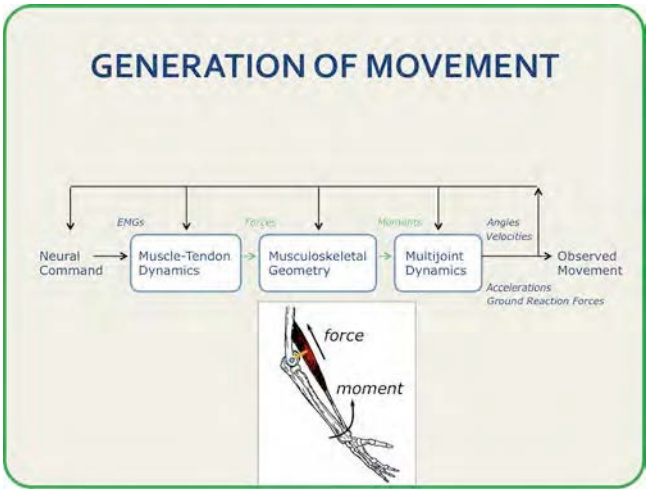

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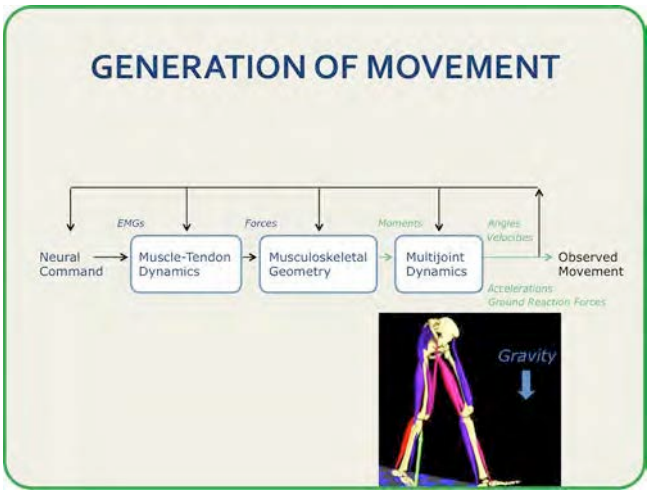

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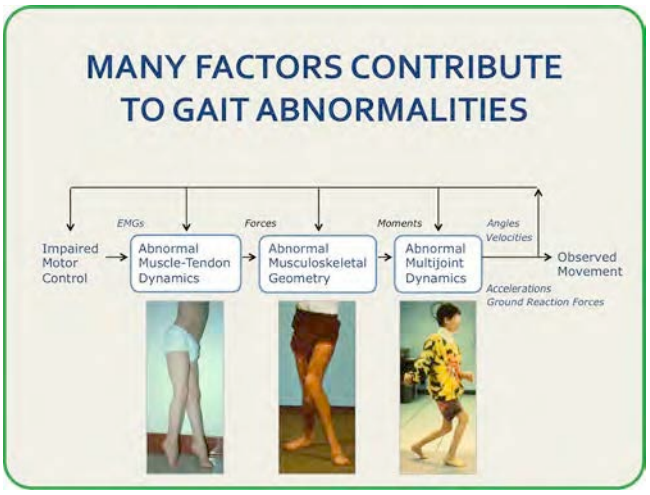

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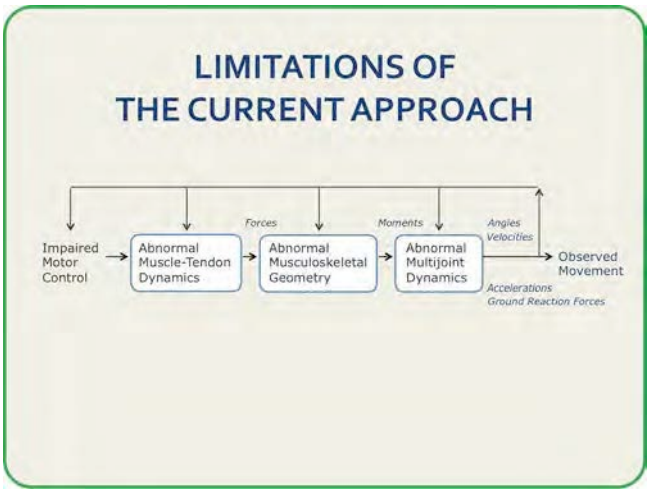

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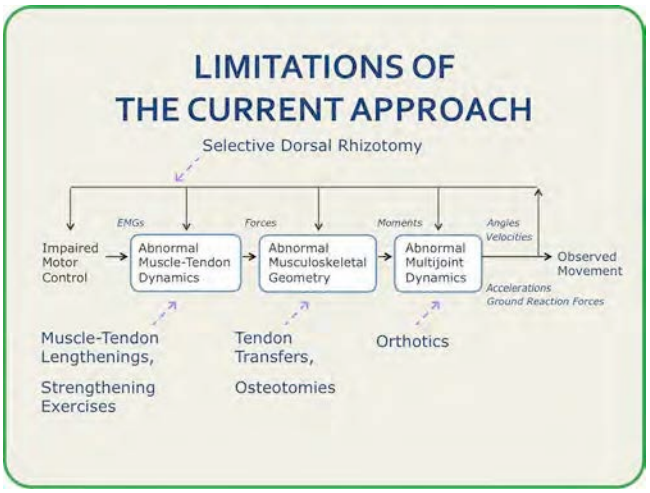


Figure 9.

The problem is further complicated because, when you think about the possible interventions, a surgical lengthening of a muscle tendon unit, strengthening exercises, a tendon transfer, osteotomies, orthotics, selective dorsal rhizotomy, they affect part of the systems that we can't really measure very well (Figure 10). So it's hard to predict what the outcome will be.

When we generate a mathematical model of human movement, we bring to light what's happening with abnormal and normal muscle tendon dynamics (Figure 11). How is electromyographic or excitation patterns of muscle transformed into force? How are those forces transmitted to the skeleton with normal or abnormal musculoskeletal geometry? And what are the physics of movement? We can generate physical equations that describe force equals mass times acceleration for the physics of movement, and we can see how the forces generated by muscles produce movement.

Further, we can go in and we can add an orthotic, we can do a tendon transfer, we can do an osteotomy, we can strengthen or weaken muscles, we can do a simulated surgery, and see how that might affect muscle forces, joint moments, and abnormal motion. We can change feedback to the central nervous system and see how, for example, a model of spasticity might, introducing that impairment, affect motion.

So potentially, biomechanical models can do a number of things. They can complement experimental approaches, certainly not replace experimental approaches, but models allow us to predict variables that we can't get experimentally. For example, if we have a model in which we have some confidence, we can estimate the forces in muscles, the forces in tendons, and the force in the joint when we walk in a crouched gait, for example, and how those might be affected with therapeutic interventions.

We can do what-if studies, so for example, what if I could diminish the force generating output of the rectus femoris, for example, in cases of spasticity? Would that improve knee flexion in someone who had had stiff knee gait?

And most importantly, we can see what's causing what in the system. We can understand cause-effect relationships. Because we have a mathematical model of this system, I can change the force in a muscle, I can increase the force due to, say, strengthening exercises and see what motions that enhanced muscle forces causes, or I can make a muscle 10-percent weaker, or remove it completely to simulate weakened or paralyzed muscle to see how that might affect motion. So we can really tease out what's causing what in a complicated system once we have a detailed mathematical model.

Musculoskeletal Models

So what I wanted to do with that precursor is just give you one quick example of how we've used musculoskeletal models to try to gain insight into a particular gait abnormality, and then, as Ralph Nitkin suggested in an inspiring email to all the speakers, talk about where this is headed in the future. What might we expect in 10 or 20 years? And how can the community of rehabilitation researchers come together to try to advance rehab science?

Let me start just with a past example and how that's been translated into improved clinical care. The question we asked was can analyses of muscle tendon lengths and velocities aid in treatment planning for crouch gait? For those of you involved in management of individuals with CP, you understand that crouch gait is very common in individuals with spastic diplegia, and tricky to figure out how to improve (Figure 12).

The reputed cause in many cases is either hamstrings contracture, that is, let's say, shortened muscle fibers, excessive passive force (Figure 13). So even when there is no excessive activation, the muscle is generating too much force inhibiting knee extension, and so, as a result, the individual walks in a crouch gait, or spasticity, when the muscle is stretched. There is an exaggerated reflex response, excessive activation, and that excessive force generated when the muscle stretches may inhibit knee extension.

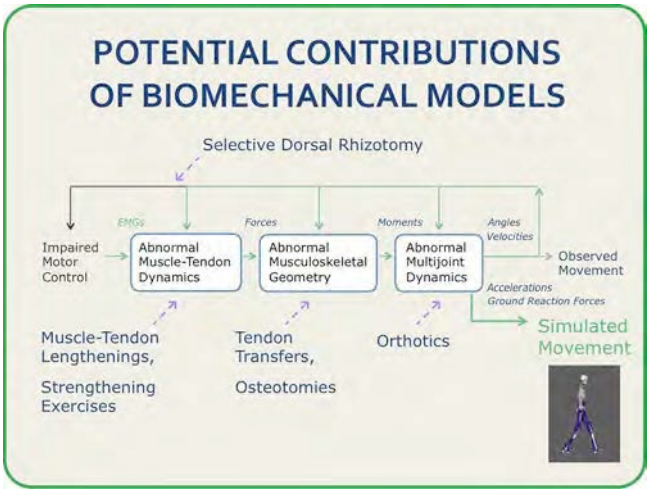


Figure 10.

Figure 11.

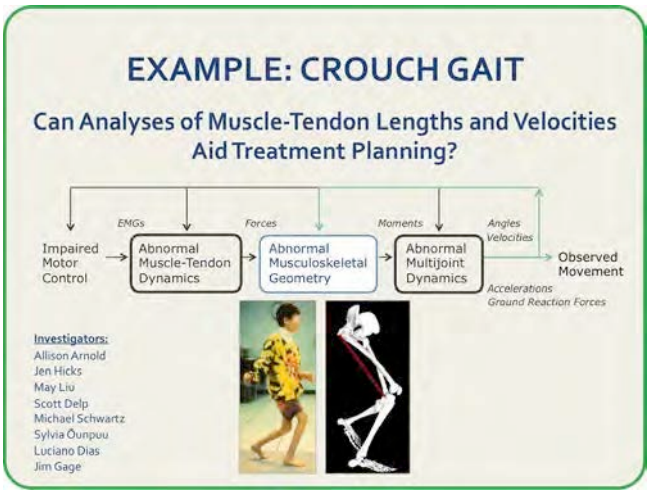


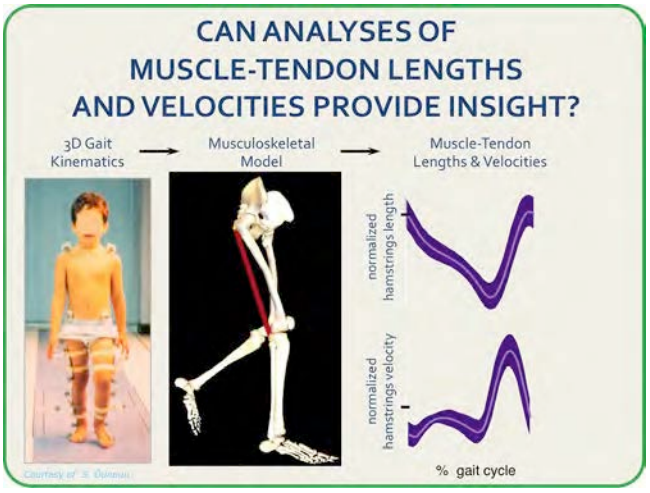
Figure 12.

Figure 13.

We were interested to see if we could use experimental motion capture data together with a musculoskeletal model to calculate the lengths of the hamstrings in their velocities in unimpaired gait and in individuals with grouch gait to see if we could gain some insight (Figure 14). We were interested in this because I had looked at outcomes of individuals who had hamstring lengthening surgery to improve crouch gait, and in some instances, they got a lot better. Instead of walking in a crouch, they walked in a much more erect and efficient gait. In other cases, they didn't get better and, in fact, there were changes to gait, increased anterior pelvic tilt, for example, which were not helpful and didn't improve gait.

We were interested in individuals with CP to calculate the lengths and to see, for example, if the lengths were shorter than normal, or if the stretch velocity of the muscle was shorter than normal or slower than normal. If the muscle couldn't reach its maximum length, like it does in normal walking, perhaps it might suggest that contracture of the hamstrings may be playing a role in limiting knee extension required for normal gait (Figure 15).

If instead the hamstrings didn't reach their normal stretch velocity, they started to lengthen but then were arrested, perhaps it might suggest that hamstring contracture may be playing a role in limiting the extension required for normal walking (Figure 16).



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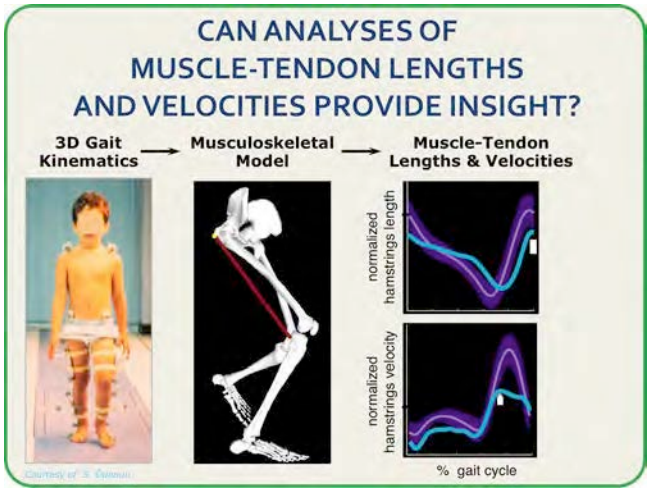

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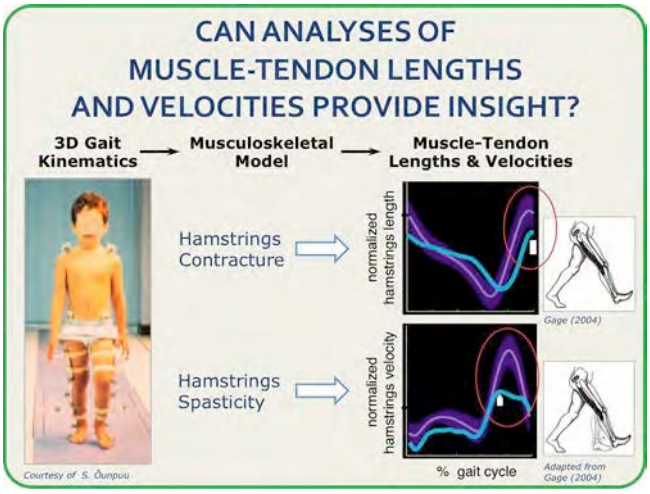
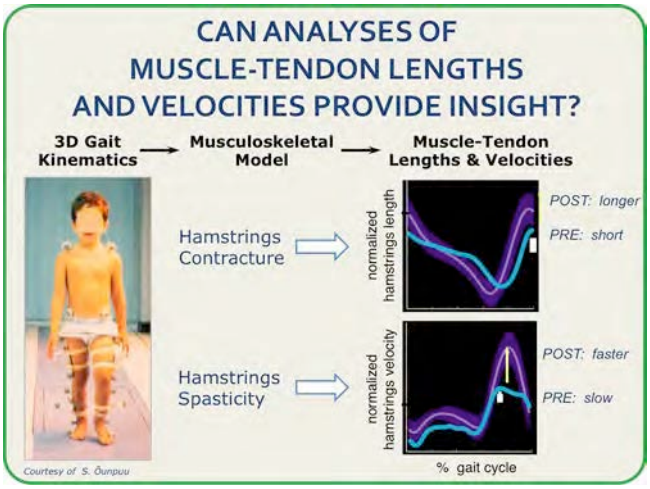


Figure 16.

If the muscle was short and the individuals had a surgical lengthening of the hamstring, we didn't even know whether the muscle would get longer or not, so that was another question we asked. Or if they were slow, and the individuals had a hamstring lengthening, would the muscle actually lengthen at a faster rate after surgery (Figure 17)? And if so, did the individuals get better? Did their knee extension improve (Figure 18)? If they were walking in a crouch beforehand, do they walk with less crouch or with normal erect gait after a particular intervention?

Those were the questions we set out to answer. We did it by taking three-dimensional gait analysis data after years of very careful assessment of the accuracy with which we could calculate hamstring lengths in individuals with CP who may have bone deformities who come in different sizes (Figure 19). We set out to define what the normal hamstring length trajectories are and what the normal velocities are, and then, just as a first study, to see how many people walked with short hamstrings.

In some hospitals, I noticed if patients walked into the gait analysis laboratory for possible treatment planning, and they walked with flexed knees, over 90 percent of them would have hamstring lengthening. In other hospitals, less than 30 percent would have hamstring lengthening (Figure 20). So it was clear that the criteria for deciding who and shouldn't have a surgical lengthening of the hamstrings were not consistent.



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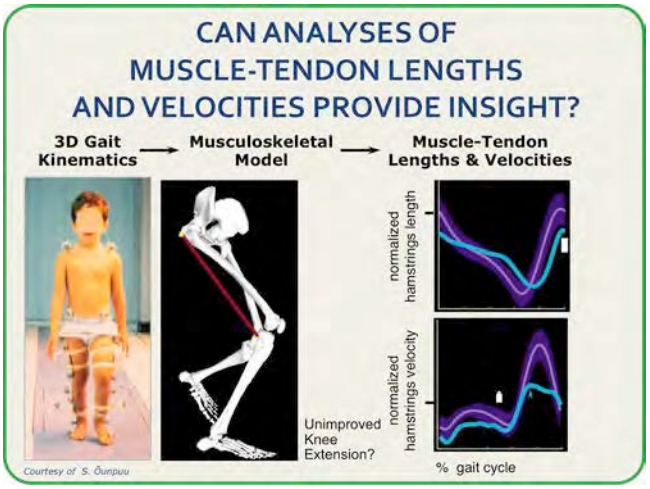

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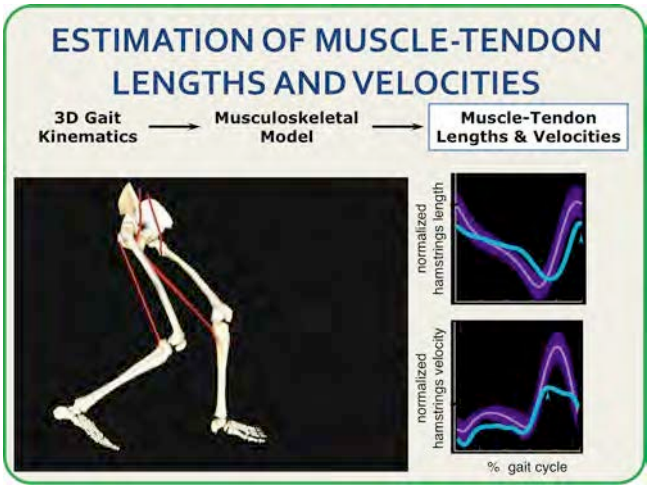

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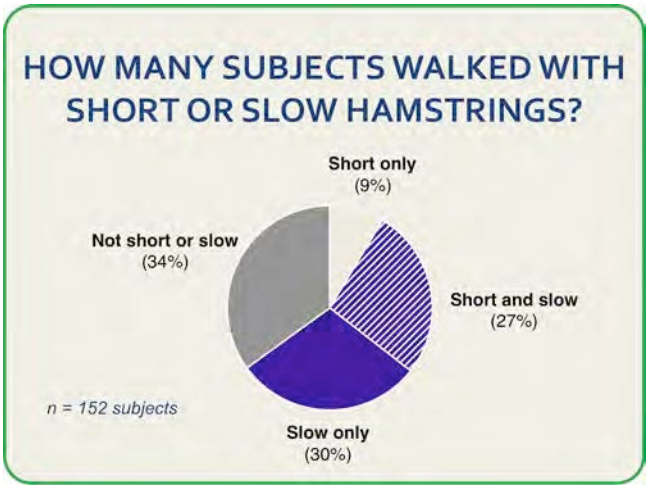

Figure 20.

So we studied about 150 subjects, and what we found was that about a third of the subjects walked with crouched gait: they all were kids with CP. And about a third of them had hamstrings that were shorter than normal; that is, they didn't reach that peak length. Almost all of the ones that had short hamstrings also had slow hamstrings: that means they didn't stretch at the normal velocity. There were about a third of the patients that had hamstrings that were of normal length, but they didn't stretch at the normal speed. And then there were about a third, 34 percent, that walked with a crouch, but their hamstrings achieved a normal length and achieved the normal stretch velocity.

Well, many of these patients had surgery whether or not they had short or slow or no hamstrings. Did the hamstrings get longer or faster after surgery? Well, if they were short, they tended to get longer after the hamstring lengthening surgery. If they were slow, they tended to get faster. If they were not short or not slow, they didn't tend to get longer or faster (Figure 21). That's not so surprising.

What about outcomes? Were the postoperative knee extensions related to these velocities? What I'll do to try to demonstrate that is to just show you a couple cases. So here is one in which a patient is walking into the gait analysis laboratory (Figure 22). We did a musculoskeletal model of her, and her hamstrings were indeed shorter than normal and were lengthening more slowly than normal. She had a hamstring lengthening surgery 1-year post-op: quite a nice improvement (Figure 23). She is, for the most part, out of her crouch, her hamstrings are operating at normal lengths and at normal speeds, and her knee extension is much improved.

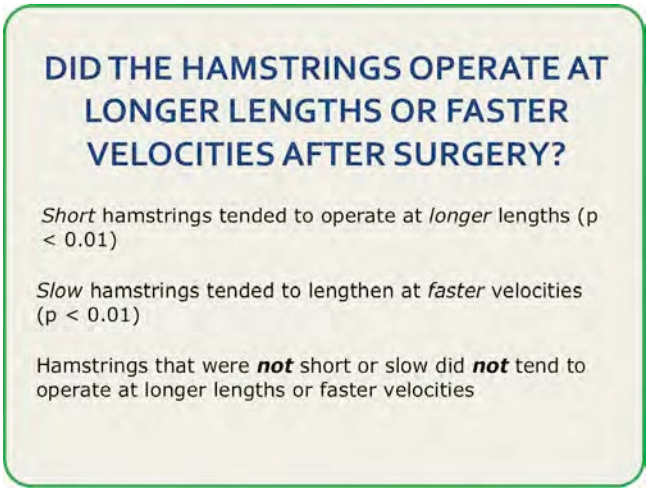

Figure 21.

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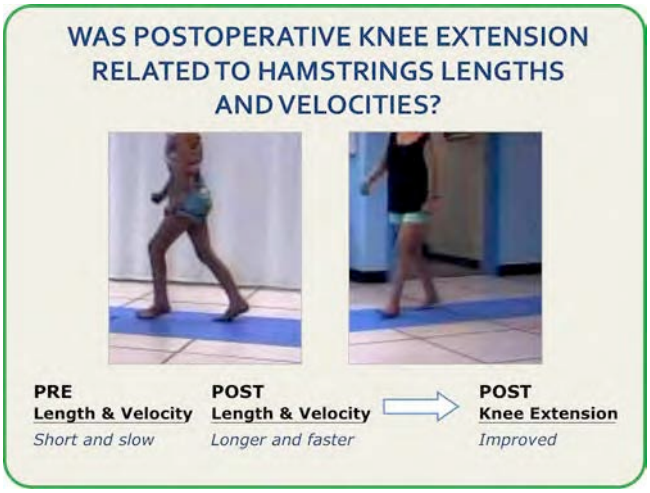


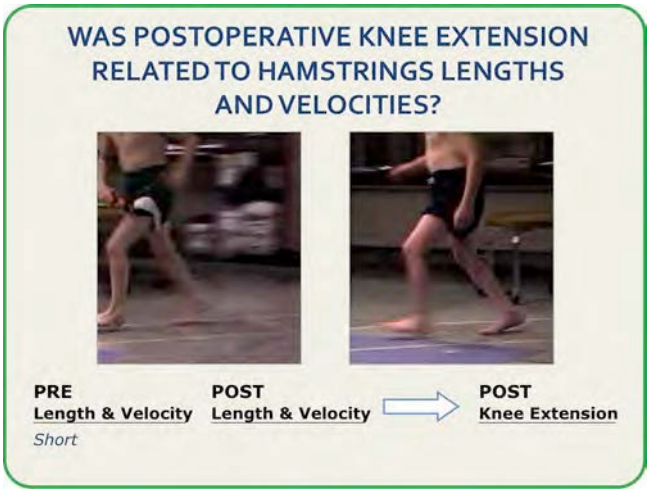
Figure 23.

I'm showing you this case example, but this was a statistically significant finding: individuals who had short or slow hamstrings, had the hamstring lengthening surgeries; their muscles got longer and faster, and their knee extension got better. So it's a reasonable paradigm that if their muscles are short or slow and they have a surgical lengthening, that in fact that treatment was addressing the underlying cause, and the outcomes were, in general, quite good.

Here's another case (Figure 24). This was a different hospital, and this patient's hamstrings are short. He did not have a hamstring lengthening surgery; he had a number of other treatments. His hamstrings did not get long or fast into the normal range, and after quite an extensive surgical reconstruction and rehabilitation program, his crouch gait was not better (Figure 25). So we identified a group of patients who had hamstrings that were not achieving normal length, their hamstrings couldn't stretch to normal velocity, they didn't, underlying treatment wasn't addressed, and the patients' crouch didn't get better.

I'm not going to show you an example here, but there were a class of patients where their hamstrings weren't short, they weren't slow, the patients had a hamstring lengthening, and they were at greater risk for side effects, that is, weakened hamstrings that resulted in additional anterior pelvic tilt and additional knee, hip flexion that's frequently associated with crouch.

We did not see that side effect when the hamstrings were short or slow, but we did see that in cases where the patients were being treated for crouch gait with hamstring lengthenings, and they didn't have short or slow hamstrings.



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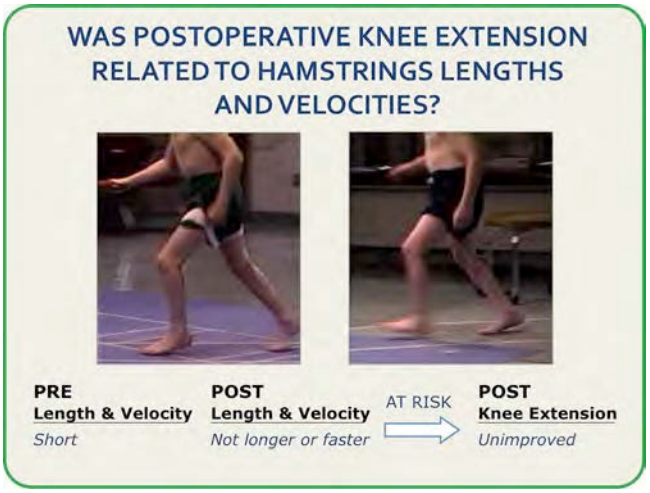


Figure 25.

So that's a useful clinical finding that maybe suggests a useful clinical guideline that we can augment treatment planning to assess with the gait analysis in a musculoskeletal model whether someone has short or slow hamstrings. If they do, perhaps they could be a good candidate for hamstring lengthenings.

But how does that turn into improved rehab in patient-specific treatment decisions (Figure 26)? If we're the only ones that can make those calculations at the hospital where I'm working, for example, and other people can't, it's not so useful.

OpenSim

So what we have done is to try to disseminate the tools that we use. Jen Hicks, who is here from Stanford, developed this website that's part of our National Center for Using Simulation in Rehabilitation Research (Figure 27). OpenSim is a software product that we produce that's freely available to anyone who wants to use it. So any of you can go to this site, download the software, get some clinical data, and do a tutorial calculating hamstring lengths and velocities. In a number of cases, some have short hamstrings, some don't have short hamstrings, and in fact, now there are a dozen or so hospitals that are using this software as a routine basis for planning gait-correcting surgeries in individuals with CP.

You can go to that site and you can get not just musculoskeletal models to calculate hamstring lengths, you can get dynamic simulations of crouch gait in which we estimate the pattern of muscle activations, the muscle forces, the joint forces for individuals with a mild crouch, with a moderate crouch, with severe crouch (Figures 28-29). You can calculate what the loads are in the knee joint, for example, to see how crouch severity relates to excessive knee loads. And you can download that simulation, run it on your computer, reproduce the results that we publish in our papers, and build on those results. So this is available to anyone, not just to individual case studies.

May Liu, who was a doctoral student, produced this small army of simulations of unimpaired individuals walking at very slow speeds, slow speeds, self-selected speeds, and fast speeds. Because walking speed makes a difference in terms of muscle lengths and stretch velocities and forces, we need to compare our CP subjects and stroke subjects with subjects walking at similar speeds.

This is all published and posted and available. Anyone can download it and build on this work, rather than start from scratch. To build this set of simulations, May devoted about 4 years of concerted work to not just create them but test the accuracy with which our algorithms were computing the patterns of muscle excitations, the muscle lengths, the joint angles, the joint moments, and the ground reaction forces.

We can make the simulations pretty quickly, and then it takes years to test them to build confidence in where the simulations are accurately reproducing patterns of neural excitation, muscle forces, and joint motions, and to identify where we don't believe the simulations, and where people shouldn't be using them because we don't have confidence in the results.

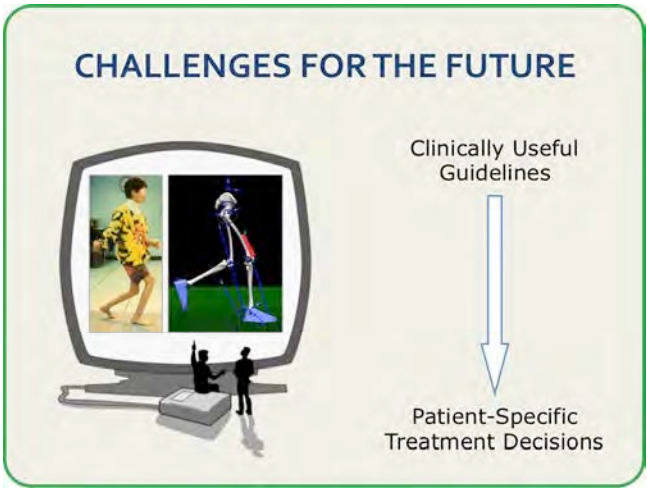


Figure 26.

Figure 27.

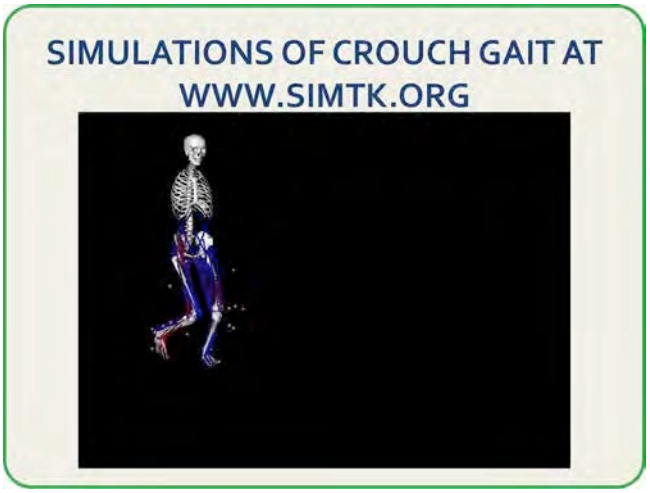


Figure 28.

Figure 29.

Cham John, a graduate student, produced this simulation of ten gait cycles (Figure 30). The patterns in muscle activations, shown by the muscle's change in color, very closely match electromyographic patterns. The three-dimensional simulation very closely reproduces the motion of the pelvis, the joint angles.

And so, anyone can download this and use it. In fact, roughly 8,000 people have downloaded this software to try to analyze not just gait mechanics but other biomechanical problems (Figure 31).

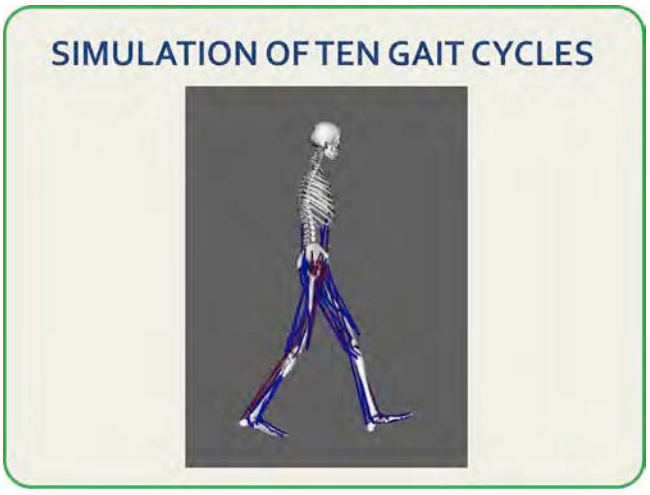


Figure 30.

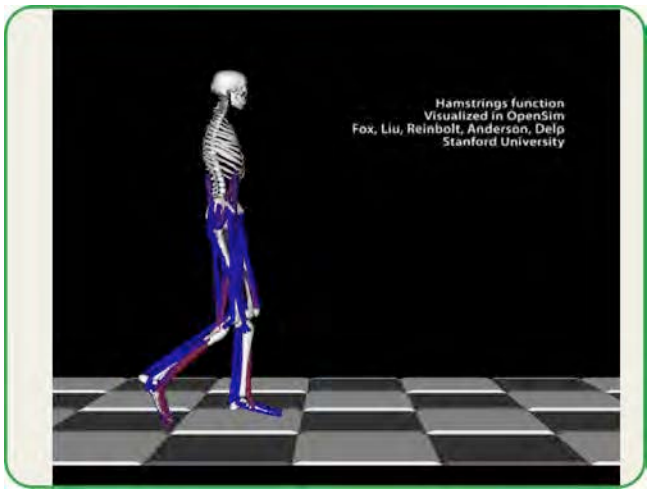


Figure 31.

Some of them are high school kids using it for their high school physics projects. Some of them are kids in college or physical therapy school. Some of them are researchers trying to build on the specific results, for example, by going into the simulation. If you want to assess what the hamstrings are doing, you can run the simulation forward so all the muscles are generating the motion.

You can remove all the muscles. You can excite just one muscle, and you can see what motions that muscle is causing. And I'll show you this because it's tricky. You turn on the hamstrings, it, of course, extends the hip, but it moves the pelvis. It actually extends, not flexes, the knee in some situations. So the actions of muscles are pretty tricky to figure out, and having a comprehensive dynamic representation of the musculoskeletal system is, I would argue, necessary for trying to understand muscle function.

Sam Hamner is a doctoral student at Stanford who made this really beautiful and accurate simulation of running with and without arms, so we can assess muscle and joint forces during running to see what actions of muscles differ between walking and running (Figure 32). We're now doing this for walking up inclines, down inclines with loads, walking in crouch, walking in equinus, so that we can really get a good sense of what muscle actions are during motion.

And it's not just our lab, there is a worldwide community of people that are contributing to this and posting their research results online (Figure 33). So Edith Arnold developed a really nice model of the lower extremity based on the muscle architecture data from Sam Ward, and Rick Lieber did a beautiful muscle architecture study measuring the fiber lengths, physiologic cross-sectional areas, and tendon lengths in muscles of the lower extremity.

Figure 32.

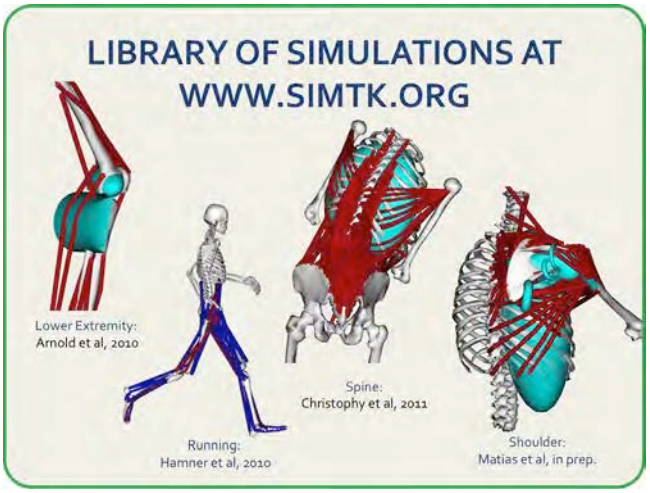


Figure 33.

Edith built that into a model of the lower extremity that represents wrapping of muscles over bones, and then she just posted that on the Web. She can track anyone who downloads it, where they are, what they're using it for, and she can correspond by a little forum to teach people how to properly use the model. Sam's running simulations that were posted.

A group at University of California (UC), San Francisco, and UC, Berkeley, developed this really nice spine model. As soon as they published it, they posted it on the website. Others can download that and do analyses. Even models to represent shoulder muscle anatomy, for example, that are in preparation, but not quite finished are being developed and posted on this site.

We have this virtual community, but we also find that it's essential to bring people together (Figure 34). So we work with about 200 people each year sometimes at conferences like this, sometimes at Stanford and workshops. They come in about 20 at a time, and our research team works very closely with them. People apply to come, they lay out what their rehab research problem is, they come to Stanford for 3 days to 3 months, and they work with our team and develop pilot data for future studies. So they may have wonderful clinical data, good motion analysis data, and then they come to us and they develop complementary simulations and pilot data that serve as the basis of their NIH grant application in the future.

So it really is bringing young folks with extremely strong computer modeling and simulation capabilities into the rehab community. Many of these people come from backgrounds in computer science or bioengineering or biomedical informatics, and they have incredible training in biology, information systems, simulation techniques, software engineering and development, and they get hooked up with rehab researchers and identify important problems that they can use as motivators for applying their computational skills. We're just seeing this time and time again.

These workshops are very highly subscribed; as soon as we announce them, they are fully booked. Participants pay their own way to come, and they're very excited to be part of the program.

It really is becoming a worldwide community. There are not just a few people doing this; there are 8,000 users (Figure 35). And like I said, not all of them are advanced rehab researchers. Some of them are even middle school students doing biology projects. But many of them are contributing not just through the hub at Stanford, but they're helping each other throughout the world because I think you all know that rehab research is a team sport, and we need people from all disciplines bringing their expertise to bear on problems of restoring mobility. This is one way to bring engineering simulation technology into the rehab field.

Figure 34.

Figure 35.

I've had the good fortune of working with a wonderful home team (Figure 36). Jen Hicks is here. She is the leader of this National Center for Simulation in Rehab Research, and this is just a couple of years ago. You'll see the members of the lab. Wendy is now at Northwestern, Kate at Wake Forest, Rob at Ohio State. Allison is at Harvard, and Sylvia is at University of Virginia. So there are young people with advanced simulation capabilities coming into rehab, getting inspired, and going out to their own institutions and starting their own rehab research program.

Of course, we would be nowhere without NIH, and I've been extremely fortunate to have one of these R24 centers, other R01s, and other mechanisms that help make the world go 'round. So with that, I'll close.

Thank you.

Figure 36.

Engineering in Rehabilitation

William Z. Rymer, M.D., Ph.D.

President, Rehabilitation Institute of Chicago, and Professor of Physical Medicine and Rehabilitation, Physiology, and Biomechanical Engineering, Northwestern University Chicago, Illinois

Let me begin by making a brief tribute to my former chair and chief executive officer, Henry Betts, who was mentioned in Congressman's John Porter's letter to the NCMRR. It was clear that Dr. Betts had a decided influence on Congressman Porter but also on Senator Ted Kennedy, Mary Lasker, and others. And the other person who wasn't mentioned before is Ted Cole from the University of Michigan who also was a key player, and they all deserve enormous credit for what they accomplished.

Presentation Overview

I'm going to take a little bit of a different approach as far as the application of engineering methods in our field over the current history of the NCMRR. This isn't to say that the NCMRR was entirely responsible, but many projects and many people that came in and around the NCMRR were pivotal. There are seven topics there, and you don't need to get nervous; I'm not going to discuss all of them (Figure 1). I'm just going to skip lightly through some of them because these are all things that have changed profoundly over the last 20 years.

And if there's any sort of theme that I wanted to promote, it's that our technology, in some way, has traveled faster than our ability to make good use of it (Figure 2). And we are seeing that, for example, especially in robotics and functional electrical stimulation, our engineers have preceded the clinicians and scientists and so forth. Their ability to create has not been matched by our ability to apply technologies well, at least to date.

Functional Electrical Stimulation (FES)

So one area that's made enormous progress over this 20-year period has been functional electrical stimulation (Figure 3). There have been some major accomplishments over that period. The phrenic nerve stimulator, which is now widely used for people with high spinal cord injury whose innervation into the respiratory system has been impaired, provides direct stimulation of the phrenic nerve, and can make a huge beneficial impact in the quality of life of people with high spinal cord injury (Figure 4).

The second area where we have made spectacular advances, although this is not widely used yet, is the functional electrical stimulation of the upper extremity and hand. This was beautiful work that's come primarily from Cleveland, from Case Western, Metro Health, and the Veterans Administration. They've shown the ability to restore very elegantly the capacity to control upper extremity movement and produce restoration of hand function.

We also know now in many, many centers that functional electrical stimulation and bicycling go together. This is a way for people to maintain muscle mass and cardiovascular capacity as well as skin quality and bone mass. There are many benefits that derive from electrical stimulation of muscle in the course of bicycling, and there is some success in standing, and emerging prospects in the area of bladder control with electrical stimulation.

This is a slide I borrowed from Hunter Peckham who has been the Director of the FES Program in Cleveland for a long time. This is just illustrating the phrenic nerve stimulation, which these things are now implanted and can be controlled from the outside and powered with batteries that are surgically implanted (Figure 5). As I said a moment ago, these phrenic nerve stimulators have made a spectacular positive effect on quality of life.

Figure 1.

Figure 2.

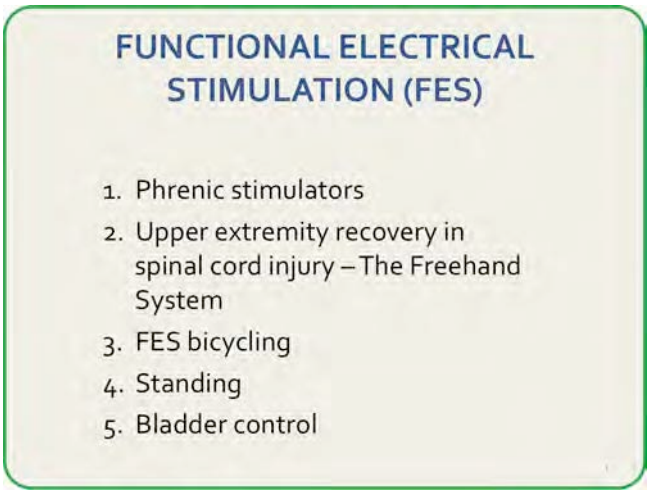
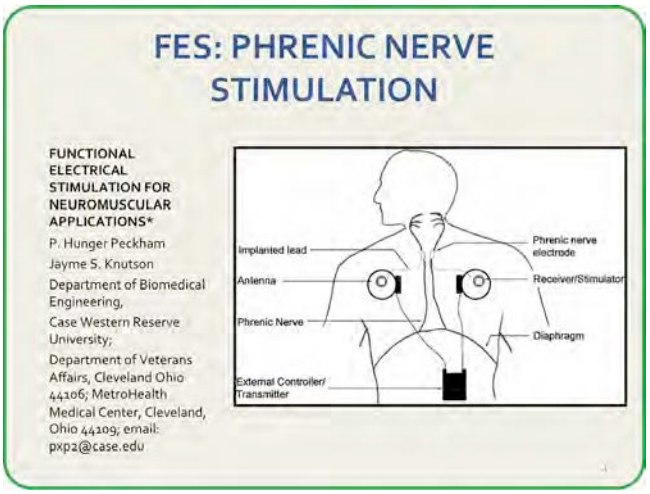


Figure 3.



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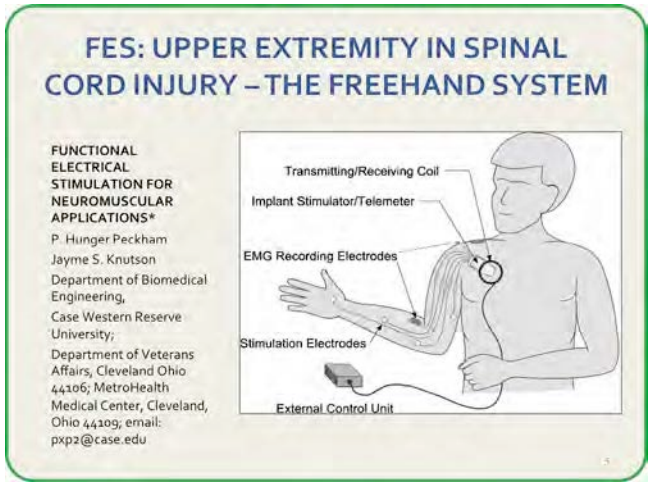


Figure 5.

Robotic Systems

In my own area, we have had an explosion in the development of robotic devices and treatment of different kinds of paralysis (Figures 6-7). One of the early ones comes from Britain. This is called Gentle/S. Another early robot is MIT Manus. My collaborator, David Reinkensmeyer at the Rehabilitation Institute of Chicago, developed this early robot.

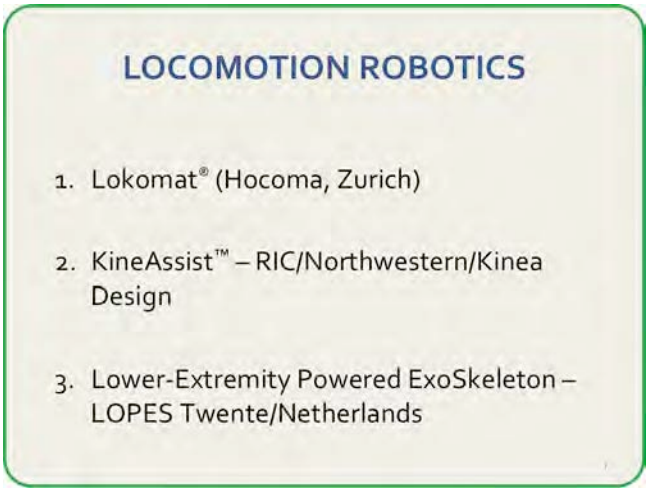


Figure 6.

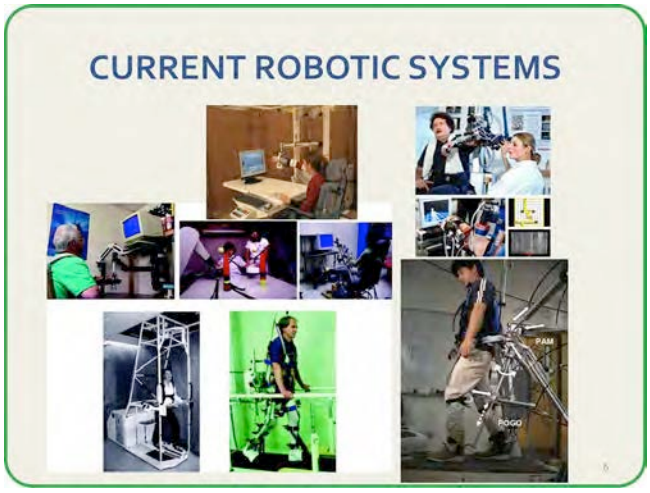


Figure 7.

Some of these devices have become quite widely used. For example, the Lokomat®. Although almost everybody has seen it in many hospitals, probably own it, Lokomat® was developed by Gary Colombo as an engineer in Balgrist Hospital in Zurich. It was developed as a form of gait training for people with a spinal cord injury. What motivated the development of the device was the need to do manual treadmill-based training of patients with incomplete spinal cord injury while they were suspended above a treadmill.

Therapists were increasingly reluctant to do this because it's very traumatic, it's tiring, and it takes a team of therapists to train somebody while they're walking on a treadmill. And not surprisingly, many therapists were unwilling to do it, and it's also very expensive to take three, four, or five therapists over a 45- or 60-minute training period to train people to walk on a treadmill.

There was also at the same time emerging information from basic science laboratories that this was a good way to restore oscillating neural function in the spinal cord of people with incomplete injury and so forth. And Gary, being an enterprising engineer, said these are physical interventions that a machine should be able to replicate, and that is indeed what they did. I'll show you that in a moment.

We at the Rehabilitation Institute of Chicago (RIC), together with other partners, have developed a machine which is perhaps an extension of the Lokomat®. This is an over-ground device that allows a therapist to work with gate restoration in patients with either spinal cord injury or stroke while not having to worry about their safety. And in keeping with the theme, I mentioned earlier, there is an elegant robot from The Netherlands called LOPES which is also a wonderful tool for retraining, and there are many, many more. These are just a small subset of the emerging numbers of robots throughout the world.

So this is the Lokomat® (Figure 8). As I said, the device was developed first in Balgrist and now is a product of a company in Zurich. There are more than 300 of these machines throughout the world, and they are widely used particularly in spinal cord injury. It is a powered exoskeleton in which there are motors at the hip and knee, and the person is suspended above the treadmill, and the treadmill speed can be also controlled. The amount of body weight that a person is supporting can also be controlled. And these are now widely used to augment body weight supported training for people with neurologic injuries.

We can also use on the Lokomat® with children (Figure 9) This has been a nice extension of Lokomat®, which was designed originally for adults. It's now been applied in children with a gait impairment and cerebral palsy. And it is finding a very enthusiastic support there as well.

This is the Dutch elegant device, which has some benefits by comparison with the Lokomat®. The Lokomat® stabilizes the spine and the back against the machine and doesn't allow free motion; whereas this machine, which is a powered exoskeleton, again working at the hip and knee, allows a great deal more freedom.

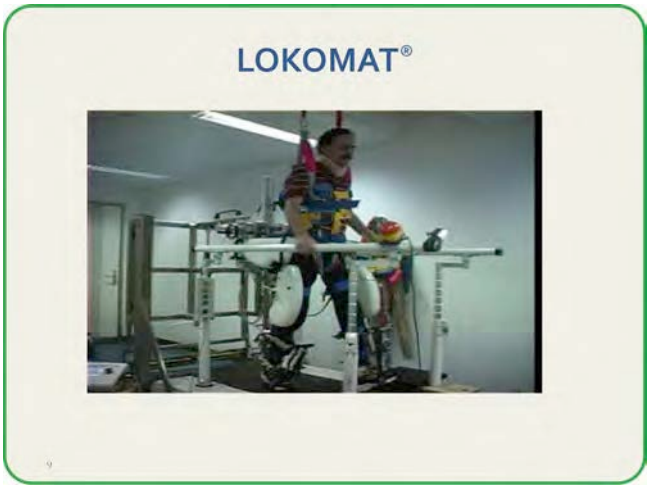


Figure 8.

Figure 9.

So these are now devices that have been entered into the rehabilitation care as devices to augment the therapist to be able to produce gait training effectively without requiring the manual labor that goes with the therapist involvement.

One of the problems with the Lokomat® is that it doesn't allow you to do normal movement because the spine is locked down and many of the natural aspects of motion, which include axial rotation, side-to-side motion, *et cetera*. None of those things are possible as part of the training protocol.

Colleagues at the RIC and at Northwestern University have developed this other device that allows a patient to be supported at the waist, and it can move freely over ground, as a therapist walks by and gives instructions about the appropriate guidance for walking (Figure 10). Because the therapist isn't consumed with concerns about falling, both patient and therapist can concentrate on key things about restoration of movement.

This is another view of the machine, which allows the therapist again to walk alongside, and we can see that the therapist is able to guide the patient quite securely without worrying about falls (Figure 11). So this, too, allows free motion. This is a machine that allows people to even try, for example, to sit down, to climb stairs, to turn, to do many kinds of activities that were impractical in some of the larger older devices.

There's been a similar development in upper extremity robotics (Figure 12). This is perhaps the best established machine. This is called a MIT Manus (IMT) (Figure 13). It is a planar machine, which allows a patient to grasp the handle and play video games on the screen. The arm can be supported if need be, and if the hand is very weak, it can be wrapped around the handle to allow the person to do simple games. The games can be escalated in complexity as the person's motor capacity improves. This machine is now widely used throughout the world. I don't know how many IMTs have been sold, but it's probably an estimated 200 to 250, and they have been used in a variety of clinical trials as well.

One of the issues about the use of this machine is that it is powered; therefore, it has motors, and with motors comes concern about risk and complexity and maintenance, things like that. So there's been a lot of focus on the development of alternative approaches that don't need motors that could use passive devices. And one of those was something that began at the RIC as a rubber band-supported device that had no motors on it. This has now been gone through several iterations of development, and it has become a commercial product called Armeo® (Figure 14).

This is a picture of the person working with Armeo® (Figure 15). The arm is supported by the springs. The person has a gripper that the computer can sense, and because the weight of the arm is supported, the computer games are rather easy for the person to follow. The person can practice the games for quite lengthy periods of time and improve his or her hand-eye coordination substantially. The device also can instruct the computer by virtue of sensors that are present at various places on the arm. So there is a great deal of information exchange between the impaired subject and the computer.

Figure 10.

Figure 11.

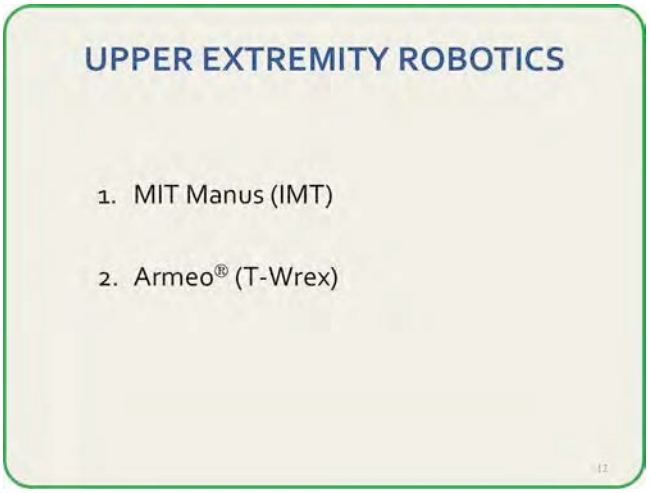


Figure 12

Figure 13.

Figure 14

Figure 15.

These devices have now been in existence in some form or another for more than 10 years, in some cases. There has been a steady flow of medium to small trials describing how well they work or, in some cases, how well they don't work. And it's clear that our expectations for many of these machines were perhaps a bit optimistic.

There have been a couple of rather sobering trials, at least summaries coming from two different agencies, the Veterans Administration and the Department of Defense (Figure 16). Together, they have said we should be cautious about the use of these devices, but their effects are still relatively limited and unproven. And similarly, there was an important article in *Stroke* summarizing the positions of the American Heart Association, which came to a similar conclusion: these devices are promising, they are very powerful to augment the capacity of the clinician, but they have not yet demonstrated themselves to be all that effective (Figure 17).

Nonetheless, given the constraints that exist on therapists, and financial constraints in our field, coupled with the enormous knowledge that's developing about neuroplasticity, it seems like robotics applications as a way to augment the therapist's interventions are here to stay. We just have to learn how to use them better.

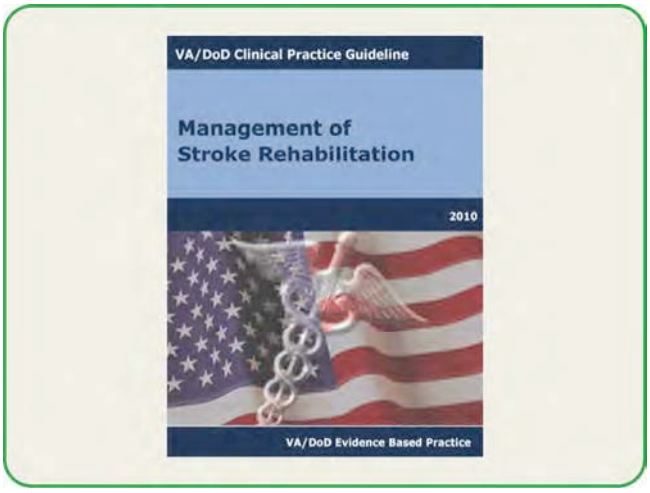


Figure 16.

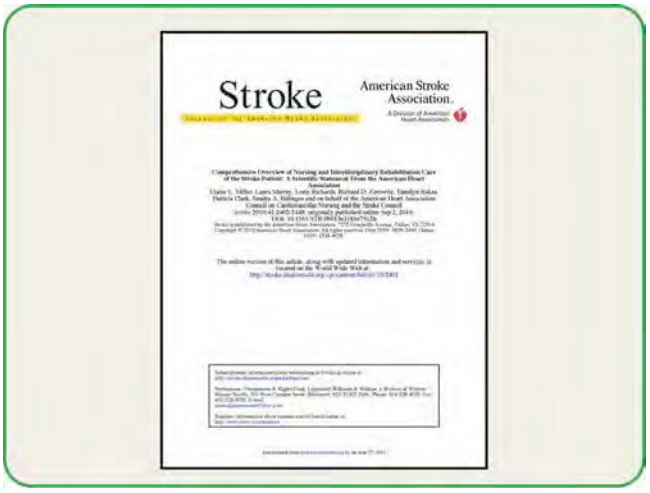


Figure 17.

Prosthetics

Another major area of advance is that of prosthetics (Figure 18). There has been, partly as a result of Defense Advanced Research Projects Agency (DARPA) interventions, a huge growth of new prosthetic devices, and in new control strategies. This is from my colleague here, Todd Kuiken, who has done elegant work in the development of novel prosthetic devices, especially with respect to controls (Figure 19).

One of the problems with the older history of prosthetic systems is our inability to control multiple joints simultaneously, and there have been a great number of studies trying to focus on developing more rational controllers that would replicate normal movement. One approach that was initiated by Todd was to take existing nerves that are in the proximal segment of an amputated limb and reimplant the nerves. In the case of the upper extremity, it's reimplanting them in the chest wall, and once the nerves reattach themselves to the muscles, we have the capacity to draw on electromyogram recordings to be able to produce a broad array of more natural control signals that are inherently intuitive in nature.

This is one of Todd's prime patients who had a bilateral trans-shoulder limb loss on both sides, and he has been able to use a state-of-the-art upper extremity prosthesis to produce more natural and fluid controls, far more natural than would have been possible without (Figure 20).

Another issue that has been a key focus has been the development or attempted development of ways to produce sensory feedback (Figure 21). One of the problems we have with artificial limbs, both upper and lower extremity, is that we don't have any obvious way to get sensory information back from the limbs. One advantage of having sensory information available on the chest wall that can be constructed as an extension of the renervation procedure is that we can take sensory input that's coming from the prosthetic device and feed it back onto the chest wall to give that person a perception of what's happening at the end of the prosthesis.

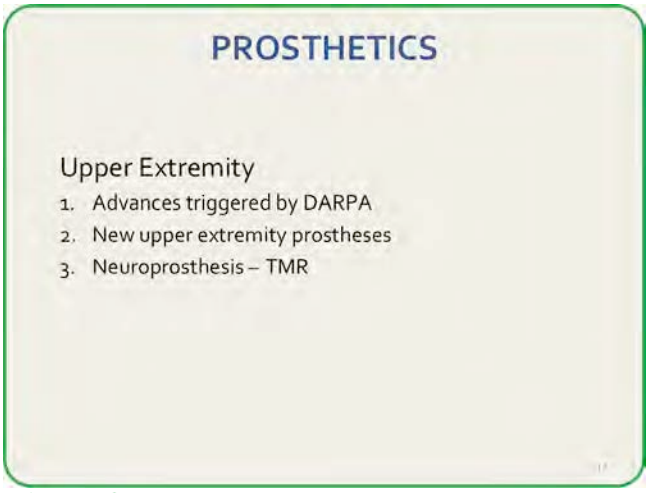


Figure 18.

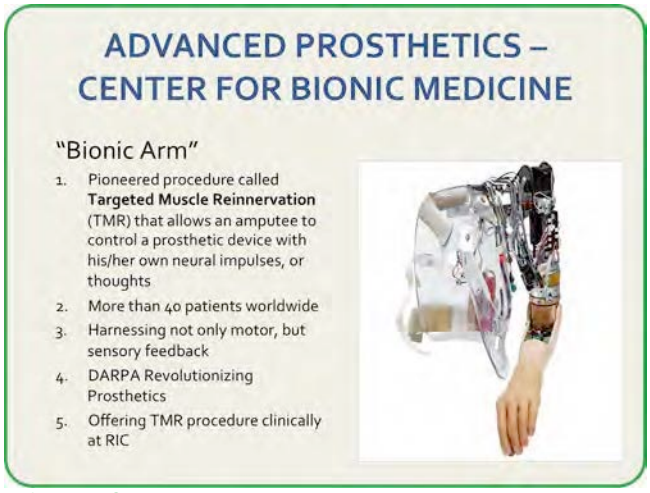


Figure 19.

Figure 20.

Figure 21.

Much of this field has now been sort of consolidated in this term, "bionics," which is a reflection of the sort of interface between engineering and electronics and our biology (Figure 22).

Brain-Machine Interfaces

Let me spend a couple of minutes on brain-machine interfaces (Figure 23). They have been hugely important from the standpoint of research opening up new possibilities about ways of replacing function in people with high spinal cord injury, locked-in syndrome, and so forth. We've had extraordinary progress in animal models, showing that primates can control devices using neural discharge collected with implanted electrodes. There has been cyberkinetics, and the BrainGate™ project, which showed that we could do similar things in humans, but one of our constraints is the relatively short-lived nature of the recordings that we can get from brain. So that has limited widespread application of these devices.

As a result, many of us have tried available sensory alternatives. In this case, our colleague (not a patient) has got recordings, wide objects on his shoulders (Figure 24). Cameras are being used to detect his arm motion, and the shoulder and head motion he can use to guide a wheelchair.

Electromyography

My final comment is about the wonderful development of new technologies in recordings—electromyography (Figure 25). I won't deal with imaging, but I have been working in the field of electromyography. We now have a spectacular array of different kinds of surface electrode grids that instead of giving us recordings at one or two sites, can now give us recordings over a whole muscle (Figure 26).

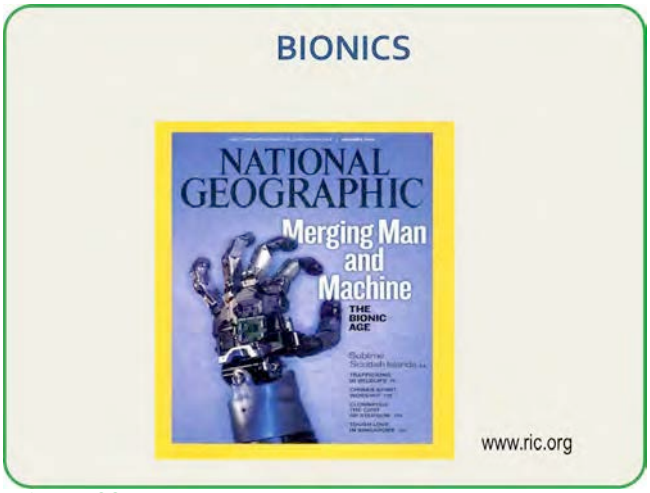
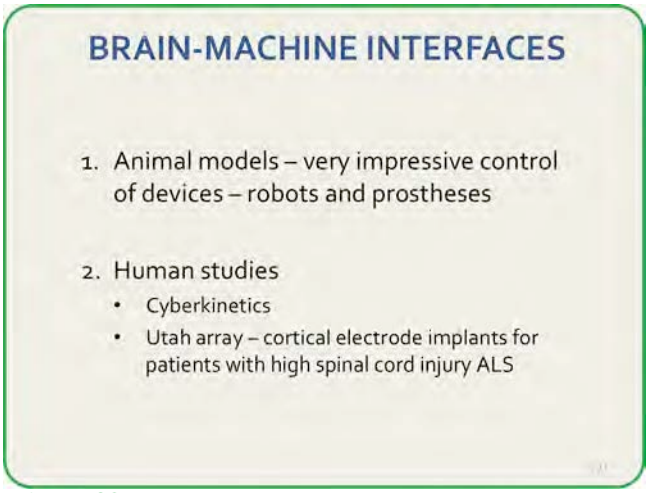


Figure 22.



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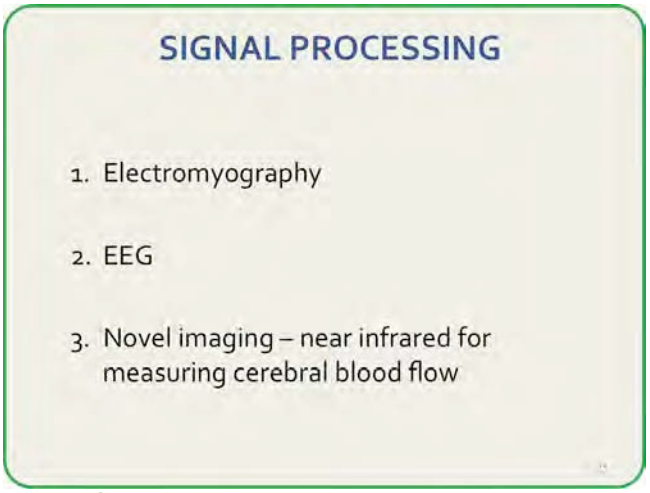

Figure 25.

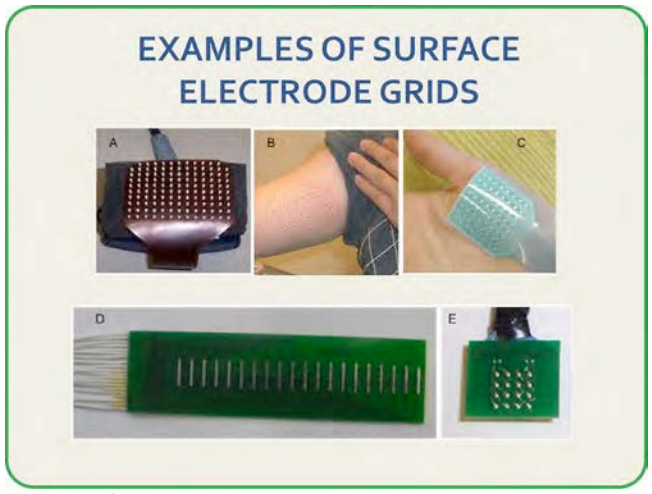

Figure 26.

And we can use that in a variety of ways, in patients, for example, with amyotrophic lateral sclerosis. We can get this rather scary picture of what's happening throughout the muscle. As many different motor neurons are dying, you see graphic evidence of the behavior of many, many muscle fibers spread all over the surface of the muscle, and that gives you a measure of the rapidity and the severity of the damage. We can also do things like figure out where the innervation point of a motor unit is by using the time delays that come as the conduction of the action potential travels down the adjacent muscle fibers (Figure 27). We can also look at how these things change in re-innervation and in disease.

Future Needs

So just to conclude, here are some things we need to think about in the next 20 years, and this is obviously an arbitrary list (Figure 28). One way in which engineering can help us is that our present outcome assessment tools in rehabilitation are still relatively crude, and given the engineering advances in sensors, mechanical measurements, and high level computing, we have much better ways now to quantify someone's performance. It's relatively easy to measure grip strength, speed of walking short distances, endurance, *et cetera*, so I think that progressively, we should be able to replace some of our more qualitative approaches with more quantitative methods.

I think we cannot do enough clinical trials to answer the questions that we must answer, so using information that we collect, some of it from sensors from both our inpatient and outpatient populations, is vital for us to make decent progress. I think in the field of prosthetics, we have beautiful elegant devices that we are hanging on soft tissues, and there are now worldwide efforts to integrate the prosthetic devices straight into bone. We've been able to do similar things in head and neck, and there is good progress on doing it in both upper and lower extremity, and I think that will be a huge advance if we can get there.

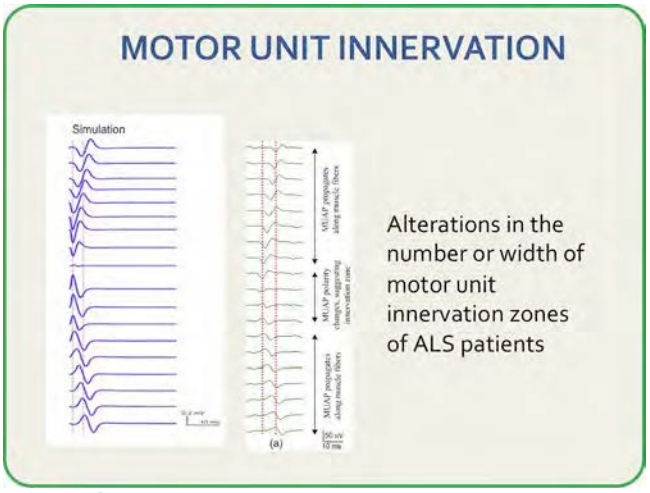

Figure 27.

Figure 28.

I think in the area of brain-machine interface and brain-computer interfaces, problems have been that the materials that we put in the brain don't last, at least they don't record very well for very long, and we need a new generation of materials and designs to deal with that.

And finally, in the area of robotics, robots are large, complex, and very expensive. They tend to cost hundreds of thousands of dollars, and that's not the way to go to meet light-scale population needs. So I think we are looking hopefully at a new generation of robotic devices.

This is one final illustration of what was previously called eLEGS (Figure 29). The company has renamed itself Ekso Bionics. It is a wearable robot that can help people with incomplete or complete spinal cord injury walk. It was developed by a company based in Berkeley, California. There are similar devices developed in Israel, and there's one in New Zealand, and so forth. So I think this is a new generation of devices to come, and I think that's an area that we will certainly see growth in years to come. Thank you.

Figure 29.

Advances in Patient-Reported Outcome Measures for Rehabilitation Science

Alan M. Jette, P.T., Ph.D.[15]

Professor of Health Policy and Management, Boston University School of Public Health
Boston, Massachusetts

I'm delighted to have been invited to this 20th anniversary NCMRR symposium and have the opportunity to spend a few minutes to talk about some of the outcome measurement research that we and others throughout the country have been working on. I must say I get very jealous when I listen to my colleagues talk about their more basic research with so many interesting animal models that they can bring to their presentations. For one of the first times in my career, I have a computer-adaptive testing (CAT) animal model that I am going to be talking about, and I'm really delighted about that because I can compete better with these other scientists.

I was delighted to hear previous speakers discuss the 1990 Hunt Valley Task Force. I had the privilege to co-chair with Dr. Bruce Gans, the Assessment and Epidemiology Panel on the Hunt Valley Task Force. It was an exciting time for rehabilitation science to come together with 100 scientists, clinicians, and consumer advocates interested in rehabilitation. Here we are 20 years later talking about how far we have come and where we are going in rehabilitation science.

Goals of This Presentation

What I would like to do today is highlight some of the recent innovations in patient-reported outcome (PRO) measurement during the past 2 decades. I want to give an illustration of the application of improved outcome metrics in rehabilitation as it applies to an increasingly important area of research, comparative effectiveness research (Figure 1).

Boston University has the pleasure of hosting one of the NCMRR's R24 Medical Rehabilitation Research Infrastructure Networks. Ours is called the Boston Rehabilitation Outcomes Measurement Center (Boston ROC) and is a collaboration among three Boston academic institutions (Figure 2). The Boston ROC is hosted by Boston University's School of Public Health, where one research core directed by Dr. Wendy Coster is on PROs and clinician-reported outcome assessment tools. The second core is based at Tufts University, where Dr. Roger Fielding leads a group that includes Dr. Jonathan Bean from Spaulding Rehabilitation Hospital, which is focused on performance-based outcome measures. And our third research core, based at Spalding Rehabilitation Hospital and headed up by Dr. Paolo Bonato, focuses on instrumented outcome measures. Those are the three research foci of the Boston ROC R24 network. For those of you who might be interested in the work that we are doing and the services and support that we can offer rehabilitation researchers, our website is http://www.bu.edu/bostonroc.

Advances in PRO Measurement

The 2 decades since the founding of the NCMRR have been transformative in the research advances we have seen in the development and refinement of PRO measurement (Figure 3). In part, I think this transformation has corresponded with the shift in emphasis from acute to more chronic conditions in our population and in our research. Research as well as clinical endpoints, such as pain, disability, and quality of life, have become more subjective, and these more complex patient outcomes are more difficult and challenging to measure.

The psychometrics of outcome measurement during the past decades have improved greatly. There has been a tremendous amount of research in trying to improve outcome measures in rehabilitation science.

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[15] Dr. Jette founded a small business in 1995 (CREcare, LLC) to help disseminate and support individuals who use PROs, and he holds founder's stock in that company.

Figure 1.

Figure 2.

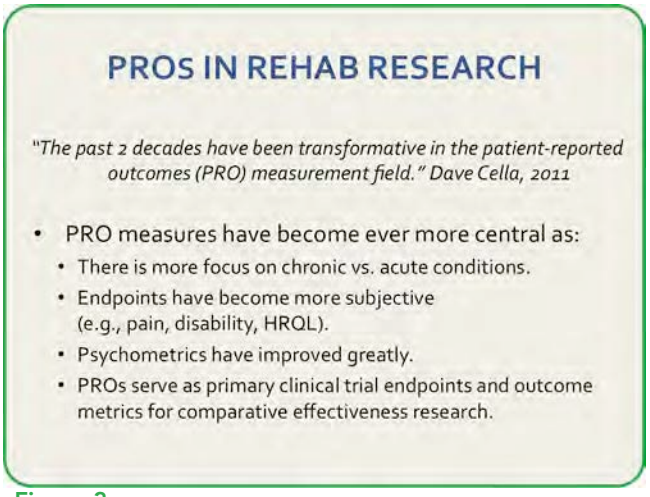

Figure 3.

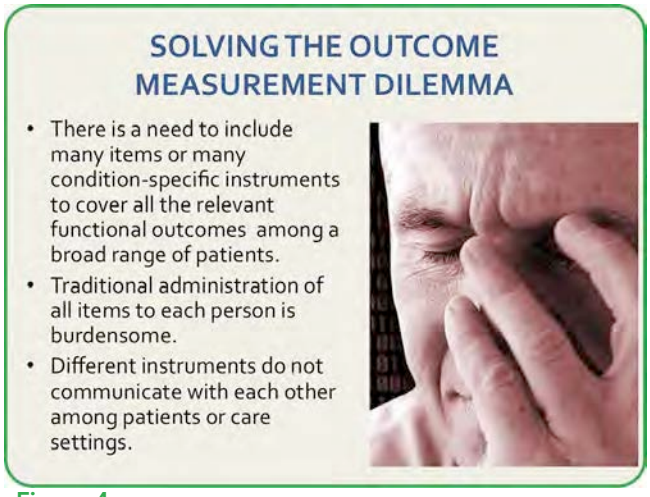

Figure 4.

The NIH and other federal agencies such as the National Institute on Disability and Rehabilitation Research (NIDRR) have been in the forefront in supporting this critical foundational research that will enable us to do a lot of other important applied research. I want to really applaud this emphasis in funding research to improve PRO measurement that the NCMRR has supported during the past 2 decades.

PROs are beginning to be seen as primary clinical trial endpoints in rehabilitation trials, and outcome metrics are increasingly being used in comparative effectiveness research (Figure 4). I think we are going to see more of that in the coming years. Researchers have traditionally faced a dilemma in measuring important clinical outcomes—those that are most relevant to the patient. There has been a need to include many items in our outcome measures and/or include many different outcome instruments as researchers tried to cover all the relevant functional outcomes that apply to a broad range of rehabilitation patients. It has been very difficult to develop PRO instruments that are psychometrically adequate for rehabilitation science yet practical to use in our research.

Using classical measurement techniques, the administration of multiple items and multiple instruments has become quite burdensome to patients and costly to researchers. To compound the problem, what has happened in rehabilitation is that historically, there has been the development of many different tools—none of which communicate with each other. This makes it extremely difficult if one wants to begin to look at what is happening to patients across entire episodes of care or to make comparisons among patients with different clinical conditions.

As our health care system continues to be transformed, emphasis is being shifted from questions within a site of care to questions about the episode of care being provided to our patients. Outcome instruments need to match these emerging health policy questions. So this has created a dilemma. You can achieve

comprehensiveness of outcome measurement using classical approaches to assessing important patient outcomes, but usually at the cost of making them very burdensome, and not very feasible for widespread use and application in rehabilitation research.

Item Response Theory Methodology and Computer-Adaptive Testing (CAT)

There have been two innovations in PRO research that I want to focus on that I think have set the stage for some transformative outcome measurement improvements. They are the Item Response Theory (IRT) methodology and CAT (Figure 5).

The innovation that I think has been the most impactful and really has been a breakthrough technology is CAT (Figure 6). Many of you may be familiar with CAT—my animal model. CATs have been used for decades in the education field and, during the past decade, these methods have been adopted for use in the health field. CATs are increasingly used to develop not only psychometrically adequate PRO instruments, but are feasible for widespread use and application. CATs are highly efficient measurement methods because, even though there is a comprehensive detailed item bank that you can draw upon to assess a patient, the technology allows you to administer a small number of items from the underlying pool for any particular patient you are assessing. Many of the PRO instruments we have developed contain over 100 items, yet we are able to achieve an accurate and precise assessment using five to ten of those items from the underlying pool.

CAT methodology is a very simple form of artificial intelligence where algorithms select the best items to assess in each patient using an iterative process. Items that are administered by a CAT are chosen based on how a person responds to the previous items. So you very quickly can hone in on an estimate of where that individual is on a particular outcome dimension. Testing stops when the person's outcome level has been estimated to the level of precision that you desire. The big payoff is that without loss of accuracy or precision you can minimize the cost of collecting information that is relevant for patient outcomes, thus reducing measurement burden on the individuals who are engaged in the assessment.

The science underlying CAT is IRT, or Item Response Theory measurement (Figure 7). Basically it is a technique that is used to develop assessment item pools selected to cover the entire continuum of an outcome, from very low to very high ability. What is illustrated on this slide is a scale we developed to measure basic mobility functioning. As you can see, there are assessment items that cover very low mobility function (e.g., turning over in bed), to very high functioning (e.g., running 5 miles).

The IRT methodology is used to develop extensive item pools and resultant scales that form the foundation of CAT assessment. Items in a particular item pool provide unique information about the outcome along the continuum from very low to very high ability on a particular outcome dimension. Using IRT methods, one is able to calibrate a quantitative score of where a person is on the entire outcome continuum. So it derives an interval score estimate on a logit scale, thus moving the assessment out of the realm of ordinal assessment into quantitative outcome assessment.

Since 2002, the NIH has heavily invested in the development of CAT health-related quality-of-life instruments through its Roadmap initiative (Figure 8). Its most visible initiative has been the Patient-Reported Outcome Measurement Information System—the PROMIS initiative. It has been invested in by multiple NIH Institutes and Centers including the NCMRR. PROMIS investigators have developed a large number of item banks that are being designed for CAT assessment within NIH-funded research, where PROs are the outcomes of interest. PROMIS assessment batteries are highly efficient, psychometrically robust, and have created publically available item repositories and CAT platforms through the PROMIS Assessment Center that can be readily downloaded and available to researchers.

Figure 5.

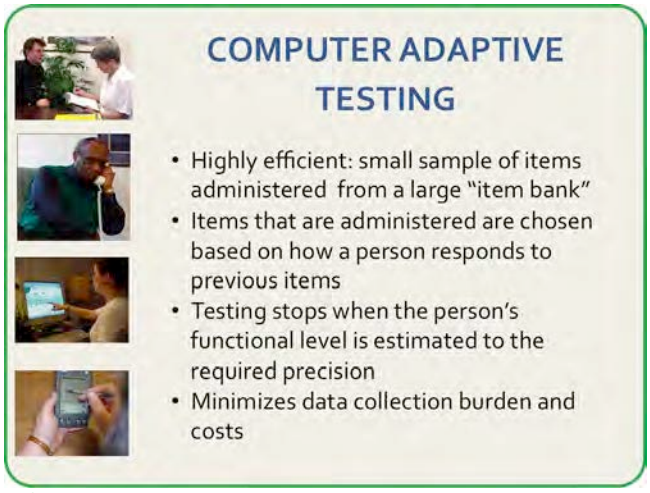

Figure 6.

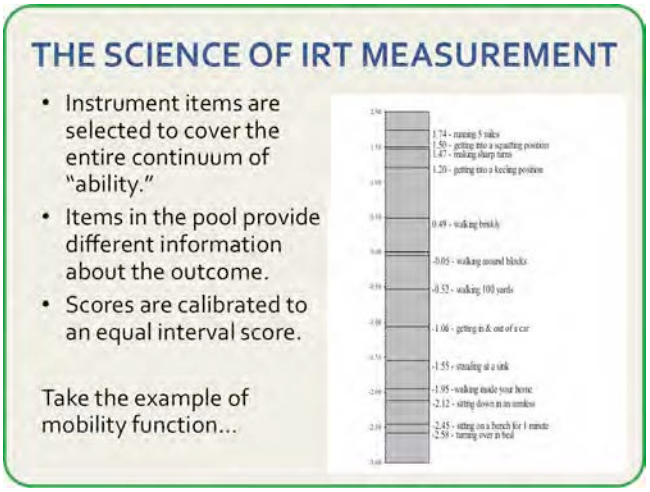

Figure 7.

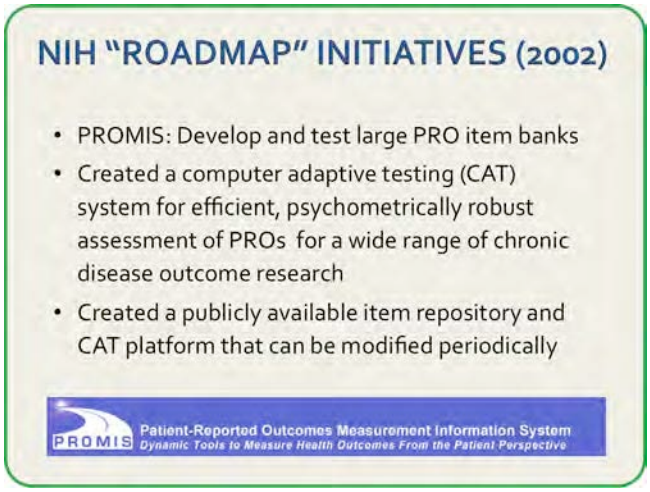

Figure 8.

Applications of IRT/CAT Outcome Metrics

What I want to describe now is one application of CAT to show some of the possibilities of this type of assessment for rehabilitation research (Figure 9). The project that I'm going to talk about is an initiative that we have been collaborating on with Dr. Leighton Chan and colleagues at the NIH Clinical Center's Department of Rehabilitation Medicine, and with Dr. Elizabeth Sandel and colleagues at Kaiser Permanente of Northern California. The Kaiser Stroke Outcome Study was supported by a seed grant from the NIH Intramural Branch and an American Recovery and Reinvestment Act grant from the NIH National Institute of Neurological Disorders and Stroke (NINDS). This is an example of rehabilitation comparative effectiveness research.

One of the clinical and policy challenges in stroke rehabilitation is that following discharge from acute hospital care, post-acute care (PAC) can occur in a variety of different settings (Figure 10). Patients can go to an inpatient rehabilitation center (IRF), a skilled-nursing facility (SNF), home with home health services (HHS), home with outpatient services (OPT), or they can go home with no formal services at all. There are tremendous cost differences across PAC settings that provide rehabilitation services for the same underlying condition, and there is considerable policy debate over the relative effectiveness of PAC provided in these different settings. For example, is it worth the investment in IRF care compared with less costly PAC alternatives? Should we be putting more resources into HHS and OPT and move away from institutional-based care? From a policy perspective, little is known about which PAC settings provide the most effective care, which calls for additional comparative effectiveness research.

Figure 9.

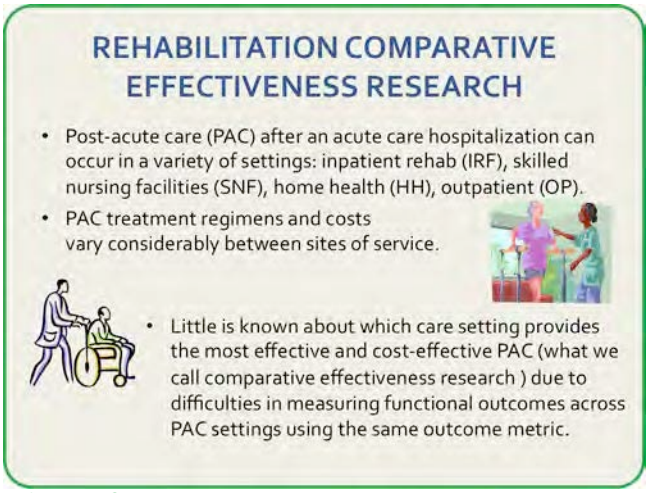

Figure 10.

One of the challenges in conducting comparative effectiveness research in PAC is that most outcome instruments used have been designed for use in one PAC setting. These tools are not designed on the same outcome metric, thus making it difficult if not impossible to track and compare outcomes across an entire episode of PAC. For instance, the traditional outcome instrument used in IRF settings, the functional independence measure (FIM™), does not communicate with the mandated instrument used to assess outcomes in SNFs, the minimum dataset (MDS), and neither can communicate with the HHS assessment tool called OASIS. Site-specific assessment instruments have created barriers to our ability to conduct comparative effectiveness research in PAC. In contrast to these setting-specific instruments, the CAT approach to assessing functional outcomes provides an opportunity to break through that barrier by providing a common outcome metric that can be used across PAC settings.

In the Kaiser Stroke Outcome Study, our initial sample consisted of 222 adults who had either an acute ischemic or hemorrhagic stroke, recruited at the point of discharge from one of four different Kaiser acute care hospitals (Figure 11). We did baseline functional assessment at acute hospital discharge and 6 months later, regardless of the setting where they received their post-acute care using the same functional outcome metric. One of our hypotheses was that IRF care would enhance 6-month functional recovery trajectories for patients following a stroke compared with those who went to other PAC settings.

The PRO measurement metric used was the Activity Measure for PAC (AM-PAC), developed at the Health and Disability Research Institute at Boston University (Figure 12). The AM-PAC was designed and validated as a functional outcome metric that can be used across different PAC settings. The AM-PAC assesses function in three distinct domains: basic mobility function, daily activity functioning, and applied cognitive functioning. Each of the AM-PAC scales takes 2 to 3 minutes to administer using CAT techniques. It can be patient-, family member-, or clinician-proxy reported. We recently published an article in *Stroke* that reported the concordance between patient report, clinician report, and family report using the AM-PAC instrument. A four-point change on the standardized scale has been determined to be clinically significant.

In the Kaiser Stroke Outcome Study, we observed 25 potential combinations of post-acute care trajectories. But for our initial analyses, we collapsed them into four groups (Figure 13). We wanted to isolate those who went into an IRF, from those who went to SNF without IRF, from those who went to HHS or OPT without IRF or SNF, and then those who went home with no stroke-related rehabilitation services at all. While we recognize this doesn't capture the full trajectory and the full richness of post-acute care that occurred, because of sample size limitations, we focused on these four trajectories of PAC. As we expand the sample size in the study, we hope to look at other combinations.

We conducted chi-square tests, t-tests, and analyses of variance (ANOVAS) to examine differences in sample characteristics and adjusted for those across the PAC groups (Figure 14). We did multivariate analyses to examine differences in the 6-month functional outcomes across PAC groups controlling for baseline function and various other factors.

KAISER STROKE OUTCOME STUDY

- Kaiser Permanente of Northern California
- Sample = 222 people with acute ischemic and hemorrhagic stroke recruited from four Kaiser hospitals
- Baseline functional assessment at acute hospital discharge and at 6-month follow-up ***using the same functional outcome metric***
- Hypothesis: IRF care would enhance 6-month functional recovery trajectory compared with other PAC settings

Chan L. et al: Kaiser Stroke Outcome Study, presented at ACRM, Oct. 2011.

Figure 11.

MEASUREMENT METRIC: AM-PAC

Activity Measure for Post-Acute Care (AM-PAC)

- Assesses three functional domains: basic mobility, daily activity, and applied cognitive.
- Takes 2 to 3 minutes per domain to administer.
- Can be patient, family member, or clinician proxy reported.
- A 4-point change is clinically significant across all domains.

NIH: R01HD043568; K02HD045354; RC1NS068397; **NIDRR** H133B100003

Figure 12.

STATISTICAL METHODS

- 25 potential combinations of PAC trajectories were collapsed into 4 groups:
  - Any inpatient rehabilitation facility (IRF)
  - Any skilled nursing facility (SNF) without IRF
  - Home health (HH) or outpatient (OP) services (without IRF or SNF)
  - Home with no stroke-related services
- Chi-square tests, t-tests, or ANOVAs were used to examine differences in sample characteristics across PAC groups.
- Multivariate linear regression analyses were used to examine differences in 6-month functioning across PAC setting.
- Controlled for baseline function, BMI, modified Rankin score or previous history of stroke, modified Charlson Index, readmission status, and total hours of PAC treatment.

Figure 13.

	Any IRF (n=66)	Any SNF w/o IRF (n=29)	HH and/or OP (n=48)	Home, no PAC (n=9)	p value
Age (years ± sd)	67 ± 14.0	79 ± 10.2	69 ± 11.2	67 ± 12.2	<0.0001
Gender % Male	50	41.1	60.4	58.2	0.3019
Race/Ethnicity % White	60.6	79.3	72.9	64.6	0.7683
Living Alone (%)	19.7	37.9	14.6	17.7	0.0755
Education % ≤ High School	36.4	48.3	25.0	26.6	0.1572
Family Income % < $49,999	30.3	44.8	25.0	39.2	0.0982

Figure 14.

This slide shows background characteristics of the sample by PAC setting at acute hospital discharge and some of their clinical characteristics (Figure 15). The next three slides illustrate the basic unadjusted findings by PAC group (Figures 16-18). The data in this slide illustrate that baseline functioning was clearly different across PAC groups and show their 6-month functional status. What these unadjusted data show for basic mobility, daily activity, and applied cognitive functioning are fairly similar rates of improvement for those who went to SNF versus HHS, or home without any services, but a greater functional recovery trajectory for those who went to IRF settings. For applied cognitive functioning, patients were more similar at baseline across the four PAC groups as compared with basic mobility and daily activity functioning. When we examined the unadjusted acute to 6-month scores for IRF, HHS, or OPT, or home with no treatment, all domains seemed to improve, but the IRF setting patients improved to a greater degree.

When we did our adjusted analyses, we observed that patients with stroke who went to an SNF had lower functional recovery in all three functional domains at 6 months compared with those who went to other PAC sites. The differences exceeded the four-point Minimal Clinically Important Differences (MCIDs) for each of the AM-PAC scales and persisted even after we controlled for total hours of therapy in the 6-month period.

	Any IRF (n=66)	Any SNF w/o IRF (n=29)	HH and/or OP (n=48)	Home, no PAC (n-=9)	p value
Stroke :					
% Ischemic	86.4	89.7	95.8	92.4	0.304
% Hemorrhagic	13.6	10.3	4.2	7.6	
Modified NIH Stroke Scale Score (x; sd)	6.0 ± 4.5	4.2 ± 3.4	2.6 ± 2.8	1.5 ± 2.0	<0.0001
Modified Rankin Scale Score (x, sd)	.05 ± .09	.09 ± 1.2	0.5 ± 1.0	0.2 ± 0.5	0.0013

Figure 15.

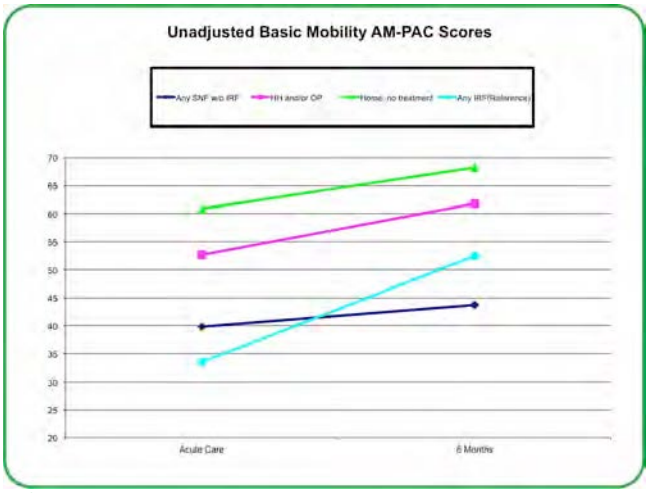

Figure 16.

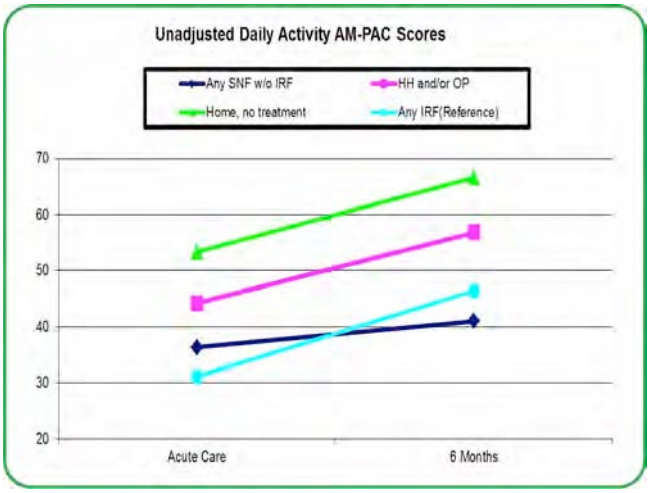

Figure 17.

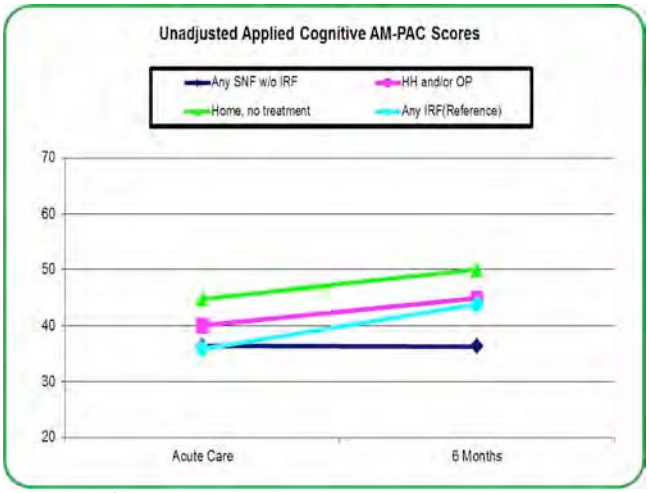

Figure 18.

Going Forward With IRT/CAT Outcome Metrics

The findings from the Kaiser Stroke Outcome Study are clearly preliminary but provide an example of the kinds of comparative effectiveness research questions that can be tested with IRT/CAT outcome metrics (Figure 19). Research that illuminates the most effective and most cost-effective rehabilitation strategies is becoming an increasingly important area of policy research (Figure 20). NIH's investments during the past 2 decades in the development of better functional outcome metrics is beginning to yield important dividends as these tools begin to be used in rehabilitation research. The NCMRR has played an important leadership role in this regard. Comparative effectiveness research in rehabilitation science has important relevance for the quality of life of Americans, and is going to help guide future health policy decisions for our country.

Thank you.

Figure 19.

Figure 20.

Secondary Data Analysis and Large Database Research in Medical Rehabilitation

Kenneth J. Ottenbacher, Ph.D., O.T.R.

Professor and Director, Division of Rehabilitation Science, and Director, Center for Rehabilitation Research using Large Datasets, University of Texas Medical Branch Galveston, Texas

I would like to begin by thanking the Foundation for the NIH for celebrating and hosting the 20th anniversary of the establishment of the NCMRR. I would also like to thank the multiple sponsors and professional associations that contributed to the celebration and made today's scientific seminar possible. Finally, I wish to thank the administrative and professional staff of the NCMRR, not just for the work they have done in organizing this event, but for their contributions and guidance in the advancement of rehabilitation science as well.

Over the past 20 years, the NCMRR has supported and encouraged rehabilitation research from molecules to populations. The speakers and topics presented in this 20th anniversary symposium are evidence of the scientific diversity represented in NCMRR's scholarly successes. This morning, Dr. Hoffman discussed exciting developments in the field of "-omics." He highlighted the remarkable advances in genomics and proteomics associated with rehabilitation research. This afternoon, I would like to discuss the other end of the continuum—epidemiologic and population-based rehabilitation research using large datasets. I will briefly review the need for large data studies and then describe some of the challenges and opportunities facing investigators in planning or conducting research in disability and rehabilitation using large datasets.

In describing large datasets, I am referring to existing data that have been collected across a variety of settings, institutions, or people. The datasets have been created for a variety of purposes, not just for research. The U.S. Census is an example of a very large national dataset designed to address planning and program functions, primarily associated with the federal government. Research using large datasets is often referred to as "secondary" data analysis because the questions addressed are frequently not the primary questions the original data were collected to answer. For instance, the Centers for Medicare and Medicaid Services (CMS) collect a large amount of health-related information focusing primarily on persons 65 years of age and older. This information is collected for administrative purposes to determine costs and reimbursement for providing health care in programs such as Medicare. The information available in the CMS files, however, is also a valuable resource for examining a range of health-related research questions and for studying health and (potentially rehabilitation) outcomes among a large and diverse population (Figure 1).

Figure 1.

The Need for Large Database Research in Rehabilitation

The development and adoption of evidence-based practice has highlighted the need for research evidence to guide decision making for individual patients. The original definition of evidence-based medicine states

that, "Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[16]

There is also a need in the field of medical rehabilitation for "population-based" evidence (Figure 2). This includes evidence that can provide direction for programs and services designed to improve population health (Figure 3). We know, for example, that hypertension screening and control is particularly important in the African American population. African Americans have an elevated incidence of high blood pressure, and they are also at increased risk for hemorrhagic strokes, which are associated with greater morbidity and mortality.[17] Research to develop strategies and programs to reduce these risks at the population level is important in improving public health and preventing disability (Figures 4-5).

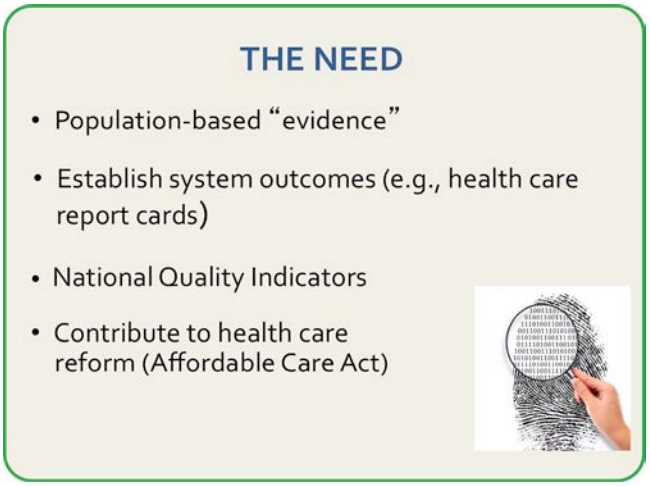

Figure 2.

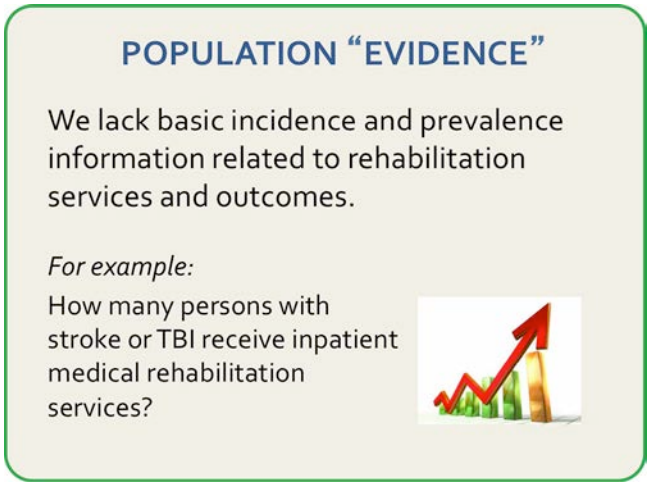

Figure 3.

Figure 4.

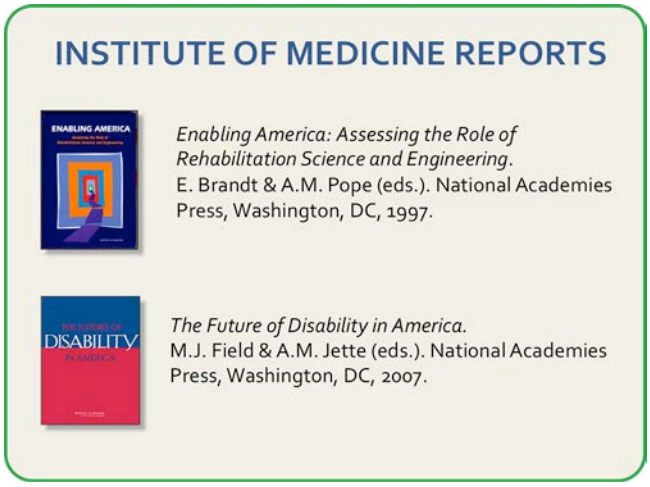

Figure 5.

[16] Sackett, D. L., Straus, S., Richardson, S., Rosenberg, W., & Haynes, R. B. (2000). *Evidence-based medicine: How to practice and teach EBM*. 2nd ed. Edinburgh, UK: Churchill Livingstone.

[17] American Heart Association. (2010). Heart disease and stroke statistics—2010 update: A report from the American Heart Association. *Circulation, 121*:e46-e215. Retreived on November 12, 2012, from http://circ.ahajournals.org/content/121/7/e46.extract.

Secondary analysis of large datasets also contributes to identifying and understanding outcomes for health systems. Well-known examples include the health report cards produced by the CMS. These include Medicare Nursing Home Compare, Home Health Compare, and Hospital Compare (Figure 6). Information and websites for these health report cards are available at the CMS webpage: http://www.medicare.gov/default.aspx.

The websites provide aggregate data at the national and state level that can be compared with similar information from individual facilities. The table below shows the outcome variables used for Home Health Compare using a hypothetical home health agency (Figure 7).

Figure 6.

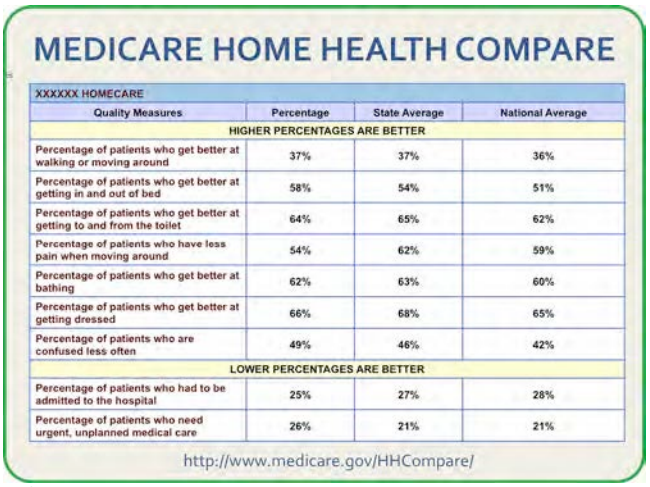

Figure 7.

There is no similar health report card system for Inpatient Rehabilitation Facilities (IRFs). With the increasing emphasis on accountability and consumer choice associated with health care reform, it is inevitable that such a system will be created. The analyses of large health-related datasets by rehabilitation investigators will help ensure the accuracy and usefulness of a future IRF compare health report card.

The development of national quality indicators is another area where the analysis of large datasets has an important role to play (Figures 8-9). National quality indicators are an important aspect of health care reform and have been developed for acute care settings.[18] Attention is shifting toward the development of national quality indicators for post-acute care and, specifically, for inpatient medical rehabilitation (Figure 10). In the August 5, 2011, *Federal Register* (volume 76[15]), CMS identified the first two government-sponsored quality indicators for IRFs. They are incidence of new pressure ulcers and catheter-related urinary tract infections. A third indicator has been proposed, but not yet approved by CMS: hospital readmission within 30 days of discharge from an IRF (Figure 11). Thirty-day hospital readmission has been identified as a quality indictor for acute care hospitals for specific diagnosis-related groups (DRGs)—e.g., heart attack, heart failure, pneumonia.[19]

[18] National Quality Forum. (2010). Hospital care: Outcomes & efficiency measures Phase I. Retrieved on November 12, 2012, from http://www.qualityforum.org/projects/hospital_outcomes-and-efficiency_I.aspx.aspx.

[19] Jha, A. K., Orav, E. J., & Epstein, A. M. (2009). Public reporting of discharge planning and rates of readmissions. *New England Journal of Medicine, 361*(27), 2637-2645.

Figure 8.

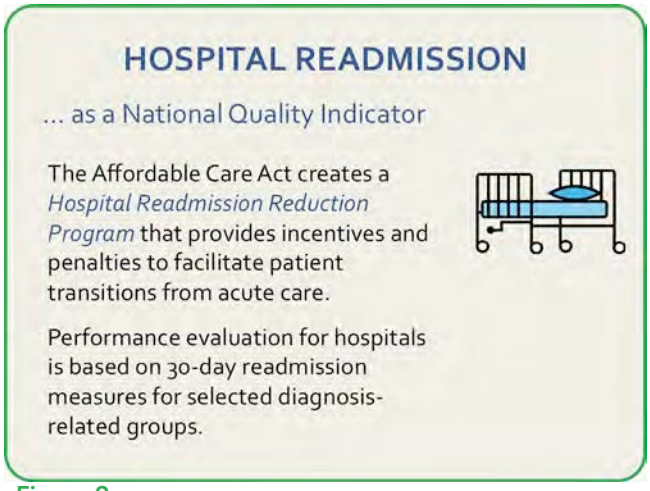

Figure 9.

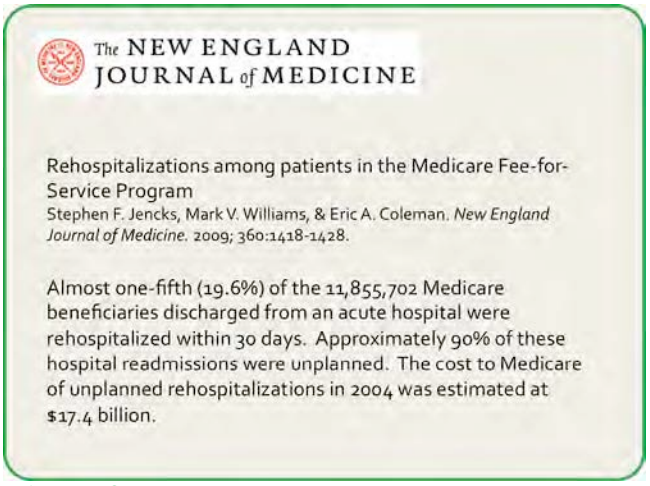

Figure 10.

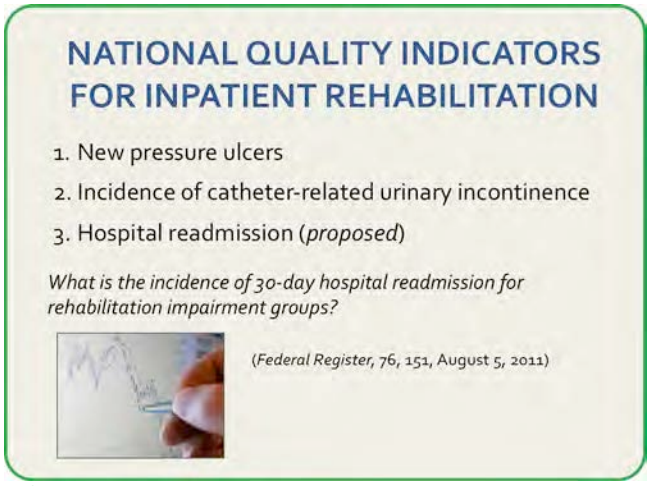

Figure 11.

To use hospital readmission as a quality indicator for inpatient medical rehabilitation, we need risk-standardized readmission rates for selected impairment groups (Figure 12). One variable required to compute risk-standardized readmission rates is the national readmission rate for the impairment group. Analyses of large datasets, such as the IRF-Patient Assessment Instrument CMS file, can help provide this information. The chart below shows the 30-day hospital readmission rates for persons with stroke, hip fracture, traumatic brain injury (TBI), and lower extremity joint replacement discharged from inpatient rehabilitation facilities from 2006 through 2008 (Figure 13). These preliminary data include persons readmitted to acute care hospitals following discharge to the community or directly from an IRF (Figure 14).

These data were collected using the CMS files and includes over 167,000 persons receiving inpatient medical rehabilitation. The ability to manage, analyze, and interpret large datasets (e.g., Medicare files) allows rehabilitation investigators to be active participants in the process of developing health report cards and national quality indicators for post-acute care, including inpatient medical rehabilitation.

Figure 12.

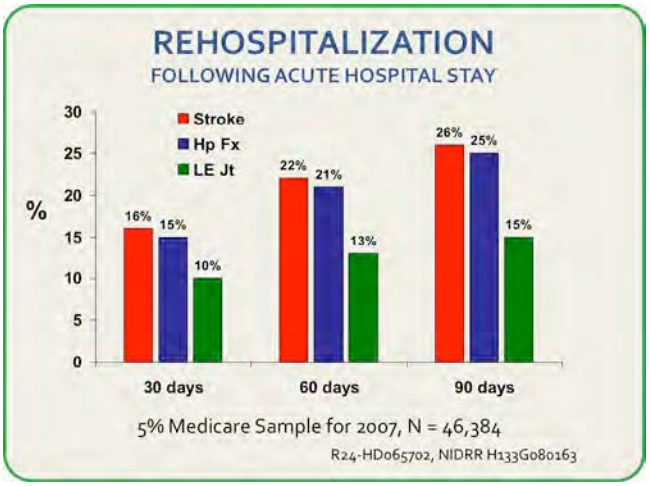

Figure 13.

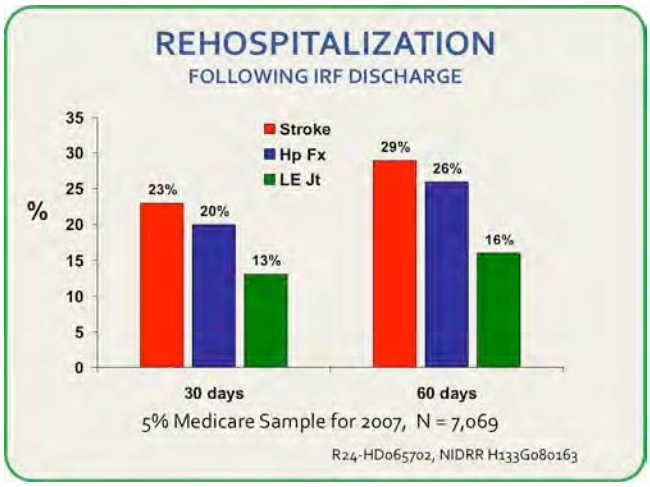

Figure 14.

The need for large population-based, epidemiological research to assist in strategic planning and the management of services and research in rehabilitation and disability has been identified as important by experts both within and outside of the field. For example, the widely cited Institute of Medicine (IOM) report *Disability in America* includes a recommendation specifically stating the need for research to establish a national surveillance system to monitor the incidence and prevalence of disability in the United States.[20] The need for this basic population-based information to help manage and monitor rehabilitation and disability outcomes has been repeated in two subsequent IOM reports.[21] This recommendation, along with others in the IOM reports, have not been acted upon or implemented at the federal, regional, or state levels. The lack of national statistics regarding rehabilitation service delivery and outcomes makes it difficult to plan and manage resources effectively, and to identify priorities and allocate funding for research and related activities. For example, in the United States we do not have accurate or reliable information for basic health system outcomes, such as how many persons with stroke or TBI receive inpatient medical rehabilitation services.

[20] Pope, A. M., & Tralov, A.R. (1991). *Disability in America: Toward a national agenda for prevention.* Washington, DC: National Academies Press.

[21] Brandt, E. M., & Pope, A. (1997). Enabling America: Assessing the role of rehabilitation science and engineering. Washington, DC: National Academy Press; Field, M. J., & Jette, A. M. (2007). *The future of disability in America.* Washington, DC: National Academies Press.

The Challenges and Opportunities in Large Dataset Research

A primary challenge in generating research to address health system outcomes and national benchmarks is the lack of research capacity (Figure 15). In their research education and graduate course work, rehabilitation investigators are trained to conduct patient-oriented clinical research. The focus on prospective clinical research is appropriate for scientific training in the rehabilitation professions. These are fields where the emphasis is on research designed to improve the functional performance and independence of persons with disabilities. Research studies are typically conducted in clinical and community settings and involve primary data collection from persons with disabilities and their family members or caregivers.

The emphasis on accountability, outcome-based accreditation, pay for performance, and the recent developments related to health care reform have created the demand for, and opportunity to expand, rehabilitation research (Figure 16). This expansion includes addressing questions that can only be answered with information from large national surveys or administrative datasets. There are vast numbers of datasets available for examination by rehabilitation investigators with the experience and skills to conduct secondary data analysis. Many of these datasets are supported or maintained by federal, state, and local agencies (Figures 17-18). A few examples of datasets with information relevant to investigators interested in rehabilitation and disability include:

1. The American Community Survey (ACS) is an ongoing survey that occurs every year and is conducted by the U.S. Census Bureau. The survey is designed to provide communities with information they need to plan programs and coordinate resources. The ACS includes questions focused on disability and disability-related services. The data are available for public use (http://www.census.gov/acs/www/).
2. The National Health Interview Survey (NHIS) has monitored the health of the nation since 1957. The NHIS includes data on a broad range of health topics collected through personal household interviews. The NHIS is managed by the National Center for Health Statistics, which is part of the Centers for Disease Control and Prevention. Survey results provide data to track health status, health care access, and progress toward achieving national health objectives. The data are available for public use (http://www.cdc.gov/nchs/nhis.htm).
3. The Medical Expenditure Panel Survey (MEPS), which began in 1996, is a set of large-scale surveys of families and individuals, their medical providers (doctors, hospitals, pharmacies, *et cetera*), and employers across the United States. The MEPS collects data on the specific health services that Americans use, how frequently they use them, the cost of these services, and how they are paid for. The MEPS survey and data are supported by the Agency for Healthcare Research and Quality. The data are available for public use (http://www.meps.ahrq.gov/mepsweb/).
4. The Uniform Data System for Medical Rehabilitation (UDSMR) is the largest nongovernmental dataset of rehabilitation outcome information in the United States. Founded in 1987, the UDSMR collects outcome information for rehabilitation facilities including patient characteristics, sociodemographic and facility factors, and change in functional status. Functional status is collected using the functional independence measure (FIM™ Instrument), which includes performance in areas of basic daily living such as eating, dressing, toileting, personal mobility, and basic cognitive function. The UDSMR is a proprietary dataset and requires permission and a data use agreement to access the information (http://www.udsmr.org/Default.aspx).
5. The National Institute on Disability and Rehabilitation Research (NIDRR) funds a series of Model Systems Centers in TBI, spinal cord injury (SCI), and burns. These centers collect patient, facility, and family information and include annual follow-ups. The NIDRR Model Systems datasets are managed by coordinating centers for each of the disability focus areas (TBI, SCI, and burns). Access to the NIDRR Model Systems datasets is managed through the coordinating centers. For an example, see https://www.tbindsc.org/.

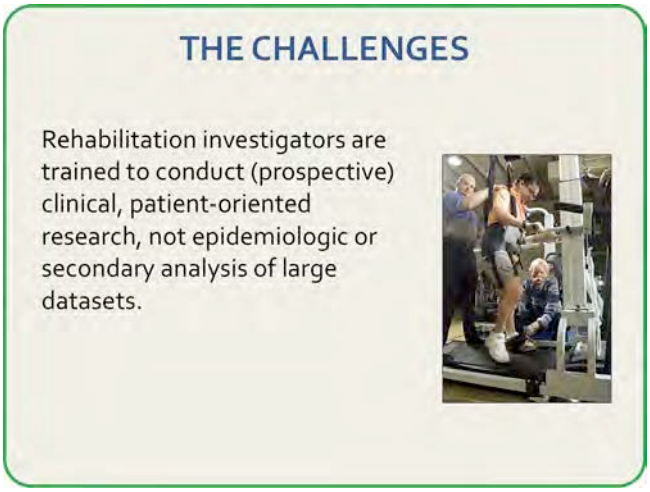

Figure 15.

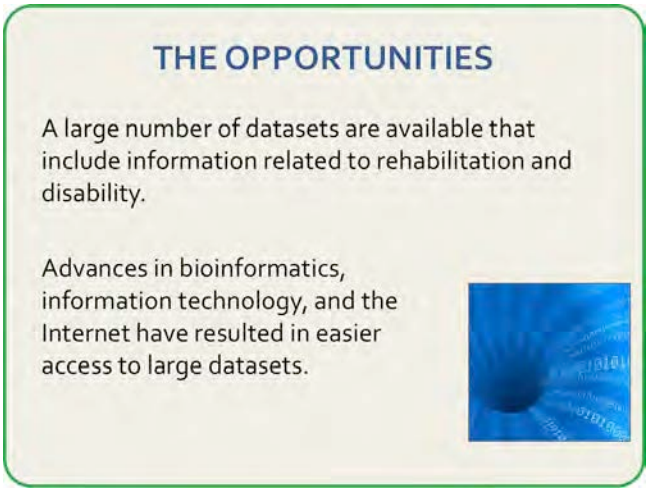

Figure 16.

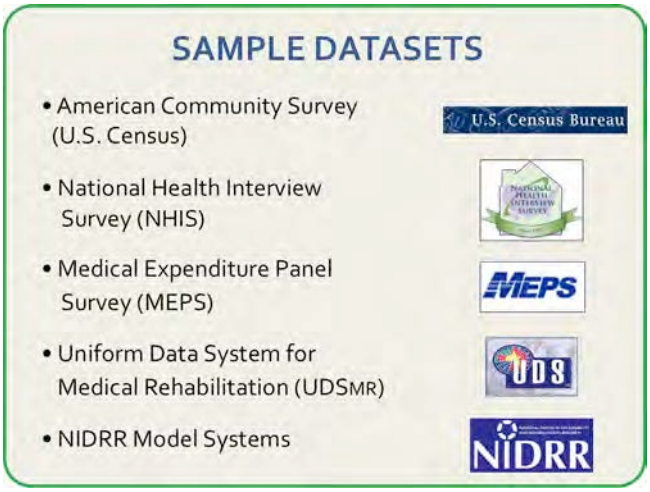

Figure 17.

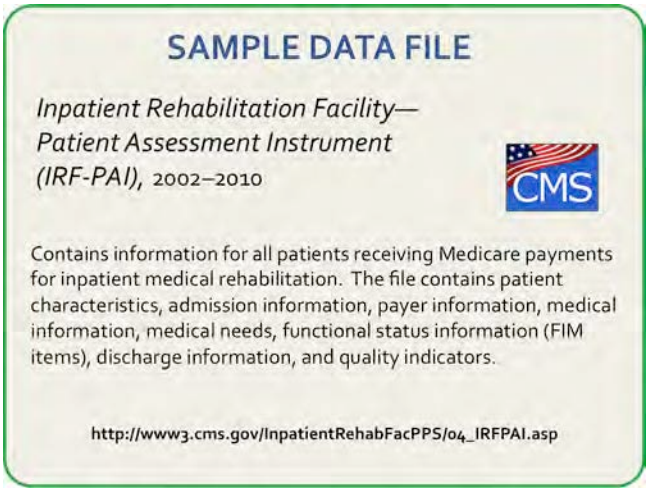

Figure 18.

These are only a few of the hundreds of large datasets that include information relevant to important questions associated with rehabilitation and disability research (Figure 19). One of the challenges facing investigators conducting research using secondary data analysis is to identify datasets that include variables and information related to rehabilitation and disability questions (Figures 20-21). The Center for Rehabilitation Research using Large Datasets (CRRLD) has developed a data directory designed to help investigators identify and obtain basic information about potential datasets. The directory is available at the Center's website (http://rehabsciences.utmb.edu/r24/data.asp) and includes brief descriptions, the purpose and function, variables, sample sizes, methods of data collection, and where additional information and documentation regarding specific datasets may be obtained.

The Future of "Big Data"

Advances in computer technology, the Internet, data processing, statistical software, and bioinformatics make it possible to store, transfer, access, and analyze extremely large amounts of information (Figure 22). These advances have also made it feasible to study rehabilitation processes and outcomes in ways that were impossible 10, or even 5 years ago.

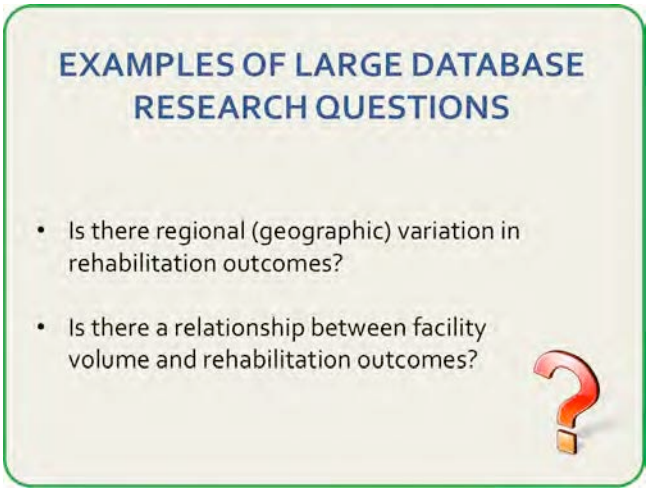

Figure 19.

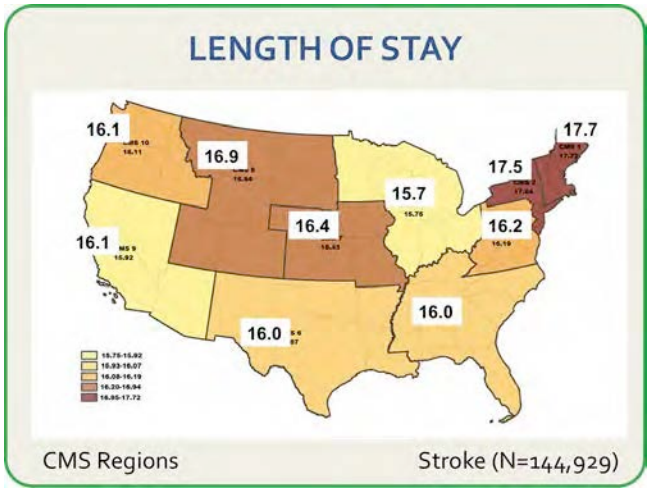

Figure 20.

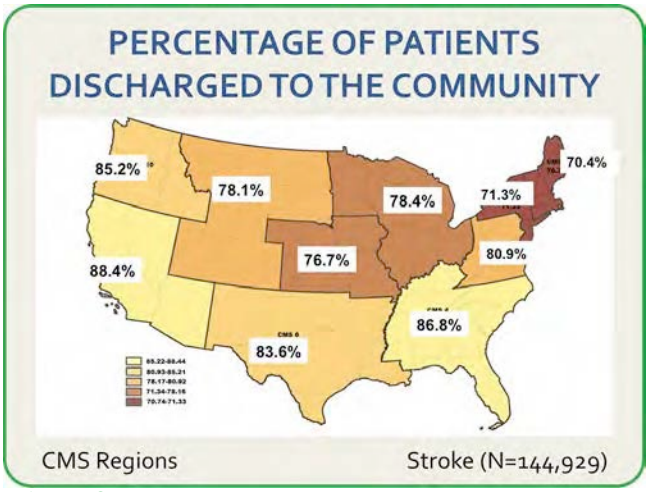

Figure 21.

Figure 22.

Improvements in data storage and software integration associated with "cloud" computing, permit users (including researchers) to store and manage very large amounts of data with relative ease and at reasonable expense (Figure 23). New developments in real-time computing technology and bioinformatics, such as Wide-Area Large Data Object (WALDO) systems, are revolutionizing real-time data collection. WALDO is a digital data archive that is optimized to handle real-time data and has significant potential in the area of personal sensing and biomonitoring technology (Figure 24).

Wearable devices now exist that provide continuous recording of biological or performance data such as heart rate, steps, or physical activity (Figure 25). These devices generate massive amounts of information. Scientists from a variety of fields are attempting to develop strategies to manage and analyze these data for both clinical and research purposes (Figure 26). This work involves researchers, clinicians, computer scientists, and experts in bioinformatics and information technology. It is essential that rehabilitation clinicians and researchers be involved in these interdisciplinary planning and strategy development efforts to establish protocols and procedures for managing "Big Data" relevant to rehabilitation and disability.[22]

[22] Roebuck, K. (2011). *Big Data: Benefits, Maturity, Vendors.* Columbus, OH: McGraw-Hill.

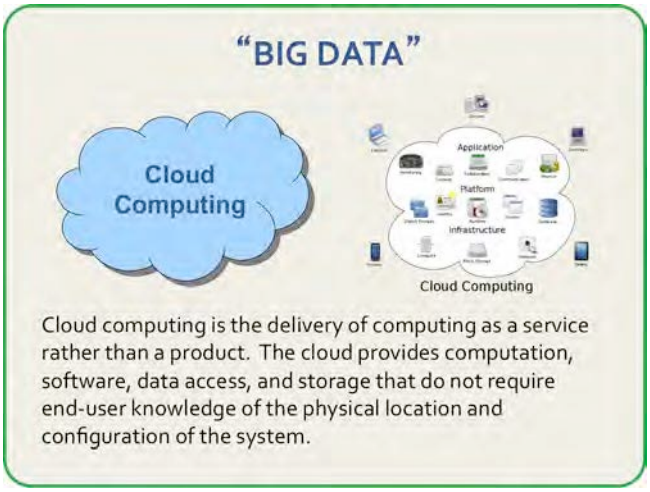

Figure 23.

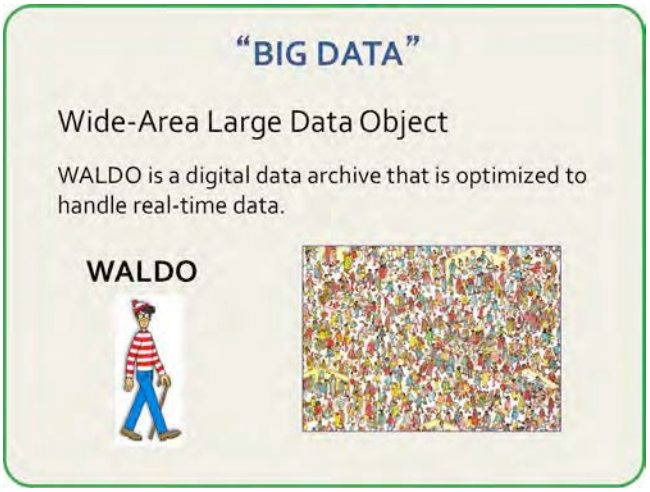

Figure 24.

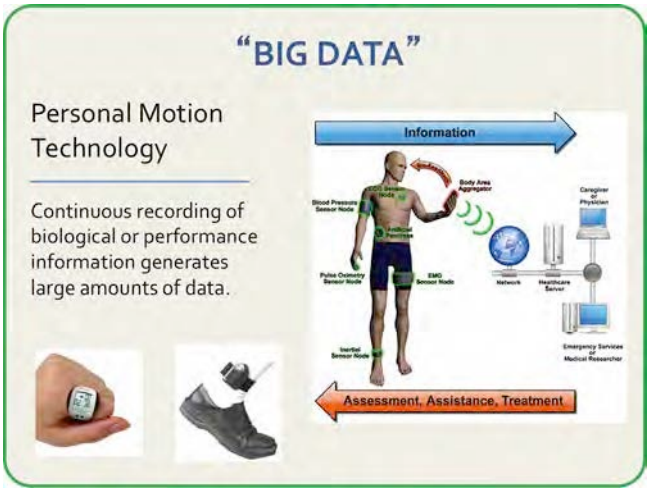

Figure 25.

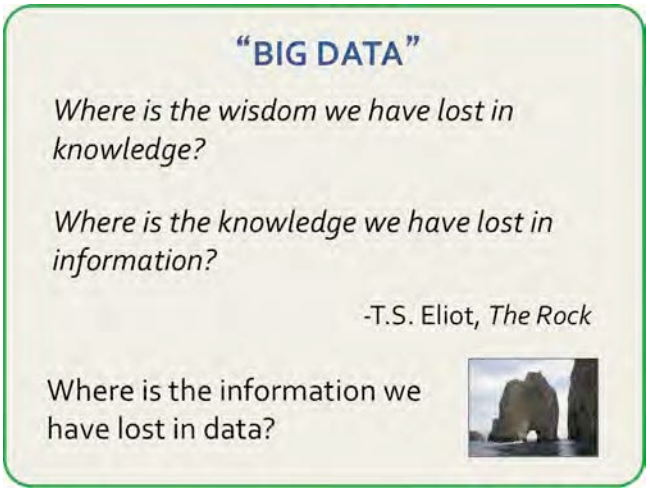

Figure 26.

The CRRLD is providing programs, service, and activities to build the research capacity and infrastructure for rehabilitation and disability investigators in this area (http://rehabsciences.utmb.edu/r24) (Figures 27-28).

These services and activities include:

- Education programs to raise awareness of the role and importance of population-based and secondary data analysis studies in rehabilitation and disability research
- Formal training activities to develop skills in managing, analyzing, and interpreting large datasets
- Pilot projects and visiting scholar opportunities to help investigators identify questions and provide preliminary data for larger studies important in establishing quality indicators and health system outcomes using existing large datasets
- Creation of a national data directory to provide information about large datasets that contain content and variables relevant to rehabilitation and disability research
- Facilitation of interdisciplinary collaboration and research to ensure that rehabilitation scientists, clinicians, administrators, and policy makers will be prepared and able to use large datasets to advance rehabilitation science and improve outcomes for persons with disability and their families (Figures 29-32)

CENTER FOR REHABILITATION RESEARCH USING LARGE DATASETS (CRRLD)

The goal of the Center is to build rehabilitation research capacity by increasing the quantity and quality of rehabilitation outcomes research using large administrative and research datasets.

http://rehabsciences.utmb.edu/r24

Figure 27.

CRRLD CONSORTIUM

- Rehabilitation Sciences Academic Division & Research Center
  University of Texas Medical Branch
- Center for Rehabilitation Outcomes Research
  Rehabilitation Institute of Chicago
- Uniform Data System for Medical Rehabilitation
  University at Buffalo
- Employment and Disability Institute
  Cornell University

Figure 28.

ACTIVITIES

- Raise awareness
- Website http://rehabsciences.utmb.edu/r24
- Education and training
- Data directory
- Visiting Scholars Program
- Pilot Project Program

Figure 29.

DATA DIRECTORY

http://www.disabilitystatistics.org/sources-rehab.cfm

Figure 30.

DATA DIRECTORY

Figure 31.

COLLABORATION

Example:

Collaboration with NIDRR Model Systems Datasets

NIDRR

Representativeness of the Traumatic Brain Injury Model Systems National Database

Corrigan, J.D., Cuthbert, J.P., Whiteneck, G.G., Dijkers, M.P., Coronado, V., Heinemann, A.W., Harrison-Felix, C., & Graham, J.E.

Journal of Head Trauma Rehabilitation (In Press).

Figure 32.

Conclusion

When I was a graduate student, my dissertation advisory was fond of telling me and his other graduate students that: "Doing outcomes research is a lot like raising children… You always think you are going to do a better job next time" (Figure 33). After almost 30 years of involvement in clinical and health science research, I appreciate the truth in this aphorism. I believe we can do a better job "next time" in conducting disability and rehabilitation research if we take advantage of the different methods and approaches available to us, and develop the skills and knowledge necessary to use large datasets to help answer important rehabilitation research questions.

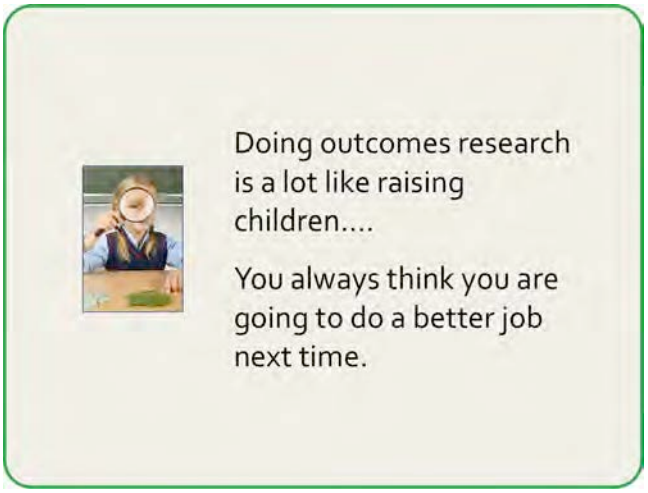

Figure 33.

From Ideation to Product Solutions: Translating Rehabilitation Science to Practical Applications

Rick Greenwald, Ph.D.[23]

President, Simbex; Co-Director, Center for Translation of Rehabilitation Engineering Advances and Technology (TREAT); and Adjunct Associate Professor, Thayer School of Engineering, Dartmouth College
Hanover, Massachusetts

Well, we have traversed a broad spectrum of scientific areas today, starting from "-omics" to muscle biology, simulation of skeletal biomechanics, engineering advances in rehabilitation, outcome measures, and large datasets—well done, Ralph. Congratulations. The medical rehabilitation research resource program (R24) is a really ambitious program. I want to focus for a few minutes on the excitement and challenges in translating rehabilitation research into products and services that can be put out into the clinic, and more and more increasingly now, into the community, and directly to families.

As a disclosure, I want to acknowledge a financial interest in some of the technology I will be discussing today. Since several of them were developed with Small Business Innovation Research (SBIR) funding, I'm happy to report that the government does retain its royalty-free license on these technologies.

Overview

I want to provide some perspective on technology transfer in rehabilitation, introduce the R24 Center for Translation of Rehabilitation Engineering Advances and Technology—we call it TREAT—and to use some real-life product development examples to help provide some insight into how we are going about this (Figure 1).

Simbex is a research and product development company located in Lebanon, New Hampshire, about 2 hours northwest of Boston and in close proximity to the Thayer School of Engineering at Dartmouth College (Figure 2). We also maintain close relationships with the Tuck School of Business at Dartmouth Medical School and the Dartmouth-Hitchcock Medical Center.

Simbex stands for "Simply Better Exercise." Our mission is to simply improve and maintain function, mobility, prevent injury, and to provide rehabilitation services and products where needed (Figure 3). Here you have an above-knee amputee who was able to keep his socket on his leg and able to get back to the sport he loved—windsurfing.

There are a lot of companies that do product development. Why is ours a little unique? One of the things I learned during my term on the NABMRR, which I thought was an incredible experience, was that there was a demand from the Advisory Board and a need for educating and taking back to rehabilitation researchers some of the ideas necessary to translate their products, and get them out into the marketplace. There seemed to be a big void there, and we were fortunate to get funded for TREAT, and now to be able to provide those services to the community (Figure 4).

Our goals are to provide these technology solutions with specific modules focused on product assessment, on prototyping, and also (through an interesting collaboration with our colleagues at the Dartmouth Institute of Health Policy and Clinical Research—you might know them from the Dartmouth Atlas Study) on facilitating and encouraging comparative effectiveness trials for rehabilitation technologies that are beginning to be ready for use (Figure 5). We collaborate with Dr. Jonathan Lurie at Dartmouth and his colleagues to help us along that way.

[23] Dr. Greenwald and Simbex have a proprietary and commercial interest in the Head Impact Telemetry (HIT) System and the Sideline Response System.

OVERVIEW

- Provide some *perspective* on technology transfer in rehabilitation
- Introduce the Center for Translation of Rehabilitation Engineering Advances and Technology (TREAT)
- Use real-life product development examples to help provide insight

Figure 1.

SIMBEX – LEBANON, NH

Simbex

Thayer School of Engineering
Dartmouth College

Figure 2.

SIMBEX MISSION

Simbex is a research and product development company whose expertise is biomechanical feedback systems.

Our goal is to create marketable products and solutions for active life improvement in the areas of human performance, sports injury prevention, and rehabilitation.

...Simply Better Exercise™

Figure 3.

NICHD

NCMRR

TREAT

CENTER FOR TRANSLATION OF REHABILITATION ENGINEERING ADVANCES AND TECHNOLOGY

"Fostering Advances in Rehabilitation Technology"
http://www.simbex.com/TREAT/

Funded by the National Center for Medical Rehabilitation Research
Eunice Kennedy Shriver National Institute of Child Health and Human Development
National Institutes of Health
Part of the R24 Rehabilitation Resources Network (www.rrnin.org)

Figure 4.

TREAT MISSION STATEMENT

TREAT is a multidisciplinary, multi-institutional, collaborative consortium between corporate, educational, and nonprofit entities providing infrastructure support and expert consultation to researchers and innovators interested in the translation and commercialization of rehabilitation research applications. TREAT has the following mission:

- To provide research translation and commercialization expertise and education for rehabilitation researchers and bioengineers with product solutions for rehabilitation technology.
- To enable and encourage comparative effectiveness trials for rehabilitation technologies considered ready for clinical evaluation and use.

Figure 5.

Problem Statement

So there is a real problem that comes up. Many of you have heard about it. What happens after the funding is gone? It's always talked about as "crossing the chasm," and I think that is both an overused statement, but also one that needs a little further explanation and discussion (Figure 6). What exactly is the chasm? Well, much of current translational research programs fall short. Once you get beyond the R01 stage, or the federally funded research, there are a whole bunch of things that have to get done before you can eventually get a product on the market (Figure 7).

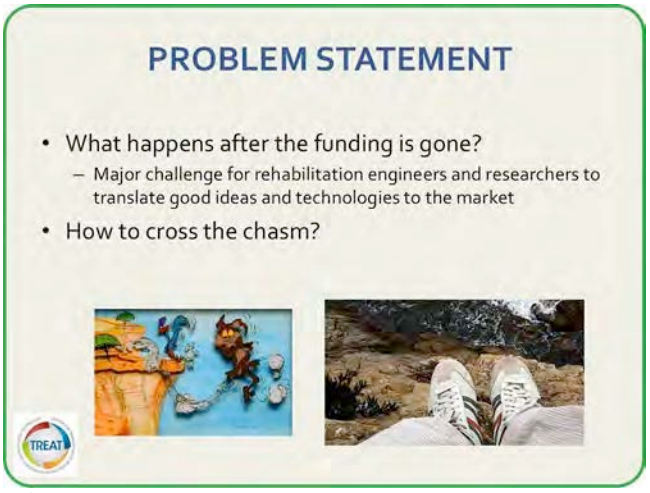

Figure 6.

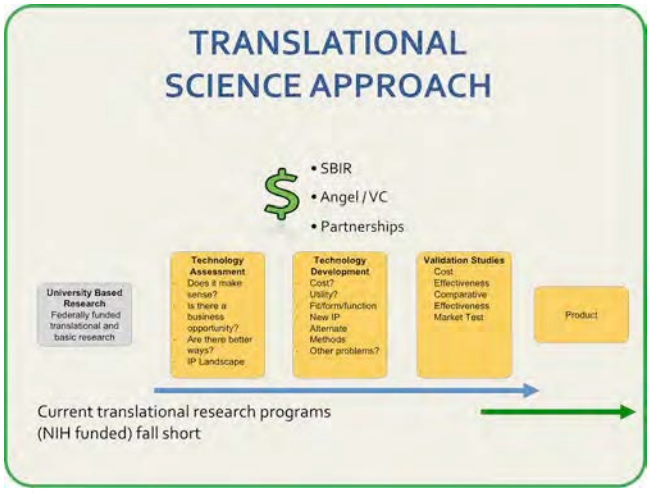

Figure 7.

There are a variety of ways to do it. It can be done through programs such as the SBIR program, which I'll talk a lot more about in a moment. You can go the angel and venture capital funding route, and for those of you who have done it, you know that is both good and fraught with peril. And you can go through strategic partnerships, licensing, and acquisition. But there are a lot of questions that still have to be asked that come along that continuum and that pathway from following R01-based research and getting it out to a product.

Does the product technology even make sense? Is there really a need for it, and is that need widespread enough to make it into a product that can serve and be scaled? Or should you just make enough to serve the small community that the products would serve well? There are difficulties in doing that, but we should be creative about getting those products out to smaller populations that really do need them.

You have to deal with the intellectual property landscape. You have to understand not just designing the prototype and getting that prototype working, and through the clinical aspects of implementation and validation, but once you have that, it would be quite a shame if you did all that work, and then you have to basically throw it out before you go back and make a product out of the prototype. You have to start early enough in the cycle—and that is what we hope TREAT is doing—starting early enough in the cycle to be designing for manufacture, and to be designing for the populations that you are going to get your products to at the end of the day.

Early on, you can best use that money that is available through government funding. Also, you have to do the appropriate validation studies, whether they are cost-effectiveness, comparative-effectiveness, or the real market-testing studies. Otherwise, you may just miss in the marketplace. It's a shame when the research goes all the way to the end game, you get to the end, and then no one really wants what you made.

The Small Business Innovation Research (SBIR) Program

The SBIR program has provided an incredible opportunity for my small business (Figure 8). I thank Lou Quatrano, Nancy Shinowara, Ralph Nitkin—everyone who helped our small business navigate these waters starting back around 2000, when we got our first SBIR grant. The SBIR program talks about—this is from JoAnne Goodnight's old slides—this phased approach (Figure 9). She describes the chasm after Phase 2 of an SBIR program as "Mount FDA." I always thought that was funny, and it is really relevant for those who are doing medical device development, but not all of these products require U.S. Food and Drug Administration (FDA) approval, and the chasm is quite different for those products. So it is not just "Mount FDA" that exists.

Just to rehash that slide—the R01 stops at some point (Figure 10). An SBIR allows you to bring it further along, but the chasm is broad. It's wide, and it is very challenging. As an entrepreneur, I look at it in a slightly different way. That was a great model for university-based research. As an entrepreneur, I simply look at it as, how do you get from the idea to your product without going broke (Figure 11)? For those of you who have done it, that is just the real challenge that exists.

Figure 8.

Figure 9.

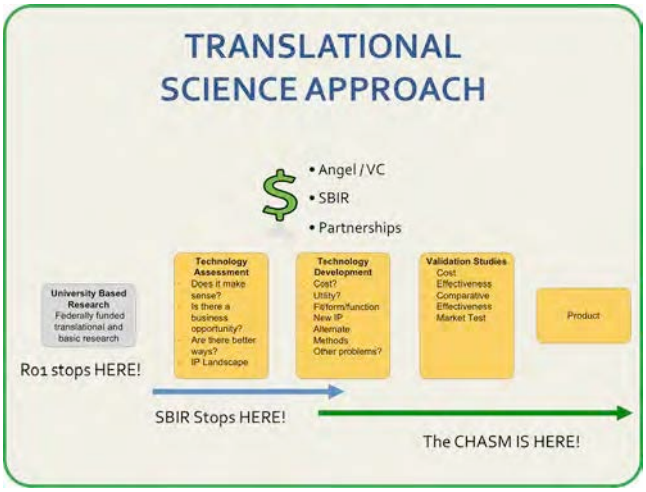

Figure 10.

Figure 11.

For example, I know that I can build a device that will prevent most accidents in skiing, but I will go broke if I try to put that one on the market. Some of you may know my colleague and friend Bob Dean, who is still plugging away up in Lebanon, New Hampshire. Bob served on the NABMRR perhaps 10 years ago now. Bob is a serial entrepreneur. He started 12 companies. He continues to create a company a year if he can. He laid out this model of the process of innovation by talking about how first you have to have a market need. Then his next step is always to go find a fanatic entrepreneur. He chased me for 7 years while I lived

in different parts of the country to come back and help him translate his smart variable geometry socket technology for lower limb amputees into a product.

Then you get into a period of chaos, which leads to the inevitable: "We don't have enough money to do the work," more chaos, get some money somehow, and then hopefully get to where you can market the product and be successful (Figure 12). So Bob's method is one way. My own experience with the Head Impact Telemetry (HIT) System for monitoring head impacts was slightly different. You bang your head against the wall enough times, and perhaps it works. We found that was necessary. We couldn't use graduate students for this kind of prototype work, so there was my colleague Trey and I trying to prove that our head impact system worked the first few times. In order to sell them around the country, I had to go and bang my head against a lot of cement walls.

Research and Development Synergy

At Simbex, we have realized that it is not just research and then product development. I think the key here is the synergy between the two, and preparing for one before you start the other. If you are doing research, and you think that it has got the opportunity to be a product sometime downstream, that process should start at the beginning, and they should be intertwined all about. That's the process we employ at Simbex to go from finding a problem, identifying a concept, providing the intervention, and then going back and testing it (Figure 13). That's a cyclic process.

You'll notice on the slide that it includes things like sales and marketing. It includes branding and public relations. These are all critical parts of actually making a successful product. If you ignore them, and you get to the end game where you have a product, many people in the market are going to turn around and say, "No, you have a nice science project." We've seen that way too often.

We've done several projects in the area of mobility rehabilitation and injury prevention (Figure 14). I'm going to talk just about two of them briefly here today.

Lower Limb Prosthesis Fit

One project is this problem that Bob Dean initiated back in the early 1990s. Bob is a transfemoral amputee, and he had the problem that most amputees have, that their socket doesn't fit well over the course of the day. The residual limb undergoes natural daily volumes and fluctuations, and the socket is just a standard fixed volume (Figure 15). This is a problem that now has been around for many, many years, but you will see that even though this problem has been solved technically, it is not a commercially viable product to date.

We developed and eventually commercialized the Active Contact System™ to solve this problem (Figure 16). The technology basically involves no motors, no batteries, nothing electronic in a suction socket, because the human, while walking, is a pump. It was an invention that Bob finally came up with that says if you have liquid circulating around the prosthesis, and you are able to maintain it under a pressured environment while you walk, the socket will maintain its volume. It also provides some interesting cooling opportunities inside the socket depending upon the materials that you use. It was durable and reliable. It was easy to install, and this research was funded by the NIH and the National Science Foundation over a very long period, starting in 1991.

I want to highlight this graph (Figure 17). It shows the typical evolution of products over 10 years. I don't know too many products that evolve into products in less than that timeframe. A couple of million dollars of SBIR funding, and it wasn't until 2000 that we took it to Phase II and began the process, and a couple of years later, we launched the product.

Figure 12.

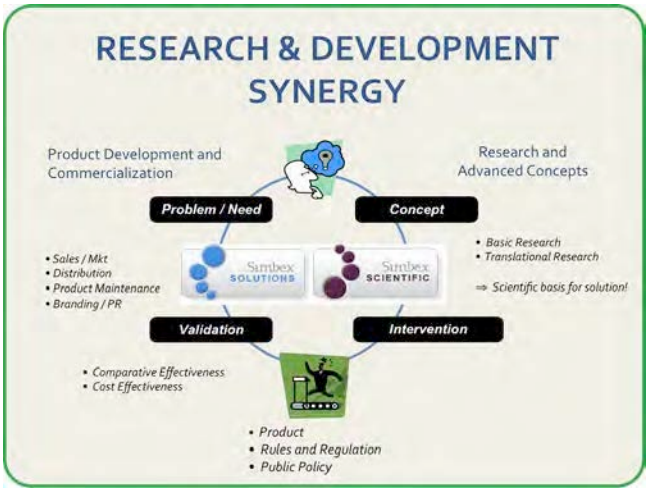

Figure 13.

Figure 14.

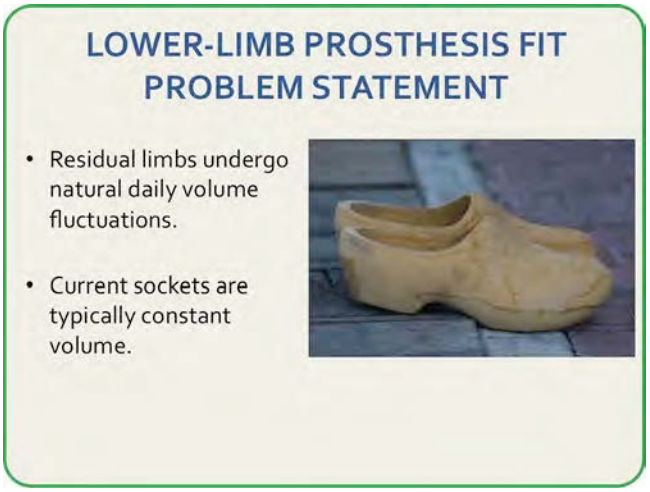

Figure 15.

Figure 16.

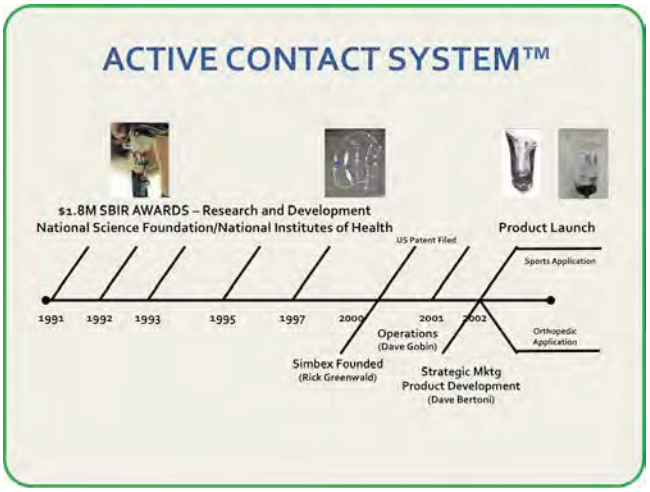

Figure 17.

A key to getting that done, which had not been done in the early SBIRs for Bob, was technology assessment (Figure 18). Bob was able to do the prototyping, but not in a way that would make it get to market. He had developed the prototype using off-the-shelf components, but those components were going to be too costly. The product was going to leak—pretty simple problem, but it was going to leak, and therefore no one would use it. Finally we had to do appropriate trials so that we could try to convince the Healthcare Common Procedure Coding System panel to give us a reimbursement code.

Here again is our product development process, just broken down a little bit more clearly, and you can see a lot (Figure 19). There is Bob on the treadmill originally. We eventually went through a development sequence to finally get to an injection-molded component that cost just about $3 or $4, which was a big help and made a big difference financially. Again, you will see that I comingle the issues related to financing and marketing, along with product development.

I want to reiterate that the process can be long. It is not trivial, and the SBIR process, for example, only takes us so far (Figure 20). So I would like to turn my attention now to another technology we have worked on.

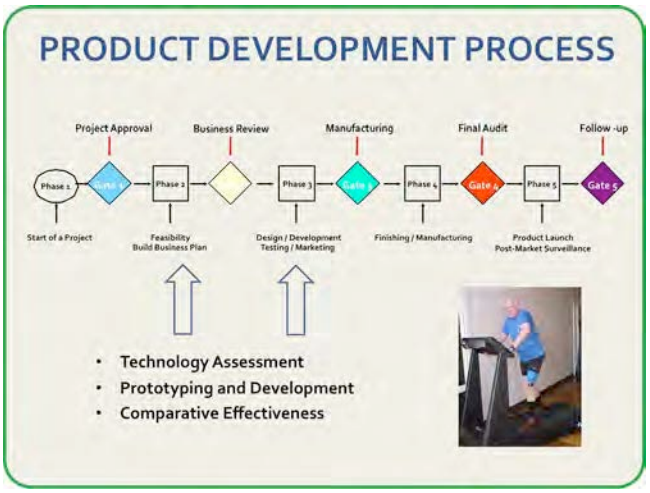

Figure 18.

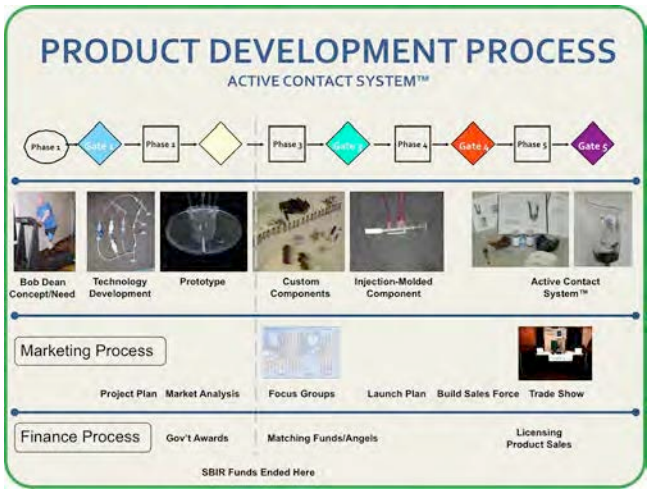

Figure 19.

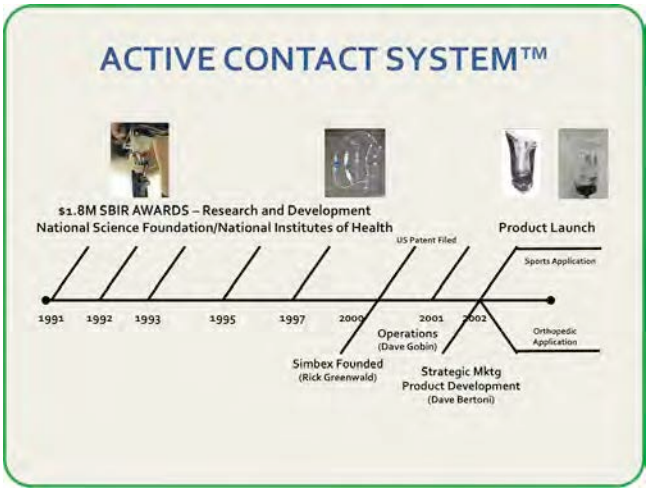

Figure 20.

Head Impact Telemetry (HIT) System Technology

This is a highlight of what we have been doing for the last 10 or 15 years—not hitting a mouse on the head, but other things more related to managing and understanding head impacts on the sports field and on the battlefield (Figures 21-22). Throughout the 1990s and long before that, there were a lot of researchers who were coming up with questions and saying, "We know how to treat traumatic brain injury (TBI) and mild TBI, but boy, it seems like most of the people who present with these injuries are quite different. And if we only knew what the impacts were, or what the input was, perhaps we could differentiate, and do a little bit better science on it."

So with help from the NIH and the NCMRR, we developed the HIT System—the Head Impact Telemetry System—which is capable of recording on-field head impacts during practices and games (Figure 23). This is a great example of how you had to build the product in order to do the research. The idea was to be able to monitor what was going on in real time on the field, and only then could we start to identify the injury mechanisms that were occurring in these athletes (Figure 24). Was it when you get hit and experience linear acceleration only; rotational and linear acceleration? These are now heavily debated topics. You probably see them every day on the front page of newspapers that cover sports and the military.

Only then can we start to enable improvement and protective equipment. The development of this technology relied on the same air-bag sensors that are in your car and some creative algorithms for estimating head motion and for filtering out nonimpacts. The folks at Analog Devices enjoyed working with us because we were doing a cool, consumer application. We put them in hockey helmets, football helmets, and a number of other helmets, and then went on the field with a wireless telemetry system. We have created a huge database of in excess of 2 million impacts to date.

This is a multidisciplinary approach to investigating brain injury, and it is supported by a large consortium of researchers under a Bioengineering Research Partnership (BRP) R01 (Figure 25). So in this case there was the Phase II SBIR that led to a BRP award that we are using to take the impact information and correlate it with the clinical data coming from the field—symptomatology, neuropsychology tests, brain-imaging tests, and balance tests—and try to better understand the mechanism of injury. Since then, we have also gotten funding from the National Operating Committee on Standards for Athletic Equipment, which is an industry-based organization. So perhaps industry is not so bad after all.

We are doing a comparison of various finite element models and comparing those results with our brain imaging, biomechanical, and clinical data. We just published a paper in the *Annals of Biomedical Engineering* about a month ago that for the first time showed that strain that is induced in the corpus callosum of the brain from an impact that occurred on a football field, correlated with the white matter injury seen on a Diffusion Tensor Imaging (DTI) scan from that injured athlete. This was a pilot study, and we have 10 athletes from whom we have that full dataset, and the results are fascinating. Again, we are just at the tip of the iceberg.

It's just so early, but to be able to take the actual biomechanics—from the real data on the field—and to use that as input to the finite element models, and then to compare the predicted tissue stresses and strains to the neuroimaging results from that impact and that athlete—there is great promise for this line of research. And it started with the technology and the tools to measure the head impacts on the field.

Here's our consortium at Virginia Tech, Dartmouth, Brown, and Simbex, and a lot of other schools (Figure 26). The broad research programs are funded by the NICHD and the NCMRR, the National Institute of Neurological Disorders and Stroke, the Centers for Disease Control and Prevention, and the National Operating Committee for Standards in Athletic Equipment, which is primarily paid for by the manufacturers. I just want to highlight something you read about in the paper all the time about the National Football League and the National Hockey League.

Figure 21.

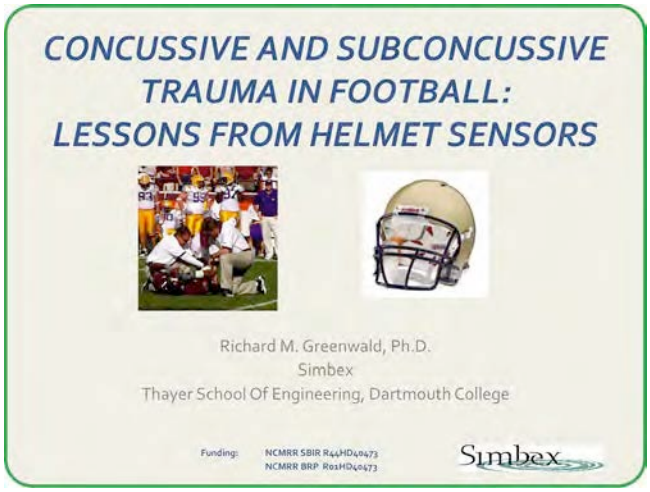

Figure 22.

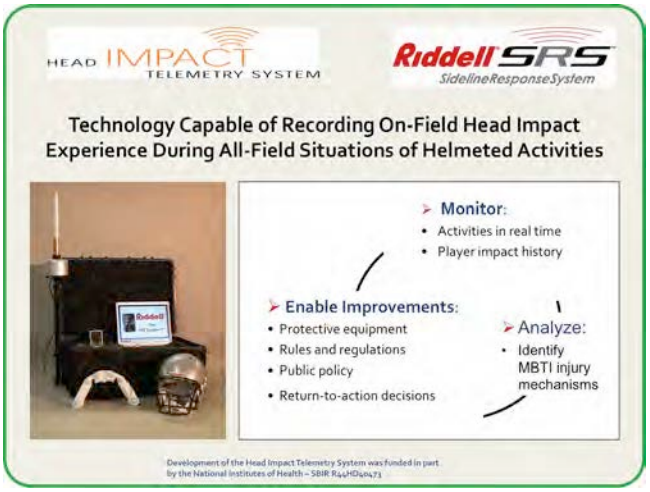

Figure 23.

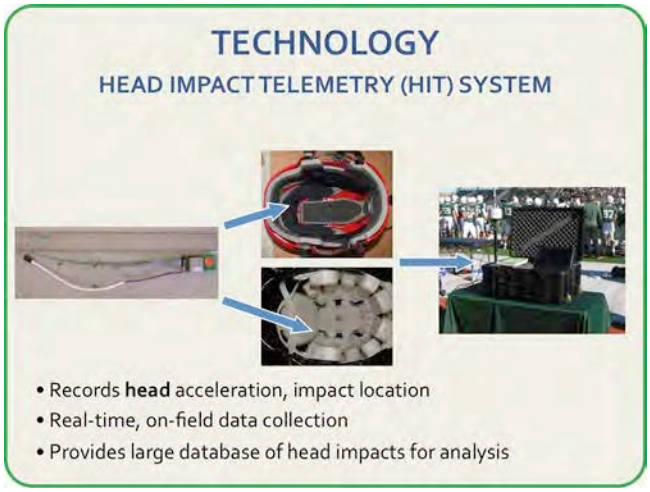

Figure 24.

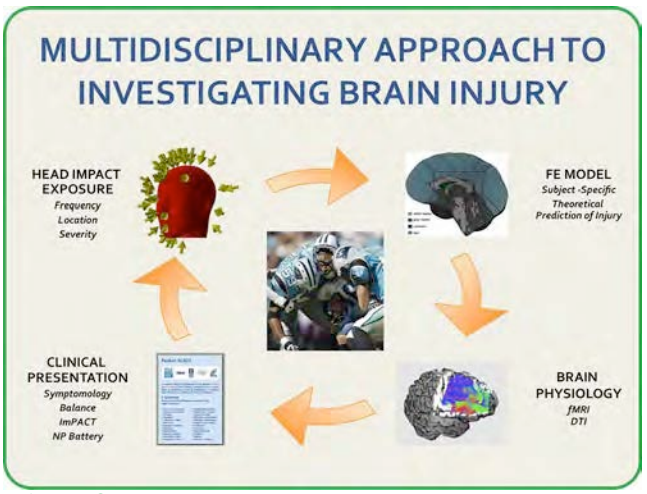

Figure 25.

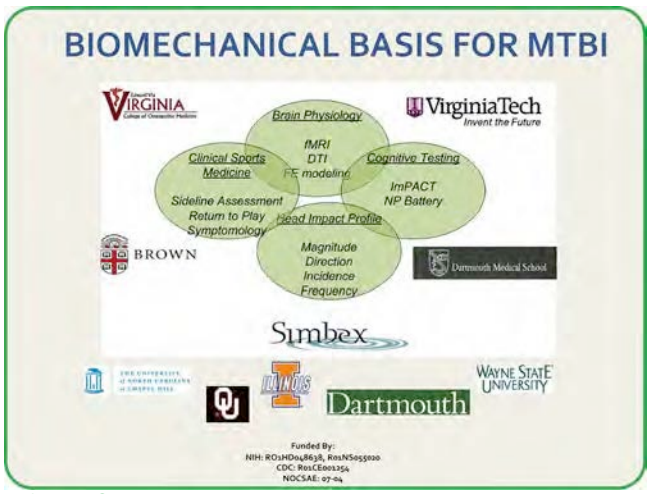

Figure 26.

Two main points I want to make here. One, I appreciate that these athletes are important to the public, but they are not our focus. Our focus is really on the kids. My son was the first subject athlete under 13 years of age to be recorded. His short football career lasted four games, and we found out from that, for example, that while he did not get hit quite as often as a college or high school players, he did get hit quite hard, almost approaching 100 Gs on one hit. He willingly, on his own, hung up his football helmet. My second point is to remember that kids are not scaled-down versions of adults (Figure 27). We can't simply take the results from adults and scale them to kids. We're very happy to tell you that the research that we started with the NIH funding in collegiate athletes has moved down to high school, junior high school, and now Stefan Duma at Virginia Tech recently started instrumenting 8- and 9-year-olds.

We now know how often, how hard, and where on the head athletes get hit. We know it by player position. We know it by sport, and I could go on for a long time. We are now comparing these different markers and biomarkers that we get, both on the field, in the laboratory, and subsequently as the athlete heals (Figure 28). Yet we are still early in the process, and we must expand our work to better characterize head impact exposure in different sports and at different levels of play, for boys and girls, and for men and women (Figure 29).

Finally, and as I promised Mike Weinrich when we got the grant, we would publish this stuff. There are more than 40 peer-reviewed articles on this topic from this group and from this research over the last couple of years—almost 20 of them just in this past year alone (Figure 30).

Figure 27.

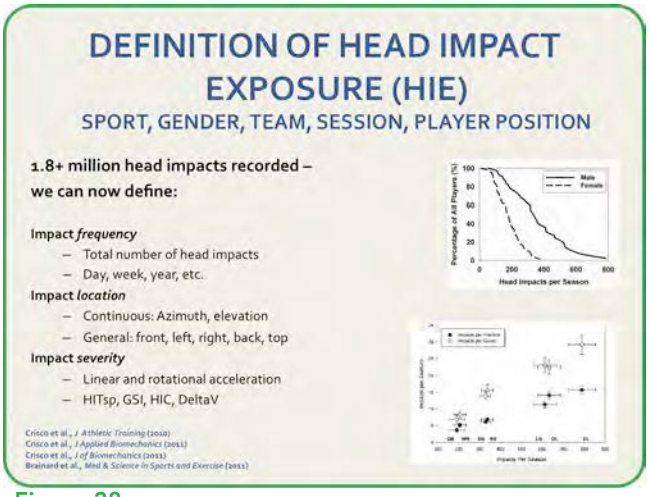

Figure 28.

Figure 29.

Figure 30.

Technology Transfer from Football

We transferred the technology to boxing. It has been used by USA Boxing, to equestrian, and to soccer leagues (Figure 31). Cindy Bir just had an article in *Medicine and Science in Sports and Exercise* come out this week on soccer heading—very interesting information.

We transferred it to children in playgrounds to try to get little children to wear caps—very challenging—to snowboarding and skiing, and to the military, who continue to struggle with the problem of measuring in the field what is actually going on with head acceleration, not just measuring deformation of the helmet when an explosion occurs (Figure 32).

Figure 31.

Figure 32.

So ours is just one of many examples, and certainly there are others out here. The SBIR program has done great. I picked a few examples, not any one in particular, but there are so many good examples of rehabilitation research that have been translated (Figure 33). But there are so many more projects that are still in the laboratory and still on the bench that have promised to be translated, and just need the opportunity and the understanding of how to go about that. It sometimes can be like a square peg going into a round hole. You have to have the idea, find the problem, and then find a good solution to get it out the door (Figure 34).

Figure 33.

Figure 34.

We hope that TREAT provides the opportunity for many to do that, and we look forward to serving anyone in the community who needs that help (Figure 35). We're just an email click or a phone call away, and we start to try to help.

I really want to take this opportunity to thank the NCMRR for your vision, for your guidance, for your dedication to all of us researchers, for your passion, and for the future of rehabilitation research (Figure 36).

Thank you very much.

Figure 35.

Figure 36.

Chapter 6: Closing Statement

Michael Weinrich, M.D.
Director, NCMRR

When NCMRR staff were asked to develop a scientific symposium to celebrate the 20th anniversary of the Center, it was actually quite easy for us to decide on a program. The NIH peer-review process had essentially done it for us! This past year, applications for the third cycle of the NCMRR Medical Rehabilitation Research Infrastructure Network (MRRIN) were reviewed. This Network was established on the advice of the National Advisory Board on Medical Rehabilitation Research (NABMRR) and has gone through modifications as a result of feedback from the field. The Network was established to serve as a set of research resources to investigators interested in tackling problems in rehabilitation. We sought to provide investigators, especially young investigators, with cutting-edge tools and expertise to complement their skills. With each cycle, the Network centers re-apply for funding; about half of the existing centers are re-funded, and half of the centers are new. We did not prescribe areas of research for the centers, so the topics they chose represent their areas of expertise and were selected by the reviewers as their "best bets" to enhance the future of rehabilitation research. Perhaps it is best to let our Funding Opportunity Announcement (FOA) for the Network speak for itself:

> The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), through the National Center for Medical Rehabilitation Research (NCMRR), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) invite applications for grants to build research infrastructure by providing medical rehabilitation researchers with access to expertise, technologies, and resources from allied fields, such as neurosciences, engineering, applied behavior, and the social sciences.
>
> Medical rehabilitation involves basic and clinical studies in the domains of pathophysiology, impairment, functional limitation, disability, and societal interaction. Increasingly, research breakthroughs and potential therapeutic strategies are the result of integrating expertise from allied fields as well as building up a core understanding of rehabilitative mechanisms and clinical outcomes. Access to technologies and approaches from allied fields is key to promoting multidisciplinary collaborations and developing research opportunities. Centralized research infrastructure will enhance the capability of medical rehabilitation investigators to understand mechanisms of functional recovery, develop therapeutic strategies, and improve the lives of people with disabilities.
>
> The aim of this FOA is to create a national network of research cores that will provide rehabilitation researchers with access to collateral expertise in biomedical, behavioral, and/or psychosocial fields that is particularly relevant to current opportunities in medical rehabilitation research.
>
> Applicants should propose a program of research resources and collaborative opportunities in a specific content area. This may be accomplished through a combination of didactic interactions (workshops, courses, written material, and websites), consultations, and pilot funding.[24]

Let us present an overview of how we organized this symposium, how we see the work of the centers fitting into the framework of research funded by the NCMRR, and our hopes for the future.
Dr. Eric Hoffman led off with his presentation on his Center for Molecular and Functional Outcome Measures in Rehabilitation, based at Washington Children's Hospital. This is the century for molecular medicine. The Center for Molecular and Functional Outcome Measures seeks to provide rehabilitation researchers with the tools to investigate genetic influences on recovery. The role of genetic polymorphisms

[24] RFA-HD-09-013: Medical Rehabilitation Research Resource (R24). Retrieved on November 12, 2012, from http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-09-013.html.

in modifying the course of disease and recovery has become increasingly clear for a large number of conditions. Dr. Hoffman presented elegant work demonstrating that understanding the detailed structure of gene mutations in patients with muscular dystrophy can help predict clinical outcomes. He then went on to demonstrate that understanding the genomic signatures of the microbial population in urine of patients with spinal cord injury may allow us to decrease catheter-related infections. Dr. Hoffman presented very exciting work on new developments in using antisense therapeutics to skip part of the translation of the mutated dystrophin genes in muscular dystrophy so that the more stable exons of dystrophin can be spliced together. This approach would essentially convert Duchenne muscular dystrophy into a much milder Becker's form—rehabilitation at the molecular level.

Dr. Richard Lieber followed with a presentation on the work of his Center for Muscle Rehabilitation Research. He began with a focus on the mechanical properties of single muscle fibers, and demonstrated how the new technologies his group developed allowed them to work up from an understanding of physiology at the single muscle fiber level to how muscles react to load, strain, and injury, as well as to the contributions of different components of muscle, that is, muscle fibers and connective tissue, to function in health and disease. Dr. Lieber's group has applied this knowledge to improve outcomes for patients undergoing tendon transplant surgeries, and to understand the mechanisms of musculoskeletal plasticity for patients undergoing limb lengthening procedures.

Dr. Scott Delp took the theme up to the next level with his presentation on the work of his Center for Simulation in Rehabilitation Research. The central focus of this center is to use detailed biomechanical modeling, including precise anatomical variations for individual patients, to create simulations of gait and posture that can guide clinical interventions. He discussed the problems in predicting outcomes of tendon lengthening surgery for patients with cerebral palsy and demonstrated how measurement, modeling, and simulation can inform clinicians about the mechanics actually operating in individual patients. Dr. Delp demonstrated the function of the simulation software his group developed that is now available to the rehabilitation community and discussed the potential for applying it to the range of problems in gait and posture encountered in practice.

Dr. Zev Rymer directs the Center on Engineering for Neurological Rehabilitation and Northwestern University's Rehabilitation Institute of Chicago. He presented an overview of engineering methods' major contributions to rehabilitation, including functional electrical stimulation, robotics, advanced prosthetics, and brain-machine interfaces. In his talk, he highlighted technical obstacles overcome and the challenges that remain to really advance the technology for rehabilitation in the 21st century. Dr. Rymer specifically pointed to the needs for better sensing for outcomes measurement and prosthetic performance, better informatics for tracking treatment effects, better biomaterials and interfaces between body and machine, and more affordable robots.

Dr. Alan Jette's presentation on the focus of the Boston Rehabilitation Outcomes Measurement Center picked up on the theme of better informatics for tracking treatment effects. He presented his work that involves using computer-adaptive testing to develop sensitive and reliable measures of patient-reported outcomes. These measures can be collected with far less patient burden and lower costs. Dr. Jette presented data from a pilot study in collaboration with Kaiser Permanente to demonstrate the superiority of inpatient rehabilitation over skilled nursing home care for rehabilitation of patients with stroke.

Extension of outcomes analysis was the theme of Dr. Ken Ottenbacher's presentation on the work of the Center for Rehabilitation Research using Large Datasets. To understand the effects of public policy changes and to provide data to guide policymakers it is necessary to be able to analyze the patterns of health care usage and health outcomes of populations of patients. His Center seeks to provide investigators with a directory of available datasets, education on methods of analysis, and tools to analyze large datasets. He pointed out the need for development of new data analysis methods to cope with the increasing flood of digitized information, including real-time continuous monitoring of patient activities and physiological functioning.

Finally, Dr. Rick Greenwald presented an overview of his Center for the Translation of Rehabilitation Engineering Advances and Technology. The focus of his center is to help inventors and entrepreneurs take promising technologies for rehabilitation from the bench into the marketplace. Dr. Greenwald outlined the steps necessary to create a successful product that can be available to the public, and the challenges in taking an academic research project through the stages of commercial development. He illustrated the process by relating the history of the development of two products produced by his company—a variable geometry prosthetic socket that adapts to patients' limbs, and a Head Impact Telemetry System to monitor the forces in sports collisions.

Not all of the exciting prospects for rehabilitation research are included in the anniversary presentations. Indeed, there are whole areas of science crucial to the future of rehabilitation research that are missing. Just as we did not have the resources to fund centers on every important topic, we did not have time in this symposium to explore all of the exciting areas in rehabilitation research. Some of these areas are very well represented in the NIH research portfolio. Neuroplasticity is perhaps the hottest area of investigation in neuroscience. It came of age nearly simultaneously with the NCMRR. The demonstration that the adult nervous system is capable of substantial structural and functional change really undergirds the entire modern conception of rehabilitation, and this concept of plasticity has been extended to the musculoskeletal system, as well. The very richness of this field may have convinced the reviewers of our Network Center applications that investigators in this field were doing just fine, and did not need the stimulus of a center devoted to plasticity. Conversely, there are new fields of scientific inquiry, for example, nanotechnology and tissue engineering, where the applications to rehabilitation research are not yet apparent. I expect that as these fields develop, exciting applications to rehabilitation will develop, and the next cycle of our Network centers may look quite a bit different.

What we hoped in funding the NCMRR MRRIN was to provide investigators across the country with colleagues, expertise, and tools to advance rehabilitation research into new directions. The field is by nature quite diverse, so it is natural that the directions of the Centers are as well. Nonetheless, we hope you can appreciate that these diverse directions have a certain coherence, and span the interests of patients, families, and clinicians. We began with the rehabilitation at the molecular level and moved up levels through impairment, function, societal participation, comparative effectiveness, and policy analysis to end with development of products to change society. The passion and commitment of these outstanding investigators is evident in their presentations. Particularly encouraging is the depth of their commitments to making this program work. The investigators collaborate to support research and education programs across their centers and disciplines to advance the field. We hope you will be as energized and excited about the future of rehabilitation research as the audience that heard their presentations.

Appendix A: Biographical Sketches of NCMRR Program Staff

Beth Ansel, Ph.D., Director, Traumatic Brain Injury (TBI) and Stroke Rehabilitation (TSR) Program

Dr. Ansel joined the NCMRR as Director of the Clinical Practice Program (now the TBI and Stroke Rehabilitation Program). She received her undergraduate education in biology at State University of New York (SUNY) at Stony Brook. She completed her master's and doctoral education in communication sciences and disorders at the University of Wisconsin–Madison. This graduate training included both research and clinical practice in the area of communicative and cognitive aspects of adult neurogenic disorders and included work at the Wisconsin Veterans Affairs Medical Center and the University of Wisconsin Hospital. A postdoctoral research and clinical fellowship at the Johns Hopkins University School of Medicine, Department of Pediatrics, and the Kennedy Krieger Institute complemented the adult emphasis of her training. During this time, Dr. Ansel worked extensively with children as a member of an interdisciplinary pediatric rehabilitation team that considered the assessment, treatment, and long-term care of trauma patients. Before joining the NIH, she served on the faculty of Purdue University's Department of Audiology and Speech Sciences, where her research focused on speech and language changes from a lifespan perspective. As part of the NCMRR, Dr. Ansel is responsible for a multifaceted research and training program that promotes basic and applied research in rehabilitation across the lifespan. Her training and clinical expertise in the rehabilitation of communication and cognitive disorders in individuals with brain damage provides a firm foundation for translating basic sciences to clinical needs.

Theresa Cruz, Ph.D., Program Officer

Dr. Cruz joined the NCMRR in 2009 as a program analyst. She received her undergraduate education from the School of Engineering at Rutgers, the State University of New Jersey. She then received her master's and doctoral degrees in biomedical engineering from Northwestern University. Her previous research at the Rehabilitation Institute of Chicago focused on motor control and gait impairments of the lower limb following stroke. Since coming to the NICHD, Dr. Cruz has assisted several NCMRR programs, particularly the Spinal Cord and Musculoskeletal Disorders and Assistive Devices Program and the Behavioral Sciences and Rehabilitation Technologies Program.

Tammara Jenkins, M.S.N., R.N., Nurse Consultant, Pediatric Critical Care and Rehabilitation (PCCR) Program

In addition to serving as a nurse consultant for the PCCR Program, Ms. Jenkins is also the research coordinator for the NICHD Collaborative Pediatric Critical Care and Research Network. She received her bachelor of science in nursing degree from the California State University, Long Beach. She completed her master of science in nursing degree, with an emphasis in pediatric critical care, at the University of Pennsylvania. Ms. Jenkins has extensive pediatric intensive care experience and has been the pediatric clinical nurse specialist at the NIH Clinical Center, supervising the care of seriously ill children and coordinating services for their families. She is also the medical coordinator for Camp Fantastic, the annual "just-for-kids" experience for children with cancer at the Pediatric Oncology Branch of the National Cancer Institute. Her research interests include assent in the pediatric age group, end-of-life care, and quality of life.

Carol Nicholson, M.D., Director, PCCR Program

In addition to being the Director of the PCCR Program, Dr. Nicholson serves as project scientist for the NICHD Collaborative Pediatric Critical Care Research Network. She is a fellow of the American Academy of Pediatrics and board-certified by the American Board of Pediatrics in both general pediatrics and pediatric critical care medicine. Her professional background includes extensive clinical experience in acute care, critical care, and general pediatrics. Her research interests include translating basic science findings into innovative therapeutic strategies in the pediatric intensive care unit, discovery of prognostic outcome indicators and biomarkers in critically ill children, as well as scientific development of the biology, pathophysiology, and psychopathology surrounding pediatric critical illness and the special needs of children with complex illnesses. Dr. Nicholson graduated from medical school at the University of Southern California; she completed a pediatric internship at Los Angeles County/University of Southern California, a pediatric residency at the University of California, San Diego, and a pediatric critical care medicine fellowship at Children's Hospital of Los Angeles.

Ralph M. Nitkin, Ph.D., Director, Biological Sciences and Career Development (BSCD) Program, Deputy Director, NCMRR

Dr. Nitkin received his undergraduate and master's degrees from the Massachusetts Institute of Technology in the area of biological sciences and his Ph.D. from the University of California, San Diego, in cellular neurobiology. His postdoctoral studies at Stanford University and later work as an assistant professor at Rutgers University focused on the cellular and molecular basis of nerve-muscle synapse formation. For the past 22 years, he has worked as a science administrator at the NICHD, first in the area of mental retardation and developmental disabilities, and currently (since 1999) in medical rehabilitation research. Within the Center, Dr. Nitkin is also active in the area of training and career development.

Louis Quatrano, Ph.D., Director of the Behavioral Sciences and Rehabilitation Technologies (BSRT) Program

Dr. Quatrano is a psychologist who joined the NCMRR in 1991. He completed his undergraduate education at the SUNY at Geneseo, and he received his Ph.D. from Northwestern University. Dr. Quatrano initially joined the NIH as a health scientist administrator in the Prevention, Education, and Manpower Branch of the Division of Lung Diseases at the National Heart, Lung, and Blood Institute, where he was involved in transferring basic science into clinical practice and directing the training program in pulmonary research. He went on to become the scientific review administrator for the Human Development and Aging Study Section and the referral officer for Small Business Innovation Research applications in the NIH Division of Research Grants, which is now the Center for Scientific Review.

Carol Ann Sheredos, P.T., M.A., Scientific Program Specialist

Ms. Sheredos joined the Center in November 2000 as a program support specialist and policy fellow. She graduated from Ithaca College/Albert Einstein College of Medicine with a bachelor's degree in physical therapy, and she received her master's degree in adulthood and aging from the College of Notre Dame of Maryland. Ms. Sheredos practiced physical therapy in New York and then joined the Veterans Administration Prosthetics Center as a research physical therapist and performed gait analyses and clinical application studies, primarily of upper and lower extremity prosthetics. She is active in the disability community, having served as chairperson of the Governor's Advisory Council on Individuals with Disabilities for the State of Maryland from 1996 to 2004.

Nancy Shinowara, Ph.D., Director, Spinal Cord and Musculoskeletal Disorders and Assistive Devices (SMAD) Program

Before joining the NCMRR in 2003, Dr. Shinowara was with the NIH Center for Scientific Review for nearly 8 years, serving as scientific review administrator for several study sections, including those for small business proposals in rehabilitation medicine and orthopedic medicine, and special reviews for grant mechanisms involving biotechnology and bioengineering. Dr. Shinowara received her bachelor's degree in biology from Mount Holyoke College and her Ph.D. in biological sciences/neurosciences from Northwestern University. She was also a Spencer Foundation fellow in the Division of Biology, California Institute of Technology, and a senior staff fellow in the Laboratory of Neuroscience at the National Institute on Aging. Before returning to the NIH, Dr. Shinowara was an assistant professor of medicine at SUNY at Stony Brook and director of renal cell biology and electron microscopy at Winthrop University Hospital in Mineola, New York. Her research interests include functional morphology of peripheral nerve, neuromuscular junction, and intercellular junctions as well as the cell biology and permeability mechanisms of the blood, brain, eye, and peripheral nerve barrier systems and renal epithelia.

Janice Wahlmann, Administrative Assistant

Ms. Wahlmann joined the NCMRR as an administrative assistant in 2005. On July 1, 1968, she was welcomed as one of the original staff members of the newly established John E. Fogarty International Center working in the Conference and Seminar Program. Later, she moved to the NICHD Demographic and Behavioral Sciences Branch within the Center for Population Research before joining the NCMRR staff.

Michael Weinrich, M.D., NCMRR Director

Dr. Weinrich is the Director of the NCMRR at the NIH. Before joining the NIH in 2000, he was a professor of neurology at the University of Maryland School of Medicine and medical director for rehabilitation at Kernan Hospital in Baltimore. He received his undergraduate and medical education at Harvard University, trained in neurophysiology at the NIH, and served on the faculty at Stanford University. In 1998, Dr. Weinrich served as the American Academy of Neurology/American Neurological Association/Child Neurology Society public policy fellow in the office of then U.S. Representative Ben Cardin. His research has spanned a broad range of areas in medical rehabilitation including the development of new rehabilitative approaches for severe aphasia, health services for vulnerable populations, and basic research on mechanisms of anesthesia.

Appendix B: Biographical Sketches of Symposium Presenters

Scott L. Delp, Ph.D., Professor of Bioengineering, Mechanical Engineering, and Orthopaedic Surgery, Stanford University

Dr. Delp is the Clark professor in the School of Engineering and Professor (by courtesy) of Orthopaedic Surgery. He is the founding chair of the Department of Bioengineering and co-director of the Center for Biomedical Computation at Stanford University. His work draws on computational mechanics, medical imaging, and neuromuscular biology to improve treatments for neurologic and musculoskeletal diseases. He is best known for the development of highly realistic simulations of the musculoskeletal system. These simulations have been used to study neural control of movement and mechanisms of musculoskeletal diseases and to design surgeries and medical devices.

Marcus J. Fuhrer, Ph.D., Former Director, NCMRR (1993 to 1998) and Scientist Emeritus at the NIH

In 1993, Dr. Fuhrer was appointed as the first director of the NCMRR within the NICHD. Prior to that, he was professor of physical medicine and rehabilitation and of psychiatry and behavioral sciences at Baylor College of Medicine as well as vice president for research at the Institute for Rehabilitation and Research. Dr. Fuhrer's current research focuses on the outcomes of medical rehabilitation and assistive technology interventions.

David B. Gray, Ph.D., First Administrator of the NCMRR (1991) and Associate Professor of Neurology and Occupational Therapy, Washington University School of Medicine

Dr. Gray is a community-based rehabilitation scientist. He teaches in the occupational therapy program at Washington University School of Medicine. He was active in developing the participation and environment components of the International Classification of Functioning, Disability, and Health (ICF). Dr. Gray served as the Deputy Director of the NCMRR from 1990 through 1995. From 1986 to 1987, he was the Director of the National Institute on Disability and Rehabilitation Research at the U.S. Department of Education in Washington, D.C.

Dr. Gray had a cervical spinal cord injury in 1976. His research involves understanding the various factors that influence community participation by people with disabilities. His work covers (1) developing and testing subjective and objective measures of participation in context by people with mobility impairments; (2) developing person-specific interventions (exercise, personal assistance, assistive technologies, secondary health conditions, health awareness, and behavioral strategies) for the purpose of increasing community participation by people with mobility, visual, and auditory impairments; (3) assessing environmental receptivity for people with disabilities; (4) implementing community engagement initiatives to improve community receptivity for people with impairments (access to urban and rural health facilities, recreational sites, hospitality industry, educational facilities, and employment sites) using the participation in context surveys as outcome measures; (5) studying characteristics of people with disabilities who work and the receptivity of their work environments; and (6) developing and testing devices that improve the lives of people with disabilities.

Richard M. Greenwald, Ph.D., President, Simbex; Co-Director, Center for Translation of Rehabilitation Engineering Advances and Technology (TREAT); and Adjunct Associate Professor, Thayer School of Engineering, Dartmouth College

Dr. Greenwald is a biomedical engineer who founded Simbex (Lebanon, New Hampshire) in May 2000 and cofounded iWalk, Inc. (Cambridge, Massachusetts) in 2006. He holds a Ph.D. (1997), an M.S. (1988), and a B.S. (1986) from the University of Utah, Thayer School of Engineering at Dartmouth College, and Duke University, respectively. He is currently an adjunct associate professor of engineering at Thayer School and a research affiliate in the Department of Aeronautics and Astronautics at the Massachusetts Institute of Technology. He was the director of research at the Orthopedic Biomechanics Institute from 1994 to 1997. He was U.S. Director of Orthopedics/Sports/Rehabilitation for TÜV SÜD Product Service from 1997 to 2000, while concurrently serving as adjunct assistant professor of orthopedics in the School of Medicine at Brown University. He was cofounder and executive director of the nonprofit National Institute for Sports Science and Safety (1997 to 2005).

Dr. Greenwald has led research and product development projects in sports injury prevention (Head Impact Telemetry [HIT] System), rehabilitation (ActiveStep® for fall prevention), and prosthetics (Active Contact System™) related to improved socket fitting systems for lower limb amputees. He is co-director of the NIH-funded Center for Translation of Rehabilitation Engineering Advances and Technology, a national rehabilitation infrastructure resource and is the principal investigator on a multiyear multicenter NIH R01 Bioengineering Research Partnerships award studying the biomechanical basis of mild traumatic brain injury.

Dr. Greenwald serves on the National Advisory Child Health and Human Development (NACHHD) Council and served a 4-year term on the National Advisory Board on Medical Rehabilitation Research (NABMRR) for the NICHD. He is the immediate past president of the International Society for Skiing Safety, vice president of the Hockey Equipment Certification Council, and past chairman of the American Society for Testing and Materials F08.26 Committee for Baseball and Softball. He actively participates in worldwide standards development for various sports equipment.

Dr. Greenwald has received numerous research and development grants through the Small Business Innovation Research program from the NIH, the National Science Foundation, and the U.S. Department of Defense. He also has received significant funding for research and product evaluation from the National Operating Committee on Standards in Athletic Equipment and the Sporting Goods Manufacturers Association. Since 1988, Dr. Greenwald has developed medical products including prosthetic fitting systems, protective sports equipment, biofeedback devices, surgical instruments, electromechanical rehabilitation devices, and interactive medical software. Dr. Greenwald has 61 peer-reviewed publications, and holds four U.S. patents with seven patents pending.

Eric P. Hoffman, Ph.D., Director, Research Center for Genetic Medicine, Children's National Medical Center

Dr. Hoffman was fascinated by the potential of recombinant DNA and its applications to human biology since conducting an independent study in high school (1976). He was then fortunate to be able to pursue this interest with outstanding mentors, first as an undergraduate at Frederick Cancer Research Center (Nat Sternberg Laboratory, 1981 to 1982, attB/attP in bacteriophage), and then as a graduate student at Johns Hopkins (Victor Corces Laboratory, 1982 to 1986, Drosophila P element transgenics). For his postdoctoral research, Dr. Hoffman sought to apply these emerging tools to human disease, and he worked on Duchenne muscular dystrophy with Louis Kunkel, Ph.D., at the Harvard Medical Center and Children's Hospital Boston. His independent laboratory has continued to work on muscle in health and disease, while taking frequent diversions to other areas, including recurrent pregnancy loss and X-chromosome inactivation disorders, Rett syndrome, ion channel disorders in humans and horses, and spastic paraplegia.

Dr. Hoffman's long-term goals of research are to: (1) develop therapies for patients with muscular dystrophy; (2) provide proof-of-principle for personalized molecular medicine (focus on metabolic syndrome and asthma); and (3) provide training to the next generation of genome-enabled basic and

physician/scientist researchers on both common and rare pediatric health problems. The faculty members in the Department Chair (30 laboratories) share a focus on providing genome-enabled services to other laboratories regionally and nationally, including data generation, software development, data interpretation, and public access to integrated datasets. His experience relevant to the current application includes directing an NCMRR Center and conducting independent research on pathogenesis and therapies of neuromuscular disease.

Dr. Hoffman serves as the elected scientific director of the 24-site Cooperative International Neuromuscular Research Group (CINRG) clinical trials organization (http://www.cinrgresearch.org). He holds a certification by the American Board of Medical Genetics in clinical molecular genetics, and New York State Certification as genetics laboratory director. Regarding the current application, Dr. Hoffman helped conceptualize and design the proposed research and will be involved in the application of the Pacific Biosciences third-generation sequencing (single molecule) aim. The goal of this aim would be to move toward point-of-contact and/or monitoring testing models, where the cost and speed of the microbiome analyses would be dramatically reduced by the PacBio unit in his lab.

Alan M. Jette, P.T., Ph.D., Professor of Health Policy and Management, Boston University School of Public Health

In addition to serving as professor of health policy and management at Boston University School of Public Health, Dr. Jette directs its Health and Disability Research Institute and the Boston Rehabilitation Outcomes Measurement Center funded by the NCMRR. He also serves on the executive committee of the Boston Claude D. Pepper Older Americans Independence Center and is research director for the New England Regional Spinal Cord Injury Center.

Dr. Jette served as dean of Boston University's Sargent College of Health and Rehabilitation Sciences from 1996 to 2004. His current work focuses on the development and dissemination of contemporary outcome measurement instruments to evaluate the quality of health care. Dr. Jette chaired the Institute of Medicine's 2007 study and report, *The Future of Disability in America,* which highlights disability priorities for the nation. From 2005 to 2006, he served on the planning committee for the Rehabilitation Medicine Summit: Building Research Capacity, which issued recommendations on expanded research capacity in the rehabilitation field. In 1990, he served as co-chair of the Panel on Assessment and Epidemiology on the Hunt Valley Task Force on Medical Rehabilitation. Dr. Jette received a B.S. in physical therapy from the SUNY at Buffalo in 1973, and an M.P.H. in 1975 and a Ph.D. in public health in 1979, both from the University of Michigan.

Richard L. Lieber, Ph.D., Vice-Chair, Department of Orthopaedic Surgery, University of California (UC), San Diego, and the Veterans Affairs Medical Center

Dr. Lieber earned his Ph.D. in biophysics from UC Davis in 1982, developing a theory of light diffraction that was applied to mechanical studies of single muscle cells. He joined the faculty of UC San Diego in 1985, where he has spent his entire academic career, and is now vice-chair of the Department of Orthopaedic Surgery. His work is characterized by its interdisciplinary nature—an approach that is relevant to those who study biomechanics and orthopaedic surgery. Dr. Lieber has published almost 200 articles in journals ranging from the very basic, such as the *Biophysical Journal* and the *Journal of Cell Biology,* to those more applied, such as the *Journal of Hand Surgery* and *Clinical Orthopaedics and Related Research*. More recently, he has implemented molecular biology tools to understand gene expression patterns in muscles subjected to high stress and to perform mechanistic studies of muscles in which genes are introduced to muscles in an attempt to change their mechanical function.

In recognition of the clinical impact of his basic science studies, Dr. Lieber has been honored by the American Academy of Orthopaedic Surgeons (Kappa Delta Award), the American Bone and Joint Surgeons (Nicolas Andry Award), the American College of Sports Medicine (Fellow), the Council for the International Exchange of Scholars (Fulbright Fellowship), and the American Society for Biomechanics (Borelli Award). His research laboratory is supported primarily by grants from the U.S. Department of Veterans Affairs and the NIH.

Kenneth J. Ottenbacher, Ph.D., O.T.R., Professor and Director, Division of Rehabilitation Sciences, and Director, Center for Rehabilitation Research using Large Datasets, University of Texas Medical Branch

Dr. Ottenbacher is the Russell Shearn Moody Distinguished Chair in Neurological Rehabilitation at the University of Texas Medical Branch in Galveston. He serves as senior associate dean for graduate education and research and director of the Division of Rehabilitation Sciences in the School of Health Professions. He is also director of the Center for Rehabilitation Sciences and associate director for the Sealy Center on Aging. Dr. Ottenbacher received his Ph.D. from the University of Missouri–Columbia and is a licensed occupational therapist. His research interests include rehabilitation outcomes with a focus on functional assessment as well as disability and frailty in older adults. He has published more than 250 scientific/technical articles in refereed journals and is the author, coauthor, or editor of four textbooks. His research has been supported by continuous federal funding since 1984. A member of several editorial boards, Dr. Ottenbacher currently serves as statistical consulting editor for the *American Journal of Physical Medicine & Rehabilitation* and as associate editor for the *Journal of Rehabilitation Medicine.*

William Z. Rymer, M.D., Ph.D., President, Rehabilitation Institute of Chicago, and Professor of Physical Medicine and Rehabilitation, Physiology, and Biomedical Engineering, Northwestern University

Dr. Rymer received his undergraduate and medical training from the University of Melbourne in Australia, graduating with honors in medicine in 1962. After completing a residency in internal medicine, he returned for doctoral training in neuroscience and motor control at Monash University in Australia, completing his studies in 1971. Dr. Rymer received postdoctoral training at the NIH Laboratory of Neural Control (1971 to 1974) and the Johns Hopkins University Department of Physiology (1974 to 1976). After 2 years as an assistant professor in physiology and neurosurgery at SUNY at Syracuse, he moved to Northwestern University, joining the Department of Physiology in 1978, with joint appointments in biomedical engineering and neurology. In 1989, he assumed the position of research director at the Rehabilitation Institute of Chicago (RIC), accepting an endowed chair, and in 2008 he became vice president for research at the RIC.

Dr. Rymer currently holds faculty appointments in the departments of physical medicine and rehabilitation, physiology, and biomedical engineering at Northwestern University, with the rank of professor in each. He is also president of the Rehabilitation Institute Research Corporation, director of an Infrastructure Network Center (R24) funded by the NCMRR, and director of the Rehabilitation Engineering Research Center for a study titled Machines Assisting Recovery from Stroke, which began in November 2002.

His research interests include the neural control and biomechanics of movement in human and animal models and the disturbances of voluntary movement and their origins in neurologically disabled subjects, particularly those suffering from spinal cord injury and stroke. Dr. Rymer was a recent member of the NABMRR and is the liaison to the NACHHD Council. He currently holds grants from the NIH, from the U.S. Department of Education's National Institute on Disability and Rehabilitation Research, and from several foundations. He has published more than 150 peer-reviewed papers in the fields of biomechanics and control of movement.

Margaret G. Stineman, M.D., Professor of Physical Medicine and Rehabilitation, Perelman School of Medicine, University of Pennsylvania

Having served both on the NABMRR and the NACHHD Council, Dr. Stineman is dedicated to the NCMRR's objectives of fostering and training interdisciplinary disability scientists. Her personal efforts through mentoring target the dissemination of rehabilitation principles across the knowledge base of all health clinicians and scientists. As a rehabilitation clinician who cares for people with a variety of disabilities, and as a person who lives a "rich life" despite being born with multiple disabilities, Dr. Stineman knows the importance of applying assistive technology, practicing person-centered care, and embracing principles of empowerment. A biopsycho-ecological framework is fundamental to her work in recognizing the combined effects of both intrinsic biologic and mental causes and extrinsic physical and social environmental causes of impairment, activity limitation, and participation restriction.

Dr. Stineman helped establish Recovery Preference Exploration as a way to clarify the personal meanings of, and cultural stereotypes associated with, different activity limitations. Adapting principles from oncology, she also helped establish staging systems for disability appropriate to a wide variety of populations and health conditions. She and her collaborators developed an impairment and function-based classification system that was adapted by the VA for quality improvement initiatives and by the Centers for Medicare and Medicaid Services (CMS) as part of its national prospective payment system for inpatient rehabilitation.

Dr. Stineman has served many government and nongovernment organizations as a consultant or subcontractor on policy-relevant questions including the World Health Organization and CMS. Currently funded as principal investigator through several R01s, she is undertaking a number of comparative effective studies involving the rehabilitation of stroke and amputation, and she is continuing to develop a variety of staging systems to better understand the triggers of functional deterioration and recovery at the person and population level. Dr. Stineman combines science, music, and art in her efforts to expand awareness, perception, and meaning.

Richard E. Verville., J.D., Principal, Powers Pyles Sutter & Verville P.C.

Richard E. Verville joined Powers Pyles Sutter & Verville P.C. (PPSV) at its inception in 1994. PPSV is a Washington, D.C.-based law firm that focuses on healthcare, education, and the law of tax-exempt organizations. His practice has focused on health care law, civil rights and disability law, and legislation. Prior to joining PPSV, he was a partner at White, Fine, and Verville, a firm with practices in Washington, D.C., and Boston, Massachusetts (1973 to 1994); Deputy Assistant Secretary for Legislation in the U.S. Department of Health, Education, and Welfare (1971 to 1973); and Assistant to the Secretary of the U.S. Department of Health, Education, and Welfare for Policy Planning (1970).

Mr. Verville played a key role in the development of the legislation that established the NCMRR at the NIH. From 1991 to 1993, he served on the Advisory Commission on Childhood Vaccines.

Mr. Verville holds a J.D. from Columbia University School of Law (1964) and a B.A. from Williams College (1961), where he was a Westinghouse Scholar and member of the Senior Honor Society. He received the American Medical Association Citation for Distinguished Service Award for service to medicine and health in 2004, the Henry H. Kessler Human Dignity Award from the Kessler Institute in 1997, the Charles H. Best Award from the American Diabetes Association in 1988, the Distinguished Public Service Award of the American Academy of Physical Medicine and Rehabilitation in 1987, the Gold Key Award of the American Congress of Rehabilitation for Distinguished Service to the Disabled in 1979, and the HEW Distinguished Service Award in 1973. In 1997, he delivered the Joseph P. Schaeffer Lecture at the Detroit Medical Center, Wayne State University, and in 2003, he delivered the 17th annual William A. Spencer Lecture at Baylor College of Medicine.

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