Transcript of NIBIB Fifth Anniversary Symposium

Changing the World's Healthcare through Biomedical Technologies

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Bethesda, Maryland

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Welcome and Introductions

Dr. Roderic Pettigrew

It is my genuine privilege and pleasure to welcome everyone to this landmark scientific symposium marking the 5th anniversary of the National Institute of Biomedical Imaging and Bioengineering as a congressionally-appropriated member Institute of the NIH. This institute was conceived and created to provide a home for the discovery of new technologies, new techniques, and new approaches to solving the major challenges that we face in the health care system today. In particular, it was cited to focus on the burgeoning fields of biomedical imaging, bioengineering, and the nexus of the quantitative and life sciences.

Last night, at a celebratory dinner sponsored by three professional organizations: the American Academy of Radiology, the American Institute of Medical and Biological Engineering, and the Coalition for Biomedical Imaging and Bioengineering Research, we enjoyed a unique evening during which we had very stimulating and provocative presentations by the 16th Surgeon General of the United States, David Satcher, and also by former U.S. Senator, former Apollo astronaut, former pilot of the lunar shuttle, and the last man to walk on the moon, Harrison Smith. We also had the opportunity to give the first NIBIB Landmark Achievement award, which was given posthumously to Nobel Laureate Paul Lauterbur. At the event last night, Dr. Lauterbur was cited for his pioneering work and contributions that led to the development of Magnetic Resonance Imaging for which he received the 2003 Nobel Prize in Medicine and Physiology. Paul unexpectedly passed about two months ago, and we were much honored that his wife, Dr. Joan Dawson, was at this event to accept the award. She will be attending the symposium today and is en route.

For today's symposium, the focus is a bit different. Today, we focus on science, we focus on health care, we focus on the good that this Institute has done and the good this Institute will do. We've taken the theme, "Changing the World's Health Care through Biomedical Technology," and on this occasion, we have the chance to highlight some of the extraordinary accomplishments of NIBIB-supported researchers, and we have the opportunity and look forward to updating the public on the positive impact that technological innovation is having on health care. This symposium allows us to recognize the remarkable contributions of the physical science community that we serve, and to share with everyone some personal stories behind these magnificent achievements. The day's activity not only marks a milestone in our history, but also provides a unique opportunity to hear and learn from many great minds, as you will all witness.

The program will be presented in three sessions: The first session recounts the historical move from the concept of a medical technology-based Institute to its realization as the National Institute of Biomedical Imaging and Bioengineering, or NIBIB. All the speakers were involved in the conceptualization of the Institute in its first session, or its earliest days. In addition, we are delighted to welcome a true pioneer of Magnetic Resonance Imaging, Waldo Hinshaw. Dr. Hinshaw was an early and close colleague of Nobel Laureate, Paul Lauterbur. He will share his experiences and reflections on the development of MRI in his lecture, which will commemorate the Landmark Achievement Award that was presented to Dr. Paul Lauterbur posthumously last night.

After a break, we will return for the second session. This session focuses on the impact of technology on medicine and promises to be a particularly stimulating session. It will highlight 21st-century health care challenges, regenerative medicine as a transformative technology, and molecular imaging as a critical tool for realizing the vision of preemptive medicine.

During our lunch break, please note that several NIBIB scientific posters will be on exhibit. These will feature research aimed at translating new technology and new technological developments into practical solutions for health care problems. Posters from the Small Business Innovation research grantees, from members of our new investigative panel that will be featured this afternoon, and from our new Intramural Research Program at the NIBIB, will be featured. I urge you to spend some time perusing these posters and meeting the authors for some informative and stimulating discussions and interactions.

Immediately after lunch, we will return for a special treat: A presentation by our honored guest, 1964 Nobel Laureate, Dr. Charles Townes, who will offer reflections on his discovery of the laser.

The third and final session today, which will commence following a short afternoon break, focuses on the future of interdisciplinary science. This session will open with a lecture on training tomorrow's interdisciplinary scientists, and for a change of pace, we will hear from a panel of young investigators—young scientists who will share their personal journeys into interdisciplinary science and their outlook on the future.

We will conclude by circling back to the beginning as the first NIBIB grantees, Drs. Duncan and Spencer, a team consisting of a bioengineer and medical physicist, and a neurosurgeon, will illustrate from personal experience, the positive impact that team science is having on the practice of medicine and on the delivery of health care. This certainly promises to be a day to remember, and I am very proud to be able to share it with all of you.

Before moving to the first speaker, I would like to recognize…if she is here…Debbie Nagy. Debbie Nagy is the wife of the late Edward Nagy, who was the former Executive Director of the Academy of Radiology Research, a person without whom we simply would not be meeting here today. We are honored that Ms. Nagy, and later, Dr. Dawson, the wife of Nobel Laureate Paul Lauterbur, have come to join us in marking the anniversary of this Institute, and we want to extend a warm welcome to both of them.

Without further comment, I would like to introduce our next speaker, and fortunately, I don't have to be long-winded. There is clearly little I could say about him that you don't already know. After all, for most of us in this audience and on campus, he signs our checks. However, I would like to note that Dr. Zerhouni knows from first hand experience the critical role that biomedical technology can play in the pursuit of scientific knowledge and in pioneering advances in medicine and health care. He, himself, has been just such a pioneer. Without further adieu, ladies and gentlemen, the Director of the NIH, Dr. Elias Zerhouni…

SESSION I: NIBIB – FROM DREAM TO REALITY

The NIH and NIBIB

Dr. Elias Zerhouni, Director, NIH

Rod, thank you very much for this introduction, but also for the hard work that you have performed over the last few years being the first permanent Director of the NIBIB. I cannot tell you how this Institute, the baby Institute of the NIH, has performed over the past few years. Before I do this, I would like to acknowledge the fact that the creation of NIBIB did not happen by happenstance. Also, I would like to say that none of us would be here doing what we do if it weren't for the role of the giants that preceded us and the shoulders on which we stand.

To me, this meeting really feels like a reunion—a 5th-year reunion, but it's more than that. For me, it's really a 30-year reunion with colleagues that I've interacted with in my twin homes of biomedical engineering and radiology.

I'd like to go on the record here to tell you what I remember about the creation of NIBIB and the giants who made it happen. I'd like to personally recognize the incredible leadership roles Dr. Baum, Dr. Maynard, Charlie Putman, Ed Nagy, and many others, Nick Ryan, Manny Hohman, who is no longer with us… At the time, I remember a phone call in 1995—Dr. Baum was then the Chair at the University of Pennsylvania—he called me up and said, 'Rick Klausner at NCI is very interested in imaging. We need to prove to him that science will be advanced if we can make a strong case about imaging and how imaging plays a role in the entire universe of science and how it can advance science in all its dimensions.

I was given this mission to work with a group of scientists across the board of bioengineering and physics to try to develop themes that would make a difference in the history of science. I remember meeting with a very multidisciplinary team of scientists and leading workshops, and I came up with this white paper on molecular and cellular imaging *in vivo*. That theme took on a life of its own at NCI and breakthroughs happened very quickly in the field in the understanding of it.

NIBIB would not exist today if it weren't for the fact that it needed to exist in the 21st century. I'd like to dedicate my lecture to the many, many thousands of scientists who, throughout the years, have followed this line of inquiry, which is a line of inquiry I personally believe in. It guides my actions in many ways, and I'd like to share that with you. That thought process started with me a long time ago.

I like to travel, and for those of you who take long airplane rides, I don't know if you experience that, but there are some thought processes that go on as you fly over the earth; you start thinking deeply about issues. One of those things I thought about was, if you were an alien traveling around the earth and you didn't know anything about civilization, and you were trying to develop a test that will differentiate a primitive society from an advanced society, and you knew absolutely nothing—just flying on an airplane… As I was flying, I kept looking at cities and going through different countries. It was a long flight, as you can imagine, over Africa. I realized all of a sudden that there was a diagnostic test that you could apply and that actually works. The

test is the following: The difference between a primitive society and an advanced society is the quality of the straight lines you see in that society's material manifestations.

If you look at the less advanced societies, the buildings are a little wavy, they're not straight. If you look at the details of the tools, the tools are not very sharp. The quality of the straight lines, the variations of the line along the mean is greater than it is when you look, for example, if you look at the lettering in this slide.

If you travel the world… If you go, for example, to Egypt and look at the pyramids and the accuracy with which these fantastic monuments were built by engineers, you see the precision in the alignment. Then compare Egypt today. If you go to certain areas of Egypt today, you see these winding roads that are not well organized. Then you go to other parts, and if you apply the straight-line test, I can guarantee you that they will have a very high correlation with the degree of engineering sophistication expressed by that society.

Now, why am I saying that? Because it ties into another concept which is that before the emergence of humans, tools did not truly exist. If you look at the history of science, the point I want to make is that it relates directly to our ability to quantitate and measure accurately the natural phenomena we encounter, but also, to be able to build tools that conform to that new accuracy and new quantitation, and that allow you to understand the natural sciences in a way that you couldn't before.

What I want to show you is… The first slide underpins my argument that there is a natural history and a fundamental driving force in science and technology, and if we ignore it, then we lose the significance of what NIBIB is all about.

Clearly, human kind has developed tools that failed the straight-line test. Then, wheels had to be made. The thing that amazes me is that the inventor of the wheel really did not apply for an NIH grant to do it, but they did it because they had the ability to measure a straight line very accurately around a radius.

When you think about that, you realize that innovation and creativity are inherent human qualities. What has happened over the history of the sciences is that there is a very strong parallel between our ability to measure and quantitate natural phenomena, and intervene in the material world to change our understanding of the natural world.

If you look at time, for example, you look at the tools that were developed many centuries ago to measure time, you see sun dials and the accuracy was plus or minus an hour. Then we went to clocks. In 1364, the first clock was within a 2 or 3 minute accuracy. Then in 1392, the turret clock… Realize that this clock could not be made without the methods that allow development of the wheels and cranks and all of these instruments that correlate the action of the human engineer with the expected measurement. In fact, there was a grand challenge in the 16th century to develop an accurate clock for navigation, and the development of accurate time measurement is what allowed exploration of the world.

I want my first argument to be that the history of science runs parallel with our ability to quantify and measure. To separate the two is a major, major mistake. We as science managers and scientists tend to think that the value of the insight is everything there is in making progress, and that the tools happen to be there at the time the insight comes. I think, as Sid Brenner did, that there is a magic circle where better tools create new insight, and new insight requires you to develop better tools.

I'm always amazed at the accuracy of atomic clocks and the femtosecond characteristics. I'm very honored to have Dr. Townes here. As you know, his work has had profound implications in the science of measurement. The atomic force microscope would not exist if we didn't have a laser beam to measure the deflection of a cantilever. Nor could you have a GPS if it wasn't for the accuracy of atomic clocks. The GPS has a system of satellites that are synchronized to universal time. You receive the signal from a satellite with a particular time stamp, and that time stamp tells you exactly what the distance to the satellite is, assuming that the speed of light is constant, which Einstein established. Again, that shows the fundamental connection between technology, methodology, and new insights.

When Einstein made his conceptual leap, it didn't come out of nowhere. It came out of a very long series of experiments. There were 14 prior experiments that showed that the speed of light was constant. The most cited is the Michelson-Morley experiment where interferometric measurements in the direction of the earth's movement, or against the direction of the earth's movement, showed that the speed of light was constant. That was related to the ability to build very, very precise mirrors to reliably evaluate the speed of light. The speed of light is the distance traveled over time, and what was the quantum leap? The quantum leap was Einstein saying, "Well, maybe we're wrong. Maybe the speed of light is constant." This then means that distance and time cannot be constant. That meant that the space-time concept we had developed for hundreds and thousands of years was wrong.

How does this apply to the world today? In my own career as a radiologist, I remember applying for NIH grants in the late 70s and early 80s, and I was turned down constantly because what I was doing did not apply to a specific disease process. In so many ways, we've crossed the desert with NIH over the many years as imagers and bioengineers because we had to prove our work had something to do with a disease process. My core theme in research has been related to this profound belief that if you can improve quantitation, you can understand biology better.

If you look at my personal work, the first work I did was in CT densitometry using the CT scanner to measure calcium content. My friends in those days remember that my work was very controversial. I remember Charlie Putman attacking me saying I was completely wrong, but at that time, we didn't have the tools, so I spent three years of my life improving the ability of the CT scanners to measure CT numbers. Using those numbers, I proved that they had a direct correlation to calcium content in human tissues. I thought this would be of great use in differentiating benign tumors in the lung, which have high calcium content, from malignant cancers in the lung, which have low calcium content. Indeed, that turned out to be the case and helped quite a bit.

The application in which this was most successful was in the area of osteoporosis. Osteoporosis research at that time had no tool to accurately measure calcium concentrations *in vivo* in tissues, and it turned out that my patent had more application in that field, which I had no intention of entering than the field in which I started.

Then I developed better methods for high resolution computer tomography, and that allowed us to study the physiology of the lung in ways unprecedented. When I went on to MRI, I applied the same core principal—how can you measure cardiac functions or extract biologically relevant information from cancers? I worked on lymphoma and others—some with success, some without success—but that was the core theme.

The question that I'd like to pose for you is that the future of NIBIB is profoundly intertwined with this concept: To make progress in the 21st century will require further progress in our quantitative abilities, the accuracy of our tools, and our ability to understand complex systems. In fact, I believe that bioengineering should set the standard by becoming the systems biology field of science.

I show you here very worrisome data. This is the number of new molecular entities successfully approved by the FDA over the past 10 years. You can see there are a decreasing number of useful, efficacious new molecular entities even though, since 1991, the pharmaceutical industry spends more than NIH, and today, the pharmaceutical industry spends twice as much as the NIH budget trying to discover effective molecules.

Why is that? Have we hit the wall? No, I think what has happened is that we have understood better and better the complexity of biology, and because of that, the challenge in front of us is to tackle this biological complexity.

I show you here on the left, a small map of the molecular elements of the cells' response to damage; how proteins respond, how they are regulated, and how they are interconnected to respond to UV light or any other damage. You realize that these graphics are as poor as the maps that were used by navigators in the 12th and 13th centuries. They're not information-rich enough for us to fully understand the behavior of that complex system.

It would be a little bit like if you were trying to do reverse engineering of a complex chip. You're that hypothetical alien who just came and found a laptop out here on the NIH campus after having gone through security and you look at the chip and you say, "What does that chip do?" First you'd look at the elements of the chip—the transistors and resistors—that's what we've been doing for that last 50 years. We've been trying to understand the elements of that system, but the key is the software. The key of the behavior of that system is what controls the software. That is the fundamental scientific challenge of the 21st century. I believe that humanity's future will be determined by how we can develop and master our understanding of the life sciences, not just for health, but for environmental remediation for alternative energy sources—this is the key to success in the 21st century.

I show you here a slide loaned to me by Allen Spiegel. This is a complex system reconstruction with mechanical clockwise objects of the solar system. The sun is in the middle, the planets are

around, and it is rotating and reproducing the behavior of the solar system as known at the time, matching astronomical observations. Now, those observations were not accurate enough, as they later became in the early part of the 19th century, to test the theory of relativity. The theory of relativity was proven because an experiment showed that the light from Mercury was deviated by 0.5 of the minute of an arc. If you couldn't measure that, you could not confirm your insight. The same is true in biology because we have these complex systems that are interacting, but let me tell you the good news and the bad news. The good news is that we know the elements in the system. The bad news is that although we are generating mounds of data, my analysis of the quality of that data tells me that we have very sparse data; that the quantitative relationships between a gene, a gene product, and its regulation are not well known; and if you ask me how much we know and how much we need to know to be effective in improving our productivity, I will tell you we know less than 10 percent.

Don't worry; there will be a lot of good research to do and breakthroughs to make. We're only 10 percent of the way there, and we need to understand biological pathways and networks and understand in quantitative terms how these systems are regulated and what our software is like.

This is why I made the strong statement that stem cell biology is not just an issue of finding cells to replace lost function. Tissue engineering is not just an issue of constructing complex tissues to replace those we have. I think stem cell biology has the potential for us to understand how the whole system is regulated and how it's programmed, deprogrammed, and reprogrammed. That's the core challenge. That's the challenge that I don't think we can be stuck in first gear with. We need to really accelerate our progress there.

That's the core scientific challenge, and where NIBIB fits into all of this is the final strategic question. Rod and I have had many conversations about this during his tenure. He's really thought about this process, and I'd like to engage the community at this 5th Anniversary in a debate about what place NIBIB has in the whole construct of science.

Let me just summarize for you the essence of observations that we need to make as scientific managers and scientific leaders about what will change: First of all, nothing will change unless the biological data we generate from our experiments doesn't change. How is it going to change? Current biological data tends to be destructive. You destroy the experiment to be able to understand it. We need to evolve away from destructive paradigms to a non-destructive testing paradigm. We have qualitative measures, and I made the point that, without better quantitation and accurate quantitation, I doubt that we can understand the complexity of the systems.

The data that we usually generate is unidimensional. You measure the presence of a protein in a gel or other parameters. Obviously, this isn't the way life is organized. At both scales, it needs to be multidimensional. We have low temporal resolution. We need a lot better resolution at very frequent intervals. We have non-localized data, and yet we now know that the essence of information transfer within biological systems is related to the co-location of the molecular surfaces that interact with each other. Signaling would not occur if you didn't have real contact between molecular entities, so this has to be spatially resolved.

You have to understand not just the contact of the hydrogen bomb, but the contact between complex surfaces of very complex proteins. The same thing is true in tissues. Metastatic processes do not occur unless you have a material interaction between the cancer cell and its matrix, so spatial resolution is important.

I talked about high data density; we have sparse data. We need to populate the information space, and we need common standards so that we can accumulate information across the board. This slide dictates the tremendous number of strategic directions.

Imaging, first of all, in my view, should play a major role. Why? It is spatially-resolved, it is temporally-resolved, and I think we should change our functional definition of what imaging science is all about. My personal definition is that imaging sciences are the sciences of extracting biologically relevant information in a spatially-resolved, temporally-resolved mode at all scales—angstroms to microns to meters. If you change your perspective, you really also change your conceptual approach to it. Remember, I said "extracting biologically relevant information"—it's not enough just to depict, you have to extract relevant information.

The same thing is true of bioengineering. If you look at the consequences of that sort of thought process, you realize that bioengineering needs to develop the multidimensional characteristics that will allow it to understand systems, but because it is engineering, you have to reduce them to practice. To reduce them to practice, you may have to develop new tools, and those new tools will have to be based on revolutionary concepts of how you intervene and extract information from an interacting system.

I will go into a little bit of the theoretical descriptions here, but this has profound implications on the way research is conducted today at NIH in ways that very few understand the consequences of, but we all know that there will be deep consequences. In 20 years time, medicine cannot be the medicine we practice today. What we do will have to change, because if it doesn't, we have failed our mission.

What does that mean? We need to understand disease pathways; we can't just understand a disease state. We have to understand a disease cycle. How does it start 25 years before it strikes the patient? If you want to do this, you need to understand that no disease is due to a single factor. We have been so lulled into believing that there are magic bullets, but that is only relatively true in the case of diseases that are external to the human body. Infectious disease is one cause; you may attract it and solve the problem.

Today, biology requires us to understand systems of targets. If you ask pharmaceutical scientists what is blocking them, it is the fact that we do not have the basic knowledge to validate biological targets for them. You need to understand the system just as we did in HIV/AIDS; it's not just one drug that controls the disease, it's three in three different molecular pathways.

The fundamental change that is occurring, in which I think NIBIB is playing a major role and continues to play a major role here at NIH, is the fact that there is a convergence in science. Disease processes that were thought to be completely separated 30 years ago are now defined to be common. There are cross-disease mechanisms like inflammation and protein aggregation in

neurological diseases. You look at Parkinson's and Alzheimer's, and diabetes, and there are theories of the diseases that relate to protein aggregation. There are theories of the same diseases that relate to inflammation, apoptosis, immune response… I don't want to make too much of it, but clearly, this will require us to understand disease in a different way in the 21st century. We will have to reclassify our understanding of diseases.
It's been shown already that one type of cancer can have multiple subtypes, and in fact, may not represent the same disease. Cancer is not a disease, it's five hundred separate diseases and conditions. Molecular and phenotyping signatures will be driving new strategies, but when I say that, lights go on in my mind that point to NIBIB. Because you'll have to develop biomarkers, you'll have more precise quantitative new research tools, whether it's microfluidics or sensors, you'll have animal models, high specificity molecular probes, and probably *in vivo* imaging with these probes, which is an area the NIBIB is leading.

The future will depend to a great extent on how visionary the leaders of the NIBIB community are, and how bold the plans that you develop are to bring that interaction between the NIH mission-related goals and a fundamental need to improve our ability to test biological systems and understand them, then eventually go to this era of medicine I call the four Ps, where we'll be able to be much more predictive, more personalized, and pre-emptive. In other words, prevent the disease rather than cure it.

This will change the health care system. We will have to distribute health care. The community will have to be involved. Patients will be at the center of the system. How do you connect a patient unless you have an engineered system that can connect the patient, their biomarkers, their vital characteristics, [and information] that allows you to intervene long before it's too late?

This is the fundamental drive, and in my opinion, justifies NIBIB's existence, not because it turned out to be an effective legislative effort or leadership effort, but because it was the missing piece that needed to be there to accelerate progress across the entire field of biomedical research and to profoundly change health care by pushing these frontiers.

To finish, I would like to share with you a planning tool that I've used throughout my career. I call it the scan wheel method.

When I switched from CT to MRI, I decided to have a strategic approach to it because we started very late, and many groups had already made good progress. I knew we needed to make progress in physics and define some parameters, such as temporal resolution, spatial resolution… I knew computing had to advance for us to quantitate what we observed and display it and reconstruct it. Then I wanted to see what I could extract information from—anatomic information, biological information, molecular, cellular, and metabolic information.

If you look at the scan, in 1985, I think you will agree that the temporal resolution is not that great, spatial resolution is not that great. At the time I started there was no MR angiography, no cardiac MR. Bone you could see well, and metabolic studies with spectroscopy were there, but not very advanced. Then from 2002 to 2006, you can see progress is being made along all circles, except in biology.

These quadrants are a gold mine. If you recall, I described the first scan, and as it turns out, the research I did was right here where there was a gap. We built a multidisciplinary team that went after these aspects of MRI and were able to help a little bit.

Let me give an example of analytical tools; when you ask yourself a logical question and ask the community where the roadblocks and opportunities are, decisions can be made. Looking at the map of CT scanning, in the late 1990s I was asked if the combination of PET and CT would be a useful tool for research. I didn't know, but I used my map and I could see that PET/CT was doing very well, so it does make sense to combine these two.

A fundamental question I started with is this: Should the future of NIBIB be central to the future of science? I think it should, because you need improved quantitation of biological phenomena on all scales—and not just imaging, but all material interfaces that contain information. Innovative technologies will be key. Understanding of biological systems behavior and implementation of complex systems intervention will be fundamental.

This defines not only the challenge, but the direct immediate goal. I think Rod has done this through the Quantum Grant program. The sum of this is the creation of the quantum leap concepts and technologies for quantitative understanding of complex biological systems. This is a core question, and whoever solves it will be making the greatest contribution to science. The goal is to transform medicine and health through the discovery process. Thank you very much.

Dr. Roderic Pettigrew
Thank you, Dr. Zerhouni. That was a beautiful overview of what this Institute is all about, what it has been about, and what it will be about in the future. It was a cogent presentation on the critical role that technological innovation plays in improving our fundamental understanding of the universe, and how gaining that improved understanding will lead to practical improvements in health care, which in the end, is the reason we are here.

I will introduce the next five speakers all at once. The first speaker has a solo presentation, but the following four presenters are actually presenting as a sort of quartet.

The next speaker will be Dr. Alex Margulis. Dr. Margulis is known to all of us in the imaging community. He was Professor Emeritus at the University of California San Francisco where he served as Professor and Chairman of Radiology at UCSF for over 25 years before his current position, which is Clinical Professor of Radiology at the Weill Medical College at Cornell University.

Alex is so well known to all of us because he crafted one of the earliest departments in the country that actually combined the physical and imaging sciences, and engineering, and physics, and so forth, in pursuit of improving the way in which we are able to investigate health care problems, and the way in which we are able to investigate fundamental questions in physiology and medicine. He is also well known as a tremendous visionary in the field of biomedical imaging.

He is a beloved mentor. He's mentored all of us who followed him in this area, and he is a prolific author whose latest book, *The Road to Success*, is a compilation of his vision and insights on how to navigate the challenging waters throughout all spheres of life, not just in the scientific and medical worlds. He will speak to us on bioimaging and bioengineering team science in the early years.

Following Alex will be the quartet of four speakers who will present a brief history on the creation of the NIBIB, its current course, and its future. [This quartet of] presenters will begin with Dr. Robert Nerem, the founding Director of the Parker Petit Institute of Bioengineering and Bioscience, and Director of the Georgia Tech/Emory Center for the Engineering of Living Tissues. Dr. Nerem will be followed by Dr. Stan Baum. Dr. Baum is the Eugene Pendergrast Professor of Radiology at the University of Pennsylvania. He had been Chair of the Department of Radiology at the University of Pennsylvania for over 20 years, and he has contributed mightily to the early development of MRI, and particularly in the field of MR angiography. The third speaker in this quartet will be Dr. C. Douglas Maynard, who was Professor Emeritus of Radiology at Wake Forest University School of Medicine. At Wake Forest, he was Professor and Chair of the Department of Radiology from 1977 until 2000. The fourth speaker is Dr. Shu Chien who has been a University Professor of Bioengineering and Medicine at UC San Diego and Director of the UC system-wide Bioengineering Institute since 2002.

Please welcome Dr. Margulis.

Bioimaging and Bioengineering Team Sciences: The Early Years
Dr. Alexander Margulis, Professor of Radiology, Cornell University
I feel privileged to have been invited to give a talk wishing NIBIB a very happy 5th anniversary and wishing them to continue this extraordinarily important work. No times were better for imaging than the present. Biomedical imaging research is advancing in all our medical schools, and NIBIB came at the right time. There is a true explosion of new laboratories, new knowledge. Radiology research has gone from anatomy to important biomedical and biology questions, to function, to quantification, and prediction, as Dr. Zerhouni so beautifully demonstrated.

Let me show you a few examples of what is happening around the country. This is Stanford laboratory. It's magnificent, with very busy laboratories. This is one of the laboratories at UCSF. There are many other laboratories throughout the country. MGH being one of the leaders, this is just an example of gene expression imaging done by one of the labs.

To advance biomedical imaging, there must be a cohesive multidisciplinary team. All advances are really based on collaboration. It is important for radiology departments to cooperate particularly with basic science departments, because that is the future. Today, the research teams in radiology are multidisciplinary. There are clinical radiologists, nuclear medicine physicians, physicists, engineers, radiobiologists, bio- and radiochemists, geneticists, statisticians, and I apologize if I missed an important discipline represented here in the audience.

An academic radiology department is basically like an orchestra. It is exceptional only if every player aspires to be a virtuoso and loves and enjoys being part of the ensemble. The conductor is

probably the most important member of that team, because he has to inspire harmony and cooperation.

The revolution in imaging that is today started really in the mid-70s and early 70s. It started simultaneously in many places. In this country, at MGH, Washington, Cleveland Clinic, UCSF, Georgetown, and particularly in New York with Professor Lauterbur. We should not forget the great contributions of the United Kingdom at Nottingham, Aberdeen, and Hammersmith, just to name a few.

This is the very early beginning. This is Dr. Ledley's first body CT scanner here in Georgetown. Rather than going through many, many universities and boring you, let me give you a few examples from UCSF which are closest to me and makes me feel very warm.

This is the first CT rotate scanner that we developed together with GE. It shows the importance of collaborating with industry. Sometimes, departments of radiology also span industry. This is the first EB—electron beam—machine developed by Dr. Boyd and his team. We cooperated with radiation oncology and this was the first CT scanner becoming a simulator. It was in the department of radiation oncology, and radiation oncology today so much depends on imaging to be precise in their fields.

The first attempt at UCSF to go into MRI was this little 0.35 Tesla rat scanner. This is the first MR scanner from Oxford in 1980. It was developed by a team of physicists and engineers. We didn't have the space, and sometimes you have to go elsewhere to acquire space. So little was known about MR that because we were near the airport, there were articles saying that we may bring down airplanes. To show you just the collaboration at UCSF, radiology faculty members were actually driving patients to be examined at that facility near the airport, which required a veritable mountain of paperwork for permissions to do this.

Then, we moved to the new hospital and since MR was totally new and wasn't in the plans, we had to have a cantilever which happened to be located under the heart surgery suites and above—of all places—where trucks were loading and unloading. We knew nothing at that time, and as a matter of fact, this was a totally new science of magnetic shielding. I was so nervous, particularly because cardiac surgery was above it. This is the map showing how precise one has to be.

To create the atmosphere of a program and lift the team spirit, you have to mentor individuals in groups. Mentoring is essential and must be encouraged. All these teams really depend on cohesion, and mentors are so important—they come in all forms, except that they must be effective and love doing it, and they must enjoy their mentees successes and accomplishments. They also must be compassionate critics of failings.

Mentors come in all types. They range from sweet grandmothers, to Dutch uncles that criticize, but criticize with love. Assigned mentors often fail. You cannot do this by CVs and by interviews. What is the secret of being a successful mentor? It is caring, establishing a bond, being always available with advice, support, listening, and learning. The important thing is not listening only, but hearing.

The best mentoring is reciprocal. The mentor and mentee establish a bond, and they both learn from each other. There is no greater joy for somebody in academic medicine to be a mentor and then to witness the success of your protégées. They all become members of one family. Having many of them become world leaders and mentors of many others makes one who is in academic medicine worth living and fulfills their life.

I have been more than fortunate to have so many people throughout the world, and particularly in the United States, that I am proud that they have succeeded and made my life worthwhile. Thank you.

History, Milestones, and Accomplishments

Dr. Robert Nerem, Director, Georgia Institute of Technology/Emory Center for the Engineering of Living Tissues

Thanks very much for the opportunity to participate in this celebration, and happy birthday to NIBIB. I'm going to take a little time as the first member of this quartet to provide a little background as to the evolution of bioengineering, including its evolution at NIH.

One of the things I think we ought to recognize is that, if you go back to just after World War II, there really wasn't a medical device industry, there wasn't a medical diagnostics industry, there weren't biomedical engineering departments. In 50 years—just a half century—we have come a long way.

Certainly, an organization that was critical in helping to drive this is the Whitaker Foundation. They have gone out of business having done what they could do, but they not only fostered biomedical engineering, but as part of that, they also fostered the development of imaging. There are many people in the imaging field that had young investigator grants from the Whitaker Foundation.

I also want to pay note to NSF (National Science Foundation), and I'll come back to this in a moment, because they funded a process that would ultimately lead to the unification of the biomedical engineering community through the formation of AIMBE. (American Institute for Medical and Biological Engineering)

What about NIH? Well, as was noted by John Watson at dinner last night, there actually was the possibility of creating a National Institute of Biomedical Engineering that goes back to the late 1960s. There were probably a lot of reasons why it didn't happen. I understand from John that there actually was a bill, but as John likes to say, biomedical engineering wasn't unified. In fact, it took 25 more years for it to become unified. It was a fragmented community that was just beginning to get involved in what engineering could do in the field of medicine.

Even though that didn't happen, there were the beginnings of biomedical engineering at NIH. Several people are in the audience—John Watson, himself—and I saw Bob Lutz earlier, and there may be others in the audience, as well. These actually were very good people who developed a national and international reputation. A major initiative was the artificial heart program that's really what brought John Watson from Southwestern in Dallas to NIH. Even

though things were beginning to happen, there was no organization that really had the responsibility of fostering the field of biomedical engineering here at NIH.

Now, I mentioned that NSF had funded the process that led to the formation of AIMBE. I remember being in an office with a few people at the office of the Assistant Director of Engineering at NSF, John White, at the time. John looked at us at the end of the meeting and said, "I hope I never see you again." I said, "John, why do you say that?" He responded, "Well, you mechanical engineers are in today, next week it's going to be electrical engineers, and the week after that it will be the chemical engineers. If you people don't get your act together, you're never going to have an influence anywhere in Washington." He was willing to put his money where his mouth was, and he funded this process that led, through a series of steps, to the formation of AIMBE with the inaugural event being held in February 1992.

Now, another important event was the congressionally-requested—and at one point, I had it as congressionally-mandated—but more accurately, congressionally-directed by the HHS Secretary, to conduct a study on the support for bioengineering research. That was to be done through the office of the NIH Director. The NIH team was led by John Watson, who was certainly a very important voice within NIH from the moment he arrived in the 70s until he retired. There was a consultant committee that assisted him and there were two reports released. There's a whole story behind this that probably would be better with a glass of wine, and John would be happy to talk about that, but this led to the formation of BECON.

I'm not going to talk to you about all the recommendations, but I will highlight just a few. The consultant committee report, which actually came out first, included five recommendations, and three key ones I would like to bring to your attention.

First, NIH should establish a central focus for bioengineering at the highest level. Secondly, NIH should significantly expand bioengineering representation on advisory groups and in the peer review process. Last, NIH should establish an intramural bioengineering research program.

A year later, due in some ways to the intervention of Senator Bill Frist, the NIH report was released. That had four recommendations, but two that I'll talk about here. It didn't talk about the highest level, it talked about how NIH had established an interagency bioengineering coordinating committee and that NIH Institutes and Centers should include basic bioengineering research with the appropriate intramural program. Clearly, the powers that be at NIH were not prepared to take the steps that the external community thought needed to be done.

Now, BECON was formed, it was authorized by Dr. Harold Varmus, then the NIH Director, in a memo dated February 8, 1997. Dr. Wendy Baldwin—I don't think Wendy is here today, but she was a key person in helping move biomedical engineering forward here at NIH. She was the organizing Chair of BECON.

My third bullet I'd like you to pay some attention to, because that was part of Varmus' memo. BECON was to provide a focus for bioengineering issues at NIH to address current needs and to prepare for the future of this emerging area. BECON was also to develop a working definition, and John Watson was again on the scene chairing that committee. I won't go over this in any

detail, but you can go to the web site of BECON to get the information, but I know we're behind schedule, so I'm not going to spend a lot of time on this slide.

I titled this slide BECON and beyond. BECON was an important step, but was there to be a next step? What did Varmus mean in his 1997 memo when he talked about preparing for the future of this emerging area? Was it the establishment of NIBIB? Well, frankly, I don't think that's what he had in mind.
I remember a meeting organized by Wendy Baldwin. A few of us met with Varmus and I tried to convince him with the following argument: I said, "You know, at a university, the way you get things going is you find an individual to be a champion, and you've got one in Wendy Baldwin. You put an ad hoc committee together, and that gets things off dead center, and you begin to move. That doesn't provide the long-term stability needed to really have an effective effort. At some point, NIH is going to have to step up to the plate and provide that long-range stability."

Well, of course, there were a lot of people, not only within NIH, but even outside NIH, that were opposed to creation of more Institutes. It's always been an issue, and understandably so. I don't think it was Varmus' idea for that to happen. In fact, as we all know, it did happen.

At this point, I'd like to turn over the podium to the next member of the quartet, Stan Baum, who will take it further. I will make one further comment about bioengineering today, and this is my final comment. Clearly, this has evolved into a discipline in its own right, and there are many ways, as Dr. Zerhouni pointed out in his talk this morning, that we can be involved not only in making contributions, but as leaders as we move into 21st century medicine.

It is a significant part of this country's biomedical engineering community. In the U.S., there are now 79 biomedical engineering and bioengineering Ph.D. programs that are going through the NRC assessment. Most importantly, the best and the brightest engineering students want to do bioengineering. They really are our future, and I'm glad that the previous speaker, Dr. Alex Margulis, talked about the mentoring issue. Clearly, what we want, are young people who are well enough trained to be able to do things, but not so well trained to realize that it can't be done. Because the impossible can become possible, and that's an important role for NIBIB.

Stan Baum, it's all yours.

Dr. Stanley Baum, Eugene Pendergrast Professor of Radiology, University of Pennsylvania School of Medicine
Thank you very much, Bob. I also want to congratulate NIBIB on this, it's fifth birthday. Sitting in the auditorium, I felt proud I'm a radiologist. When I heard Dr. Zerhouni give his talk, the insight and the way people can articulate the future of a discipline… Well, the way he conveyed it to us in this way is a real talent. I really loved hearing your talk.

Over the next 15 minutes, I'm going to try to give you some perspective from the imaging group as to what happened leading up to the year 2000 legislation. I think it's fair to say that the road leading up to the establishment of NIBIB was certainly a long one, it was a bit torturous, but it was also an incredibly exciting time.

When I look back on this, I think of Lombard Street in San Francisco. Those of you who have gone down Lombard Street know that there are many turns, and much potential for accidents as you go down.

I would like to also briefly go over some of the things that happened at NIH that had nothing to do with imaging, but indirectly affected where we, as a discipline, were in radiology.

When Congress established NIH in 1949, they added two newly created entities: One was the National Microbiological Institute, and the Experimental Biology and Medicine Institute. Now, you'll note that their names are a little unusual, but they really mirrored the academic structure that existed within medical schools. Medical schools had microbiology departments, they had experimental biology and medicine, and here you see the organization... Very soon it became obvious that if you're going to have Congress support Institutes, it is a much better strategy to have Institutes named after specific diseases.

Shortly after that, in 1950, the Experimental Biology and Medicine Institute was absorbed by the National Institute of Arthritis and Metabolic Disease. In 1955, the National Microbiological Institute became part of the National Institute of Allergy and Infectious Disease.

Now, the problem we have always had as an imaging community was that imaging research did not have a home within the NIH, as we heard earlier today. If you consider NIH the greatest biomedical research operation, certainly in the county if not the world, not being part of this was a major, major problem. It was a problem not only for the fact that research was not occurring in the NIH in basic imaging research, but this also created great problems for the Chairs in academic radiology departments. We could not go to the Dean and ask for research space. There are many stellar departments of radiology, even today, that have almost zero research space within a medical school because the deans and senior individuals do not understand what the basic science of imaging really is. NIH did have programs that supported radiology, and most of the grants were actually within the NIGMS (National Institute of General Medical Sciences) or NHLBI (National Heart, Lung, and Blood Institute).

In 1982, the academic imaging community decided that we really had to have a group that would promote imaging research at the NIH, and the Diagnostic Imaging Research Branch (DIRB) was established in the NCI. The program remained there for the next 14 years.

In 1996, the NCI recognized medical imaging as an extraordinary opportunity and Rick Klausner testified before Congress and said we really should be investing resources in this, and they established the Diagnostic Imaging Program that became the Biomedical Imaging Program and that later became the Cancer Imaging Program.

You'll note that even though this program has been extraordinarily successful, it promotes and supports cancer-related basic translational and clinical research in imaging sciences, and to get support for something, you would have to tailor your proposal to fit into cancer.

The NCI, just as in all Institutes, really views imaging as important to the specific mission of its own Institute. Again, the basic sciences never had an advocacy group at NIH or the general

population. People do not suffer from imaging diseases, and we do not have a Michael J. Fox to go out on tour to try to raise money for imaging research.

Because of that, in 1978, the imaging community decided that we would have to be our own advocates, and we were going to have to do our own lobbying as a group, and the Conjoint Committee was formed. Many people in this room were involved in that, and certainly, Dr. Margulis a leader in that. It was supported by the Association of University Radiologists, the American College of Radiology, and the Society of Chairs of Academic Radiology Departments. Its' mission was to increase federal funding for imaging research.

Most of the radiologists knew nothing about hypothesis-driven research or quantitative research, and for that reason, the Conjoint Committee sponsored many grantsmanship conferences and hundreds of people were trained. National consensus meetings were held in 1984 and 1988. Lynn Holman led the last one in 1994, and again, this was in collaboration with the NCI.

The budget to run the committee came from those three organizations I mentioned, as well as 79 academic departments of radiology. It was the first effort at lobbying by the academic radiology community, and it was a forerunner of the Academy of Radiology Research.

In 1995 and 1996 when it really got started, the Academy of Radiology Research was an outgrowth of the Conjoint Committee, but in many ways, it was more inclusive. The Conjoint Committee was a group of academics, and somehow, we realized that if we were going to lobby for this, we needed the entire imaging community.

Those three organizations and additional members, including the RSNA (Radiological Society of North America), which is the largest imaging organization in the world, and the American Roentgen Ray Society supported us. All the broad-based societies were now supporting the Academy. It was inclusive and every subspecialty society—23 of them—recognized how important this was going to be and joined the Academy. We had as members about 100,000 professional. In additional to radiologists, we had the medical physicists join, the radiographers became members, and the Washington office was opened in 1996.

You've seen this picture of Ed Nagy and you've heard about him. As someone who worked with him closely, I can tell you, in my view, we would not be here today if it weren't for Ed Nagy. Ed was a driving force behind all of it. He understood Washington and worked for ten years as Chief of Staff for a Representative from North Carolina, Representative Valentine, and was the Press Secretary for Senator Nunn. He understood the ins and outs of Washington and led us by the hand. He was committed to the cause and wanted to see this succeed because he was convinced this was correct and right.

I should also mention two other individuals, and you've heard their names. One was Charles Putman. Charlie was Chair of Radiology at Duke and later became Senior Vice President at Duke. He was President of the Conjoint Committee and was the first President of the Academy. The shame is that he died the year before the NIBIB was established. He would have loved to have been there, but he was a great friend and leader of radiology. The other person is Lenny

Holman, who was Professor of Radiology at Brigham and Harvard Medical School, and also an officer of the Academy, whose passing was also untimely.

Going back to the Academy, we now had a budget of $450,000, because we had all the organizations contributing. The mission was to build support for imaging research at the National level, and the ultimate goal was the establishment of an Institute.

There were many roadblocks. There were pockets of people within NIH that supported this, but I think it's fair to say that the rank and file of the institute, the Director of NIH, did not see this as a major advantage. Despite all of this, the NIH Board, and again, with the support and encouragement of Ed [Nagy], we decided the ultimate goal was not to have a Center, we wanted an Institute.

Richard Burr, at that time, was a representative from North Carolina. Actually, Doug Maynard was a native [of the State] and a friend. Doug convinced Richard to support and introduce a bill in the House for biomedical imaging. Unfortunately, it died in the House. It was reintroduced in 1997, and also had a Senate version, but that also did not go very far.

Then the critical point, the pivotal point, was joining with AIMBE. Again, it's obvious to me that we would not be here today if we had not made that decision, and if AIMBE had not been willing to join the imaging community to go in for a joint Institute. Once we did that, we represented a much larger scientific community, and one that made a lot of scientific sense.

Again, we went back to Congress with the help of Gary Glover and Ron Arenson—Ron being from the UCSF and Gary from Stanford. We were able to convince Anna Eshoo, [Congresswoman] from California, to introduce a bill for an Institute of Biomedical Imaging and Bioengineering. That was done in 1998. We had a similar bill introduced by Senator Trent Lott. Note that then, we had a bipartisan bill; the Democrats were in favor of the bill, as well as the Republicans.

Since the Clinton administration had only one more year, we decided that the pivotal year would be from 1999 to 2000, and if this was going to be accomplished, we had to do it now. Otherwise, with a new Administration, we would have to start all over again.

We decided to make a major push, and with organized radiology and bioengineering, 13,000 letters were sent. All members of the House and Senate were contacted, and I suspect, that half the members of the House and at least half the members of the Senate were personally visited. Ed Nagy took us around and we made our case. We had 171 co-sponsors in the House and 11 in the Senate.

To convince the House that this was not just something a few people wanted, we had Chairs of three major departments in different parts of the country testify before the House subcommittee—Nick Bryan of the University of Pennsylvania, Reed Dunnick from the University of Michigan, and Bruce Hillman at the University of Virginia.

Then, lo and behold, on September 27th, our first success in that the House bill passed by a voice vote. On the last day that the Senate was in session, which was December 15th, the Senate also passed the bill by voice vote. This was a Friday night, and I remember, we got a call from Ed, and we were all ecstatic. The next day, the bill went in to the desk of President Clinton. Then Ed reminded me that the House and Senate were both in recess, and he asked me if I remembered what a pocket veto was. The last time I heard that was in a civics class in school, and just to remind you… When the Congress is in recess, the President has ten calendar days, excluding Sundays and National holidays, to sign the bill. If it's not signed by that time, it's a pocket veto, and you have to start all over again.

Well, if you do the arithmetic, we had two Sundays and Christmas between December 15th and that took us to December 29th when President Clinton signed the bill. NIBIB was established by law and we all know the rest.

It was an exciting journey. I don't think any of us were more pleased with anything in our careers as what had happened on December 29th when NIBIB finally became a reality. We were all delighted then, and we are delighted to be here celebrating this birthday and hope to be here to celebrate many, many more.

Thank you very much.

Dr. C. Douglas Maynard, Professor Emeritus of Radiology, Wake Forest University School of Medicine

Good morning! I hope that most of you were at the party last night. It was a smashing event and a great celebration for the NIBIB birthday of five years. I'd like the staff that organized that event to stand, and let's give them a round of applause this morning.

I certainly am happy to be here, Rod, and I appreciate the invitation. It's very important to me, and we worked on this very hard, and as has been pointed out, it took dozens and dozens of people over the years in order for us to accomplish this. It was not just two or three people, but hundreds of people, including Congressmen and Senators. The second thing I'd like to say is that I was on the selection committee that recommended Rod Pettigrew to be the first Director of the NIBIB, and I was on the first Advisory Board, so NIBIB is very important to me.

The group gave me the task—the fun task, really—of talking about the achievement through the first five years. I have to thank two people: Bill Heetderks and Karen Peterson, who are on the staff here and helped me over the last several weeks while I was trying to get the information together to present this morning. I will tell you that the achievements have been so great that it will be impossible for me to cover all those things, so I promise you I'm going to be brief and I will only cover those things which I feel are most important. This is an outline of what I plan to go through this morning, but very briefly.

First of all, we went after our first Director of the Institute, but I would like to comment that Donna Dean, who was our Acting Director at that time, did a superb job of getting us started. When Rod showed up, we were quite ahead of the game because things were already assembled and organized.

The committee looked at a lot of people, and one of the things pointed out last night by John Watson, was that we recommended to the NIH that Rod Pettigrew be the first Director. As John said, it was clear to us that he had a unique background that made his appointment obvious to us. He has a Masters Degree in Nuclear Medicine and Engineering, a Ph.D. in applied Radiation Physics, an M.D. Degree, and he had done residency programs in Internal Medicine and Nuclear Medicine. While he was on the staff at Emory, he was a Professor of Medicine and Radiology and Bioengineering. In addition to that, he did pioneering work in MR research. He had all the qualifications necessary to lead this joint venture between the bioengineering group and the imaging group. I might add that he's done an absolutely superb job these first five years, which has been pointed out by a number of people.

The first Advisory Committee that was appointed basically mirrored the background of Rod. We had a mixture of people from different disciplines, from different parts of the country, different ideas and different backgrounds and talents. This is the list of the first who were appointed, and this is the current list, which is quite similar to the first list regarding the backgrounds of people.

Last night at the party, I ran into a large number of those who had served on our first Board. Some are here today, and there are also some from our current Board here today. I would like to ask all the Board members, both past and present, to stand and be recognized.

You need to realize that we have had a lot of distinguished members who have served on the Board. We have Presidents and Vice Chancellors of universities, we have Deans of medical and engineering schools, we have CEOs of medical centers, we have Chairs of departments of Radiology and Engineering, world-class researchers in clinician scientists and educators and industrial members. They have all done a superb job and met 14 times since the beginning of the NIBIB, so they've put a lot of time and effort into this.

Let me just talk briefly about the early years. The first is that, right from the start, it was decided by the staff and the Board, that the research that was going to be supported had to be both discovery research, and applied research, and they wanted to stress interdisciplinary training programs. I think, as was already pointed out by Dr. Zerhouni, that's what we really needed to be doing, and that's just what has happened over the first five years. That set the groundwork for what we were trying to do.

Although the first grant was given in 2002, 2003 was probably the first full year of operation of the NIBIB. A lot of the researchers who would be applying to the NIBIB didn't realize that this was available to them at the time; we didn't have large numbers of people applying for R01s that first full year. The staff decided that what we really needed to do was put out a number of RFAs of broad topics. They put together 10 RFAs, which in my understanding, is a lot of RFAs for one group to be putting out in one year. As a result, we got tremendous response and over 1100 people applied, and interestingly enough, something that will be a theme throughout my talk, about half of those were new investigators at NIH, which isn't so surprising because they couldn't actually apply before. Additionally, the quality of the responses that came in response to the RFA was great.

I want to just briefly mention the strategic plan. Not to cover it in any detail, but any of you who are interested in the people on the staff at NIBIB, it's worthwhile going on the web and looking at their site, because it is superbly done. I go back and look at it all the time because it has so much material and outlines what Dr. Zerhouni said we needed to do. It's extremely well done, and I direct you there.

I would like to point out one thing about it. It talks about the areas of focus that came out of the strategic plan. There is point-of-care technologies; image-guided, minimally invasive interventions; regenerative medicine; optical imaging; biophotonics; biosensors; large scale bioinformatics and data acquisition; standardization and access; low-cost technologies; and interface of quantitative and life sciences. That's what the original focus of this strategic plan, which was developed in 2004, is all about.

I'd also like to mention briefly the outreach programs. I think that the NIBIB staff has done an absolutely superb job in trying to reach the people that should be applying to this Institute, and this started from the very first day. I know Donna Dean started it in her first year, and Rod has continued it. Throughout the country, they've been putting on regional grantsmanship seminars to acquaint people with the possibilities of applying for grants at the NIH. They have also been putting on exhibitions at scientific meetings to try to reach as many researchers as possible, and it just continues. Events are coming up in the summer of this year; the next will be June 21st in Keystone, Colorado. Just to give you an idea of what it looks like on a map, here are all the places at which they have already either had exhibits or put on training programs for potential researchers. They have really tried to cover the field and get input and make the NIBIB accessible to as many researchers [as possible], both in the imaging and bioengineering communities.

I think the group has come up with a very large number of innovative programs and unique policies to try to move the NIBIB forward. I'm going to mention just a few of those.

The first is very important, which is trying to get new investigators into the NIBIB. Right now, they're identifying the new investigators and giving them a break on the pay line to enable more to get R01s. We think this will improve the number of R01s for new investigators, and I might point out that this is a policy that applies only to program announcements and R01s.

As has been said several times, Ed Nagy was a superb individual. As Stan Baum mentioned, he and I always worked with Ed throughout his career as the Executive Director of the Academy. He was instrumental not only in helping us get the NIBIB, but I can tell you that Ed also was very instrumental in helping the NIH. His loss is not only to the NIBIB, his loss is to all of us, because he had such an interest in what was going on at NIH and had such great contacts on both sides of the aisle in both the Senate, and House of Representatives. It's just unfortunate that he's not here to help us get our doubling of the NIH budget in the future, which I'm sure he'd be happy to do.

I think it's very appropriate that the New Investigator Award will be named after Ed. I really appreciate Rod and his group for doing that, because it's extremely well-deserved and people will remember Ed forever.

Just to give you an idea of how successful NIBIB has been in attracting new investigators, this is a list that was given to me by Bill that shows the number that has been approved each year. The largest number was in 2003, and that was the year we basically started, so that was the year when we all of a sudden had investigators who had never applied to NIH before. We had a large bump there, but you can see that it has continued.

Just to give you an idea of how it fits into the NIH, NIBIB gets only 1 percent of the total NIH budget, but regarding new investigators, they're at 2 percent. They're doing a much better job of getting new investigators than some of the other Institutes.

I think also, NIBIB is very interested in the bridge to integrate the life and physical sciences. I think that's something that has already been talked about, and I think that's something that will occur. I think that's quite innovative and I think they're doing an excellent job of that.

Also, trying to support high-risk and potentially high-impact research… I have heard for many years, and I'm sure many in this room have as well, people saying, "Well, I sent my grant into NIH, but I was so different from everything else and I was so farsighted that they didn't understand what I was doing and I got rejected." This is some way of trying to answer that problem that investigators at least think they have. Their goal is to identify and fund at least one or two or more R01 applications that look at highly innovative or groundbreaking ideas. They would be granted if they were within a certain pay line or score.

I've been reading a biography on the life of Albert Einstein—maybe you all have read that—and I think he would be smiling up there because one of his comments is that imagination is more important than knowledge. I certainly think that was what this was trying to address.

Something that Dr. Zerhouni mentioned is the Quantum Grant Program that Rod came up with. I think it's superb. The whole idea is to develop a quantum level program that advances health care by funding research and targeting projects that would develop new technology and modalities for diagnosis and treatment and prevention of disease. It's some major breakthrough that we're looking for that may be high risk, but let's take a chance and maybe this will do it.

The very first one that they have funded is one on neurovascular regeneration by Karen Hirschi, a researcher at Baylor University College of Medicine, whose goal is to engineer neurovascular regenerative units *in vivo* for implantation into the damaged cortex of stroke patients. As we get a little older, we would like to have something like that. Her Co-Primary Investigator is an individual in London, Robin Lovell-Badge. This is the kind of program that the Quantum Grant is for, and hopefully, there will be many more studies like this in the future.

When I was on the Advisory Board, I was chairman of the training committee. One of the important things is to train more researchers. The priorities of NIBIB are feeding the pipeline and helping the transition to independence, which is going from training to an independent researcher. Training at the interface, which Dr. Zerhouni talked about, is so important. We've got to bridge the gap between all these different disciplines, and we've got to develop more clinician/researchers. I've been hearing that for years, and that's still true. Of course, we've got to increase minority representation.

The goals are to attract students into research and bioimaging and bioengineering, to provide training opportunities, to fill the critical gap in career curriculum, to anticipate workforce needs and prepare for them, and to have more participation by underrepresented groups.

Also, NIBIB has done a great job in working with other Agencies and Institutes, so there are a number of interagency partnerships that have developed. These are with the National Science Foundation (NSF), and Institutes at NIH, and also with the National Institute of Standards and Technology (NIST).

As I pointed out, training at the interface has been one of the hallmarks of what NIBIB wants to do. Although there are a large number of grants that address this issue, the one thing that I will mention is the Howard Hughes Medical Institute and NIBIB Interface Initiative where any institution in the United States that has a Ph.D. program is eligible for participation in a grant proposal, and it's to develop the university-level programs and give Ph.D. students the knowledge and skills necessary to conduct interdisciplinary research, to reduce barriers to interdisciplinary graduate science education, and develop best practice methods that other universities might apply in the future.

Also, as I mentioned earlier, in trying to get more clinician researchers, medical students, and resident fellow programs, I would like to mention one program that's unique to this Institute, and that is the Supplement Program for Clinical Residents. This came out of a recommendation from a group meeting and workshop we had on training. The whole idea was that, in Radiology, we had a hard time identifying fellows and residents who were attracted in the research field, and we wanted to get them interested in research. How can we do that? Basically, this provides one or two years of training for people who have existing grants within the department who can then take on a supplement resident to work with them. Hopefully that would attract them to careers and make them want to get additional training in research.

My understanding from Bill Heetderks is that we have 12 people who have done this now. I believe NIBIB is the only group doing this, and I would like to encourage you in the audience who have imaging or bioengineering grants in your institutions to consider doing this, because we would like to have as many more clinician scientists as possible.

Radiology has been trying to figure out for years how to increase our numbers. A lot of programs have been created by the scientific societies trying to do just that, and it's obvious that we have been somewhat successful. In 1993, we only had 32 M.D. Radiologists who had NIH grants. In 2002—and that's the last year I could find a number—there were 238 M.D. Radiologists who had NIH funding as Principal Investigators. Now, that's a lot more investigators, so we've been doing something right, and I hope we continue to do that.

I just briefly want to mention that we started the Intramural Research Program and to point out that a committee of external reviewers came in and made recommendations, and they decided we needed a small intramural program. I think the biggest area of discussion was that this Intramural Program would not compete with people at universities and that it would be unique to NIH and could work with the other research programs at NIH. That is the goal of the Intramural Program.

Last year, we appointed Richard Leapman who is just starting to lead this program, and I hope that in the next year it will really evolve into a major resource for the Institute.

I was asked to give just a few personal observations at the end of the talk, and first, I just want to say that NIBIB has done a great job. It has far exceeded in the first five years anything that I ever thought could happen, and I think the group is very pleased at where they are. Although, as pointed out by Stan, the marriage of imaging and bioengineering was a political issue when we were trying to get NIBIB started, there were a lot of us that felt like it was a great marriage to begin with. I think that has proved to be absolutely correct. I think it fits right into what Elias was saying about where we're going. We're going into team research. That's where it's at. Bob Nerem said the same thing. Research of the future is not going to be one or two individuals; it's going to be a team of individuals from multiple disciplines doing it.

There's an old African proverb that says, "If you wish to go quickly, go alone. If you wish to go far, go together." I think that's what we are trying to do here—to go together—because as has been pointed out, there is a lot of information we don't have yet.

We have been very innovative at NIBIB. I think I've shown you that the staff look for things they can do to make a difference. We've attracted many new investigators to NIH, but I can tell you, it is the tip of the iceberg. I will warn you that there will be many more, particularly from the bioengineering community, that will be coming. I was on the advisory board of the College of Engineering at Virginia Tech for four years and just went off recently. There are tons of faculty mentors and graduate students there that are doing great research and it would certainly be applicable to medicine if they just knew it. When they find that out, they'll be coming here. There will be a lot more, but they'll be coming from engineering schools.

The last thing I'll say is that all of us in this room that can legally do it—some of you can't—should lobby Congress and the White House for more funding for NIH. We need to double the budget again. We have had a huge surge of monies over the years, but new research has come out every year, and we can't afford to lose that collective power of knowledge and wisdom of those kids by not having enough money for new investors come in. It's very important that we increase the funding of the NIH. A little prejudiced to the NIBIB, I would like to see us get more of our share, and I'd like to see this institute grow from where it is right now at about $300 million per year, to about $1 billion, which is midway among all the Institutes.

Thank you very much.

Dr. Shu Chien, Professor, Department of Bioengineering and Medicine, University of California - San Diego and Director, University of California Bioengineering Institute
Good morning everyone! It's indeed a pleasure and privilege for me to be a part of this celebration of the 5th Anniversary of the NIBIB, and to follow my three distinguished colleagues, being the last of the quartet.

The NIBIB has the mission of improving human health by leading the development and accelerating the application of biomedical technologies. The Institute is committed to integrating the physical and engineering sciences with the life sciences to advance basic research and

medical care; you've already heard this a few times. The vision is that the NIBIB would profoundly change health care by pushing the frontier of technology to make this possible to become a reality.

The programs and focus areas of NIBIB covers a wide range, and Doug—Dr. Maynard—just covered seven of a list of 20 items which goes from—well, not quite A to Z, but A to X. I will not be able to cover all of these, but I will choose a few examples to show what NIBIB has done in the short period of five years under the wonderful leadership of Dr. Rod Pettigrew through the wonderful work of the staff within the NIBIB.

This slide shows the interface technology used to engineer tissue for cartilage repair. What we have here is the work from Dr. Eliseeeff from Johns Hopkins where, in order to get an engineered cartilage surface to work on the normal surface of human tissue, what she and her colleagues have done is they have removed the debris and used hydrogen peroxide to clean this up. Then they used collagen with other materials with UV activation to polymerize the material to improve the interface with the native cartilage so this cartilage implant can grow as a normal cartilage. This is the use of technology for regenerative medicine.

This is the work that Doug Maynard just mentioned. It's a Quantum program in neurovascular regeneration. The goal here is to engineer a neurovascular regenerative unit *in vitro* to implant into the damaged cerebral cortex of stroke patients. This slide shows the neuro stem cell niche *in vivo* and what it is like. What Dr. Hirschi and her colleagues have done is to make a microvascular network, and have quantitated cell-cell and cell-matrix associations. Then, they put these together to generate the niche *ex vivo* to have endothelial cells for the blood vessels and neural stem cells for the nerve tissue, and then put it together. Then, the ultimate aim is to implant this into the stroke-injured cortex so we can regenerate the brain function of the stroke patients.

Now, in order to do tissue engineering, we have to go to the cellular and molecular level, and to understand how the cells move and behave, and how they differentiate. There are studies supported by NIBIB to do this.

This example is from Dr. Chris Chen who used to be at Hopkins, but now is at the University of Pennsylvania. In this example, he uses a smooth muscle cell, but you can use any kind of cell, such as a mesenchymal stem cell, and you put it on an array of pillars that are flexible. When the cell is seated on here, due to the cell motion, you can band these pillars and you can register motion of each pillar and deduce the force the cell exerts on the substrate, as well as the interplay between the cell and the matrix.

Early detection of disease is very important in saving money and to improve health care. This example is for the detection of pathogens in the urine by the use of array technology, and it's automated to detect microbes at the point-of-care. Normally, it would take at least a couple of days to get the results back and before the doctor can decide what kind of antibiotics to use, but with this technology, it's a matter of an hour or less to do that. This is an ultrasensitive chip on which various kinds of probes are put on which are specific to certain types of pathogens. You take the urine with the microbial organisms that have RNA that can be isolated as a target, and

that interacts with the appropriate probes on this chip. This chip produces results that come in the form of a digital readout very quickly, which facilitates diagnosis and accelerates treatment, which will lower the cost of care tremendously.

Now, to have drugs to treat diseases, we have to know the structures for intelligent drug design and discovery. About one third of drugs are those acting on the G protein-coupled receptors, called GPCR. The structure of the GPCR is generally not known, except for rhodopsin. Dr. Opella has used a homology-based model because of the 25 percent identity in 230 residues of rhodopsin. In this particular GPCR, which is the cytokine receptor, he was able to deduce the structure of the CXCR 1 without being able to perform crystallography, because there is no crystal. From that, he can do the reverse and transfer to NMR data. Knowing this deduces the structure generating AMR data. If you use labels for isoleucine specificity—there are about 20 of these—then you can look at the isoleucine AMR spectrum, and you see the alpha helix and the beta sheaths in these two regions. These are simulations totally from the deduced structure and reverse AMR prediction, and here are the direct AMR experiments; they are very closely related. This approach may allow one to deduce many GPCR structures and to design drugs intelligently.

This slide is on three-dimensional optical coherence tomography (OCT). This is a novel, real-time, high-resolution technology that allows one to look at structures and functions of various tissues. In this case, it's a developing brain. You can get inside the developmental biology and functional genomics. This is the OCT picture, and here is the hematocapsuling using a staining histology picture where we see very close correspondence between the two in terms of the various structures in the brain. This will be very important in the future, and it's already starting now to look at developmental biology and clinical diagnosis.

Nowadays, there are many ways to do surgery by robotic assistive device so that a surgeon doesn't have to touch the operation field. As a result, you lose the sense of touch, which is haptic. This study has developed visual feedback and sensors, which will allow surgeons to get a feel for the tissues in the operating field through these devices even though he or she cannot really touch it. This will accelerate the surgery and improve the effectiveness of the surgery.

There are image-guided procedures, for example, in cardiac ablation—this is the work by Dr. Robb. In this electrophysiological technique, we localize the region of the heart that has abnormal electrical impulses that cause an arrhythmia. By using this particular image-guided approach, he is able to get 3-D information on the electrical activity, as well as the structure of the heart. He then can decide where to guide the RF ablation of the region. You get better visualization and reduce treatment time.

This is a picture taken at a U54 center supported by NIBIB together with NCRR and others, including General Electric and Brigham and Women's Hospitals. This is a kind of surgical suite where, in the future, a combination surgery and real-time MRI will be housed. You will have the latest combination in imaging and surgical tools put together for the surgery team so that you can have real-time acquisition of the surgery information and do the surgery in correspondence to the dynamic information that one gets with this particular approach.

NIBIB has grown since the first year of its establishment from giving out about 284 grants to about 750 grants today. In the last four years, the number of grants have leveled because of the funding restrictions, so the number of grants and the number of dollars have been around $250M to $260M level for the last four years. Although many of these grants go to new investigators, this figure has lowered. In the last three years, it's gone to 33 percent, but this is the highest among the NIH Institutes. Another quarter of them are small business grants, or SBIR grants, to support basic research, so there are many important features of the NIBIB grant portfolio, and the pay line is really quite high. I was mistaken before. I thought it was much lower than this. It's amazing that it can be kept this way, but the funding is really very limited by the budget. As Doug said, we should push for $1 billion. That's definitely what we need to do.

One last thing that I'd like to say is that the training grant funding has increased both the number of trainees and the dollar amounts. This shows how NIBIB emphasizes training, even with a limited amount of funding. I want to show you the NIH 5-year doubling. Unfortunately, NIBIB came in when the budget was leveling off, so we need to double this in a very short time again.

I'm going to skip these two slides and just sum by saying happy anniversary NIBIB, and warmest congratulations Rod and your colleagues and Dr. Zerhouni and everyone here at NIH. I wanted to express on behalf of the community a sincere thanks to all of you who are leading this wonderful effort and have made these great achievements. We pledge our wholehearted support to the NIBIB and to the NIH. All the best wishes for a marvelous future for NIBIB.

Thank you very much.

Dr. Roderic Pettigrew
Thank you Shu, and thanks to the quartet of four and Dr. Margulis for their presentations.

In 1973, Paul Lauterbur took a bit of a detour from his area of research, which was MRS (Magnetic Resonance Spectroscopy), known at that time as NMR Spectroscopy. He actually conceptualized using this phenomenon to produce images of living organisms, and potentially, the human body. That was published in 1973 in *Nature.* It was a seminal publication that started this whole field of MR imaging.

In 1974, a young Ph.D. postdoc met Dr. Lauterbur and began a collaboration between the two of them, and a friendship that continued up until Dr. Lauterbur's recent passing. That postdoc was Waldo Hinshaw. Waldo is a well-known pioneer in MR imaging to all of us in the field. He produced some of the very earliest images of animals and living organisms and was cited by Dr. Lauterbur in his Nobel address in 2003.

As a result of his development and early experience in this field, he was recruited by Harvard early in his career to begin an MRI development program at Harvard, and was later recruited by industry at Johnson & Johnson to lead a development team there to create the very first MR machines produced by Johnson & Johnson. He led that effort, and after working there as the chief officer, also continued to work in conjunction with Harvard Medical School, and later matriculated to the West coast to pursue another industrial avenue of research.

He has continued, however, to be interested in the mathematical underpinnings of imagery construction and is an expert in this area. I can think of no one better suited to deliver this commemorative address in recognition of the Landmark Achievement Award that we presented [posthumously] to Dr. Lauterbur last night. Please welcome an MRI pioneer, Waldo Hinshaw.

Commemorative Lecture in Recognition of the NIBIB Landmark Achievement Award to 2003 Nobel Laureate Paul Lauterbur: Reflections on the Development of MRI
Dr. Waldo Hinshaw, MRI Pioneer
Thank you. It's an honor to help you celebrate a birthday. It's also sad, on the other hand, that you have to listen to me instead of the intended speaker. As I said, it's an honor.

I think no one is more appropriate than Paul Lauterbur to receive such an award. As always when some big development occurs, many people are involved, but we tend to pick one person and hold that person up as the inventor. Often, that one person didn't contribute as much as some other people did, but in this case, it's different. There's one person who stands as the person who conceived this whole field, and that's Paul.

He was a conductor, as Alex Margulis said. He kept the group working in the field at the very beginning—he kept them friends. He visited each site, encouraged, and had all of us working together as friends and communicating, which was a little unusual, and he was a mentor to all of us.

I'm going to try to give you a feel for what was happening in those early days, and I'll take it from before the conception all the way up through the day we started getting into the industrial effort. I'll do that in less than 20 minutes, so I have about twice the number of slides I should have, and I've got less time than I need, so I may skip slides, but I still hope to give you the feel for what happened.

The story can be broken into different phases. Preconception is NMR before imaging, and I'll deal with a little misconception that got the whole thing started that is not well known. Paul had his ideas in 1971 roughly, and it took about ten years before this technology really was born and got into the clinical environment, and then, of course, there was celebration.

Rabi was the first one to use the phrase Nuclear Magnetic Resonance back in 1938, and when I was doing NMR research back in the physics lab, this was the kind of equipment we dealt with. To think that it could be put into a hospital was a bold idea.

You can't mention NMR without mentioning Felix Bloch and Edward Purcell, one on each end of the country, who really did the first work. A lot of people early on were interesting in applying NMR to biological materials, and I'll just pick one example: O.J. Singer who worked on the West coast. He was putting mice in the spectrometers. In 1952, he published a paper in *Science* with a picture of his daughter, and he measured blood flow. Also, people were well aware of the use of gradients, so one-dimensional imaging, if you can call it that, was well known from the very beginning.

Here's another example of people trying to do biological work with NMR. This is at the University of Nottingham. There were two imaging groups that grew there. One headed by Raymond Andrew, who I was working with, and the other, Peter Mansfield, who was the center person in that slide. Bill Darbasher on the right was making measurements of fish using NMR with an industrial grant because he claimed that if you killed the fish after struggle, the flesh wouldn't taste as good as if you killed the fish peacefully. He was killing fish in various ways and measuring the NMR properties. This is the atmosphere where Paul found himself.

I'll go through this quickly…structured water… There was almost a cult, if I can call it that, of people who believed that water structure was the key to disease. I put this in thinking I had more time, but the word "prophet" and other almost religious terms were involved by people in that group. They believed that water had two forms in tissue, and if the tissue was healthy it was one structure, and if it was unhealthy, of any sort, it had another structure.

Freeman Cope was one of the advocates, and he went to a small company outside Pittsburgh to do NMR measures, and later, Raymond Damidian followed that, as well, and was part of that effort. He did NMR measurements looking at water to see if tumors had different NMR signals from healthy tissue. He published a paper in *Science* in 1970 and this was my first awareness of people trying to diagnose medical conditions using NMR.

Later, others did the same. Paul Lauterbur was at a small company for a year and he saw people coming in to measure tissue and he said to himself, "You have to be able to find out where it is. It's not good enough to know there's a difference, you have to locate it." He wrote these notes and had countersigned on September 2, 1971, in which he said that it is possible using gradients to determine where the signal is coming from, and that is really the conception.

Later, Damidian patented, and this became important. I wouldn't have mentioned Damidian except that a lot of you have heard of him, I'm sure, and the conflict that arose around him. This particular patent, and I have spent much time with it, and it doesn't mention imaging and doesn't hint at spatial localization in any form. The real important publication occurred in 1973, and this is the first published NMR image of any sort. (Article by Lauterbur, Oct. 30, 1973, in *Nature*)

Soon after this, it was in August of this year; I had attended a meeting in Krakow, Poland, and heard Lauterbur's work referred to. Also later that year in Bombay Paul Lauterbur spoke, and that was the first time I talked to him. Then on the plane flight back to England where I was living, I began to think about how that could be done without a computer, since I didn't have one, but I did have NMR equipment. That meeting actually occurred in January of 1974.

Now we get into ten years of development. In February of that year, my claim to fame is that I did the second NMR image. Being second is not so bad sometimes. Peter Mansfield, as I said, had a second group going, and a year or two later, he published an image with surprising symmetry involved.

Going through a little bit of the contributions, Richard Ernst suggested using Fourier transforms and that really changed the approach because prior to that it was all back projection. Peter

Mansfield and Al Garroway developed a way to select a slice, which was another big step forward.

In January 1975, I had moved back by that time to the University of Pittsburgh, Raymond Andrew and Bill Moore at Nottingham had applied for the first-ever grant to do NMR imaging from the MRC—the Medical Research Council of Great Britain. As soon as the grant was awarded, they called me and said, "You've got to come back and do this. We've got the money, but we don't have any people." I went back.

These are the images they used to apply for that grant. These were done in a traditional NMR spectrometer. Since there was no computer, it was a sensitive point kind of method scan. It was very slow, but it did show that there was potential.

Now I'm just going to go through some of the images. These are Peter Mansfield's first recognizable images from the other group at Nottingham. One of the first human images, which is a finger, of course.

These are two kids that did the machine development along with Paul Bottomley, who I didn't get into the picture, that's Neil Holland and myself. I don't have many pictures of people. I now wish I had taken a camera and used it more.

Here's a publication in *Science*. A lot of the early work was published in *Popular Mechanics* or newspapers. You might recognize some of the people in this photograph. Jay Singer, who I already mentioned; and Joseph Frank I think is probably in the audience, is in the back looking a little younger; and Ted Becker, of course, looks exactly the same; then Paul Lauterbur on the far right; Jim Hutchison also on the right who was at Aberdeen—they didn't have money to do NMR development, but they were clever, and Jim, in particular, was extremely clever and did some good early work. Paul gathered people together, and as a result, we all became friends in those few early groups.

We're now well into the gestation period. That's Paul's group back then and a picture of his magnet. I was there in his lab the week the magnet was delivered. Paul was not happy. This magnet was supposed to be quite a bit larger. It had four coils, and the central coils were supposed to be the outside coils so you could get people in and do whole-body imaging, so that was a big disappointment. That was the first human NMR imaging magnet.

I think Paul's major contribution was advocacy. He did do images in the lab, but he spent, I think, probably more time out lecturing and convincing that this was the technology that warranted attention.

There's a lot of stories about that; that particular machine is supposedly here in Washington in a museum. That's Damidian's lab book that was used in many court cases and his pictures.

UCSF had an early imaging group with RIL—Leon Kauffman and Larry Crooks and Alex Margulis. This set of images really doesn't indicate how really strong and useful that group was. In fact, I think one of the most important things that occurred during this period was Alex

Margulis stood up at meetings and said, “This is important! This is coming!” No matter how much we scientists and engineers said that it was great, it took somebody who was respected by the clinical community to advocate before it became real.

Neil and Paul Bottomley and I published a paper in *Nature* without putting our Principal Investigators names on the paper, which probably wasn’t a wise thing to do, but you can’t undo that now. This is Peter Mansfield’s whole-body image. He was one of the first to do that.

I think the first recognizable human image came out of EMI labs. They were engineers who put together an NMR head imaging system and turned it on and nothing happened. They called us at Nottingham and said, “Come on down and help us. We don’t know what’s going wrong.” It takes not only engineers, it takes scientists. Those are the first head images from 1978. I was still working on small things like fruit.

This is Aberdeen’s imaging system. It was hand built, very innovative, and small. Jim Hutchison was a small person, so he was the subject usually.

I’m pushing this analogy [about birth] perhaps a little too far, but in the early days, there was a lot of conflict. I had people coming to me saying, “Is it just imaging? It should be science. Don’t do just imaging.” I’m not sure those were really the right questions or the right pressure. I think that imaging and science are the same, but people were searching at that time. It wasn’t clear where this was headed—whether it was to be spectroscopy or something else. Paul did a lot of the early work in different directions.

Here, you’re looking at several different chemical shifts. At Nottingham, we looked at fluorine and Paul looked at phosphorous. When I was at Harvard, the head of cardiology came to me and said, “If you don’t image phosphorous, I’m not interested and pulling my support.” I think you almost have to let technology grow in its own direction rather than push it too much. Paul and Dave Kramer, who I worked with later, were also imaging vectors.

Now, birth, which I take to mean the time that science is translated into the clinical environment, the meetings started, a society was formed, a journal began, and industry began to put money in it. I guess Dysonics and Technicare were the first two to get FDA clearance.

I think you could call this the first NMR imaging meeting. Other meetings highlighted imaging as talks. It was held at Vanderbilt in 1980. You can see that the first speaker was Paul Lauterbur; I followed; Neil Holland; Tom Butinger, who some of you may know, was one of the key people in starting the new technology and setting up the new society and so on. The second meeting a year later was at Wake Forest and here (referring to photo) are most of the speakers. Paul is there, Tom Butinger, Peter Mansfield, David Holt who worked at NIH is on the bottom left…

Hammersmith worked with EMI in London—just an indication of where the technology stood in 1981. Here are some of the images from the Wake Forest Meeting, just to show what the technology looked like at that time. I think Norbert Pelc was working at GE while I was at Technicare.

Then a year later, the Society of Magnetic Resonance in Medicine had their first society meeting. Here I show the first page from the book of abstracts just to show who was involved. Paul Lauterbur was Chairman, Alex Margulis was one of the two or three people who put the society together, Gerry Pohost, followed by a list—a sort of Who's Who in 1982. Here, the image quality has improved by 1982.

Just in case anybody's interested in some of the conflicts that were involved during that time of gestation, the book on the left (*A Machine Called Indomitable)* was really written by Raymond Damidian. It's a fascinating story from a very biased point of view, I think.

Don Hollis who was the one person to go up and check the measurements at NMR Specialties in the Pittsburgh area. He wrote a book (*Abusing Cancer Science*) trying to straighten out the record about who did what and about what happened and what made sense. Then he shortly disappeared. When Paul was inviting people to join him at the Nobel ceremony, he had a lot of trouble finding and getting word to Don Hollis, because… Well, it's a long story; it's a fun story, though.

Then there was a party. I did have a camera there and took a few pictures. We're sitting here in the auditorium waiting for the awards ceremony to begin. That's Tom Butinger on the left, Don Hollis and Tom and Miriam Hollis. I had my picture taken a couple of times. Paul and his family were all there and were very close.

Paul gave his Nobel lecture and you can still find it on the internet. It's an interesting lecture. I included this. We were supposed to give out titles, and I didn't know the title meant "the honorable" or "Lord" or "Earl" or something, so I put Ph.D. thinking perhaps that was my title, as did my wife.

This is a picture of the ceremony from where we sat. That's Paul down there, and here's a picture taken by a professional that you've all seen.

The banquet was a big part of the party. That's the main table. Al Gore was there, so I've had dinner with Al Gore. I snuck a picture at my table, just to give you a feel for what it was like.

I'm really pushing the analogy too far here. These are a couple of images from Stanford showing the technology today. This is a 7T Vespin image, and I'm told the iron in the putamin can be seen in this at 7T. I hesitate to point to it since I'm not a radiologist, but a very impressive picture if you could see it up close. Here's "time of flight of MRA" provide by Ann Sawyer and Gary Glover.

I hope I've given you little feel for what happened and the atmosphere, as well as Paul's enormous contribution to those very early days. Thank you.

Dr. Roderic Pettigrew
Thank you, Waldo, for that overview of the early days in the development of MRI. You have given us some insight into what really took place. It's interesting to see these kinds of historical presentations and the types of seemingly formidable challenges that stood in front of a big idea.

Realizing that gives us inspiration to go forward into the future and reach for even greater heights.

Because of the time challenge and our desire to finish in the neighborhood of 12:30 or so, so that we can have lunch, I would like to ask the next two speakers if they could be as time efficient as possible and help us in that regard.

We are privileged to have as our next speaker, a person who is certainly known to the NIH community. He is the past Dean of the Harvard School of Public Health, and past Provost of Harvard University. His career and interests focused on medical decision making and he actually founded the Society for Medical Decision Making. Currently, he is President of the Institute of Medicine, Dr. Harvey Fineberg. Dr. Fineberg will address us on the subject on which he is certainly an expert, and that is Health Care Challenges in the 21st Century.

SESSION II: TECHNOLOGY IN MEDICINE

Healthcare Challenges in the 21st Century

Dr. Harvey Fineberg, President, Institute of Medicine

Thank you very much. It is a pleasure to be here with all of you. When Rod informed me about this celebration and invited me to be part of it, I found it irresistible in measure because of the luminaries represented here, the leaders that have done so much for this field. The fact that this Institute has launched itself in such a remarkable way in its early years to really bring so many new young investigators and open up opportunities for collaboration that just previously did not exist.

My task here is to introduce a different perspective—a kind of context—for the discussions through the day. We have had wonderful introductions from the vantage point of the trajectory of science and the place of bioengineering and bioimaging. We've heard in this most recent presentation from Dr. Hinshaw about the time trajectory that is required. A very important lesson beneath this and how long it takes, and how important it is to maintain that perspective of time.

We heard from others about the remarkable and dramatic progress in bioengineering and bioimaging that has occurred. My job, in the next few minutes, is to try to provide a context of the health care system and where this all fits.

I was assigned to look ahead to the health challenges of the 21st century, and I was reminded of that sentiment that Neils Bohr was supposed to have expressed about prediction. He said, "Prediction is always risky, especially about the future." I'm going to be very cautious and I'm going to be talking about the challenges that we know about now as we look ahead.

Before we look ahead, let's take a moment to look back. This a graph of life expectancy at birth in the United States of America over the course of the 20th century. What you can see here is that in the year 1900, life expectancy at birth, for men and women, was below 50 years of age. The beginning rise of this life expectancy actually started in the middle of the 19th century, but the 20th century was a period of improvement in fundamental health and the life expectancy of the

population of the United States that was historically unprecedented. There was a change from under 50 to over 75 years, so over 25 years of improvement in life expectancy in the course of one century. If you think about that, that's 3 months average per year. That's one of the best arguments for birth control I've ever encountered, so you wait one year and the baby will have three more months of life expectancy at birth.

Now, if you'll notice this rather dramatic exception, in the course of the 20th century, I want to point out that it was not because [in 1918] the Red Sox happened to win that year, because you'll notice that there was no similar dip in 2002, but indeed, it was due to that extraordinary experience of the 1918 flu epidemic. This is just a reminder that there are still threats to set us back and to cause us to reexamine the nature of health and progress.

Now, in thinking about those extraordinary times, life expectancy and infant mortality… It's hard to imagine now, but in the time of our grandparents or parents, in the year 1900, if they had a child more than 100 per 1000 newborns died by the age of one—more than 10 percent. Just imagine how dramatically that has changed over the course of one century.

Death from cardiovascular disease is one of the most dramatic examples. Death from cardiovascular disease was not the leading cause of death in 1900. It didn't become the leading cause of death until around the 1920s. It peaked in the 1960s just around the time of the first surgeon general's report about smoking and health. It then began to decline and has declined by more than half.

The NHLBI estimates that if the age-specific mortality that applied back in the 1960s were suddenly transposed and applied to the population as it exists today in the United States—larger by half and older by some and you take the age-specific mortality for heart disease—this year, more than 900,000 people would die from heart disease as compared to 1960. The progress is just staggering, and most relevant from our point of view here at the NIH and at the NIBIB, that we are recognized today as the world leader in biomedical research and medical education.

Now, when you think about what is going to drive the challenges to the health system in the future, I just want to outline some of the elements that are relevant, and I'll just say a word about a couple… The demographic and epidemiological transition refers to two fundamental facts of aging of a population—number one—and increase of the prevalence of chronic diseases partly related to aging, but also partly related to lifestyle and other manageable matters, for example, those illustrated by the tremendous rise in diabetes in the United States.

The second biggest driver is going to be the continued discovery, application, and translation of the innovation such as we've been discussing this morning. Environmental change is partly a wild card depending on what happens over a period of time, in terms of climate. Where that may harm health or where that may change the patterns of disease in different countries, but also just the elements of air pollution in developing countries, particularly with the growth and income and the increase in automobile use and other industrial discharge, is going to be a very serious challenge.

Globalization—just one contextual issue here… Of course, this refers to all implications of the movement of people, the movement of goods, the movement of vectors and the movement of disease, but it also refers to the movement of human resources for health from one place to another, and the movement of patients from one place to another.

I remember conversations with the head of Radiology at the Massachusetts General Hospital in the 1980s anticipating a time when, because of digitization, he thought it would be possible for people in all parts of the world to send their images to the experts in the United States for interpretation. Instead, what we're seeing is that the Radiologists, some of whom received training in the U.S., working in India, are overnight interpreting the images that are coming back to us today. Globalization works in many directions.

Rising public expectations partly related income, partly related to the wonders of progress that increase people's appetite and expectation for what can be done for them. Finally, financial pressures… I sometimes think when we talk about genomics and proteomics and metabalomics, we ought to be talking about economics, because the challenge we're going to have in the ability of society to sustain the kind of investment—not for research, but for care—especially in the United States, is a fundamental challenge.

We are now spending one in every seven dollars in the U.S. economy in health care. A lot of people will say well if we're getting value for our money, what's wrong with that? We'll talk about that in a minute. There's nothing wrong in principal, except for the reality that industry, business and the public, find this overwhelmingly expensive. That pressure, felt at every level, is going to be a force that we have to reckon with.

Now, I just want to outline some of the challenges, each of which also represents opportunities in terms of the development of science and the role of improvements of health and health care. First and this relates specifically to our circumstance in the U.S., the failure of the U.S. to insure every American for basic health insurance is a kind of national tragedy. It is the only industrialized country in the world that has failed to do it, but we have a number of interesting experiments going on in several states now. Some of our candidates for the next Presidential election are beginning to talk about their plans for increasing insurance, but this is clearly, in terms of health policy, the number one, dominant challenge to our society for health.

High costs and rising expenses, and I've already alluded to the amounts.

Deficient quality and safety… Here, the problem is in multiple parts. We are not innovating enough. In one sense, that is a problem of unrealized quality. We are not evaluating sufficiently available technology and using evidence to define what is the optimal approach to the care of patients. Finally, we are not implementing the available knowledge very successfully in the delivery of care to people.

A recent study by Beth McGwynn and others at RAND looked at 30 different conditions in 18 cities and defined and tested how well care was being delivered to patients. On average, the bottom line across all conditions averaged over all of the cities is, if you were a patient with one of those problems, you had about a 50/50 chance of getting the indicated treatment in its entirety

for you during the course of that year for that condition. That's certainly not a record we can be proud of.

The Institute of Medicine, when it did its report on errors in health care, estimated that every year, tens of thousands of people are dying from errors in our hospitals every year. If you think about it, 99.9 percent is not anywhere near successful enough for safety in health care. If the airline industry had 99.9 percent safety record, that means that every day at the Newark airport, there would be a plane crashing and killing everybody. That's not good enough. If we're going to move from 99.9, to one in 10,000,000 errors in health care, that's a huge challenge technologically, organizationally and culturally.

Inefficiency… Well, for any of you who have worked in the health care system, I don't really have to elaborate.

Underinvestment in prevention… This problem is a huge untapped potential for reducing costs and improving health.

The disparities in health in access and outcomes, particularly across different racial groups, but also by geographic and economic strata in the United States, are very important problems for all of us.

Workforce shortages in the health care system, particularly around the nursing shortage, but also, if you look at the number of physicians today who are going into the caring fields… Newly trained physicians who are going to be in a position to take care of that rising number of older patients with chronic diseases, it's hard to imagine, but last year, 300 new physicians became certified as geriatricians; more than that retired last year. Even Radiologists age and this is going to be a problem for us as we get older.

Information overload… I won't spend time on that. Malpractice is something that all of us are aware of.

Health literacy is a problem at the other end with patients. It's estimated that 80 million Americans lack the basic conceptual and literacy skills to be able to understand what they need to know to take care of themselves.

Have any of you ever actually looked at a package insert for any of the medications you have been prescribed or any of your family members has been prescribed? Bruce Albert, who was President of the National Academy of Sciences, a very distinguished cellular biologist, and author of the leading textbook in the field, once handed me a package insert from a medication he had been prescribed. He had circled the chemical formula in the insert and had written in the margin, "This is the only part I understand."

Strains on academic health centers and failures to meet global health needs are very critical problems, as well…

Now I want to just make one main point in my comments. Innovation comes in many forms, and is essential for improvement if we are going to progress both on what we *can* do to improve the health of patients, and how well we *deliver it* to actually improve the health and lives of people…

Here, I'm just making a very basic distinction between innovation that is disease and biologically and technologically driven to protect, prevent, preempt, cure, restore and rehabilitate and mitigate the possibility, presence and consequences of illness. This is the kind of innovation, some of which we've been talking about, in areas ranging from robotics to smart prosthetics, and everything else in between. I also want to stress, especially in the bioengineering aspect of the future of NIBIB, that there is an enormous opportunity and challenge for system-driven innovation to provide and emphasize the kind of high-value, cost-effective, eminently distributable and affordable technology that can make the difference of closing the gap between what is possible to do, and what actually gets delivered to people. This is in areas such as information technology, operations research, better designed equipment and tools for safety, decision support systems, communication, and so forth. All of which are eminently ripe opportunities to make the kind of difference that will actually transform the experience of health care, and ultimately, the health of people equally toward the innovation that will allow us to do things that were previously unimaginable.

Where could this go? If we look ahead and proceed to invest what's needed in both people and in ideas for innovation that will produce new things and deliver better what we already know we should deliver. We can move toward a system that is population based and looks at the needs of a community, as well as the needs of the individual: One that stresses prevention before illness starts and is more than just intervention after disease occurs. One that is universal, accessible, and affordable, and doesn't suffer from piecemeal coverage and inequality, but instead, is centered on the needs of people and not driven by the designs and desires of institutions. One that is innovative, scientifically based, and evidence-driven, and not based on anecdote—and remember, the plural of anecdote is not evidence. Entrepreneurial and well-managed systems that give us the efficiencies that we require, and a system that is driven by quality and value. If we can emphasize the value of what we get, the difference it makes for health at an affordable or acceptable price, that is a much better basis on which to make our case rather than to simply argue about price alone.

I believe that the National Institute of Biomedical Imaging and Bioengineering has every opportunity to make a huge difference by encouraging the kind of innovation and development of human resources that can resolve these needs for the American people and for people all around the globe.

Congratulations on this anniversary and thank you very much for including me.

Thank you, Harvey, for that very eloquent presentation, and for underscoring what we all realize and embrace here, which is that technological innovation is really the engine of scientific progress and the means by which we will be able to bridge the gap between what is possible and what actually happens.

Dr. Roderic Pettigrew
I doubt that there's a single person within the sound of my voice who has not been impacted by the research discovery of our next speaker. Dr. Charles Townes is a University Professor Emeritus at UC Berkeley. His research began in the area of microwave spectroscopy and nuclear molecular structure, quantum electronics, and he developed and holds a patent for a device that was the precursor to the laser known as the maser, which the acronym stands for microwave amplification of stimulated emission of radiation. This led to his landmark invention of the laser, which stands for light amplification through stimulated emission of radiation.

In 1964, this work was quite understandably awarded the Nobel Prize, or Dr. Townes was awarded the Nobel Prize, for his work in the development of the laser. Without further adieu, I am so delighted that Dr. Charles Townes has honored us by coming here today and presenting us with this special treat of a lecture. Just after lunch, I couldn't think of anybody else that you would want to put in such a challenging time slot. That was our thinking, Dr. Townes. He is going to provide us with what I think is a very rare opportunity to hear a Nobel Laureate describe his work leading to his Nobel Prize winning discovery, and particularly for something that has had such a major impact on the lives of everyone on the planet. Dr. Charles Townes…

Honored Speaker: Reflections on the Discovery of the LASER
Dr. Charles Townes, Nobel Laureate, Physics, 1964, Professor Emeritus, University of California, Berkeley
Well, thank you, Dr. Pettigrew. It's a pleasure to be with you, and it's interesting to learn a little about all the wonderful things that are going on in biology, biotechnology, medicine and so on. Congratulations to all of you. It's a growing field.

I'll be talking about the laser and its associations. I'm sure you all know the laser and know something about what it does. It touches a wide variety of fields. Historically, you'll see some of our human limitations. You'll also see some things I think we all need to keep in mind.

First, that there are exciting results that come out of basic research that are unexpected and unpredictable. Second, is the importance of interaction between different fields of science, and between science and engineering? I know that's something very much emphasized here. Interactions of the different fields is important. Third, a field grows as a result of the contributions of many people, including scientists and engineers associated in the field. Many contributions—you might make a start, but things grow as a result of many, many people's contributions. Fourth, basic research that can pay off financially enormously. The laser is now billions of dollars a year, and in industry, many billions of dollars, and if you think about how much it cost to do basic research on it, you can see basic research has paid off enormously.

Now, unfortunately, it takes a decade, or two decades for a basic research idea to get into industry in a large way. Politicians and administrators—they want something to happen now, and that's part of our problem. We have to convince the community and our congressmen that, in the long run, basic research is a very, very good investment.

Finally, I want to emphasize that new ideas—really new ideas—are frequently resisted, and maybe especially, by the experts. They resist new ideas, especially if they don't have them, that is. I will show you some examples of that.

I was working in the field of microwave spectroscopy. That is, I was using microwaves (gesturing) about so long, to study molecules, atoms, and nuclei. It was a powerful and interesting field. I wanted to get waves down shorter and shorter waves because I knew the absorption would be greater and greater, and the effects would be greater and greater, and I wanted to get down into the infrared. Infrared starts at about 1 millimeter then goes on. I wanted to at least get down at least below a millimeter, and still shorter, if possible.

I had been working in the radar business. I had done engineering and radar, and that's why I was doing microwave spectroscopy, because I had all the techniques. I knew about oscillators, which engineers knew about, but not many scientists were involved with them at that point. I wanted to see if we could get an oscillator to get shorter and shorter waves. I thought, and well, a lot of people are trying it. Some of my students said to try this and that, and some of it worked, but not very well.

I was appointed Chairman of a national committee that tried to examine how we could get this thing to work. Well, we traveled all around and listened to everything, but we just weren't getting anywhere. We decided we better fold up, but we were having our last meeting in Washington, D.C., and I woke up early that morning and I kept asking myself, "Why haven't I been able to get shorter waves?"

I went out in a park and sat on a bench. It was beautiful light and the azaleas were out. I wondered why I hadn't been able to get an idea, and I thought about this, and I thought about that. I thought, now, molecules and atoms can produce short waves, but you have to heat them up so much before they produce much energy that they fall apart. Thermal dynamics says that you can't get more than a certain amount of intensity depending on the temperature. I thought, that's too bad.

Hey, wait a minute! They don't have to obey thermal dynamics. You see, an atom can be in lower state or an upper state. Thermal dynamics says that more of them will be in the lower state than up here. If a photon comes along, it gets absorbed by the lower state and excites the upper state to fall down and give up a photon. There's always absorption, because the lower state is always more filled than the upper state.

That was it. I thought, maybe I can get molecules and atoms with more of them up here than down here. I pulled an envelope out of my pocket and wrote down some equations on how to do it and I said, "Hey, this looks like it would really be done. Wow!"

I didn't tell our national committee about it when I went to the meeting. I thought, well, maybe I'd better work it out some more and see. Our national committee wrote a report saying, "We're sorry. We haven't really been able to find any real answers, but maybe somebody should keep trying to make smaller and smaller electronic oscillators." That was it.

I went home and thought about it some more and wrote it in a notebook so I could get a patent on it for one thing. Then I persuaded a graduate student, Jim Gordon, to try it out as a thesis and try to make one. Now, to make one, I thought it might be best to try it in a microwave region, because I thought, I have all the techniques and the equipment here. We could try to get molecules amplified in one centimeter wavelength and see if it worked.

Well, we worked and worked on it for a couple years. Then, J.I. Robbi—the picture you saw up here earlier—a wonderful physicist and a Nobel Prize winner, came to my office along with the Chairman of the department who also won a Nobel Price, and they said, "Look, Charlie, that's not going to work. You know it's not going to work. We know it's not going to work. You're wasting the department's money. You've got to stop!"

Well, fortunately, by then, I was an Associate Professor and I had tenure. They couldn't fire me. I said, "No, I think there is a really good chance of it working, so I'm going to keep on." Well, they marched out of my office angrily, and we kept going.

Just about three months later, Jim Gordon dashed in my classroom and said, "It's working! It's working!" The whole class and I went out to see this thing, and yes, sure enough, we were producing amplifications and oscillations by microwave by molecules.

Well now, they produced a very, very pure frequency, which I knew they would. Many people doubted these things, but I looked up my notes from my quantum mechanics that I'd taken at Cal Tech about 20 years before that—my classroom notes. I could prove that they would have to be going to be coherent and very uniform in frequency. Sure enough, we built another one so we beat the two together, and found that, yes, both of them—a very pure frequency.

I was visiting Neils Bohr in Denmark shortly after that and he asked me, as scientists do, "What are you doing now?" I said, "Well, we've got this oscillator using molecules that amplify at very, very pure frequency."

He looked at me and said, "No, that's not possible. No." He said, "You must not understand." I said, "No, we have it. We tried it out." He still said, "No, no, that can't be."

I still think he was thinking about the uncertainty principle, but he was applying it for single molecules, but this is a group of molecules. He said, "Well, maybe you're right," but I don't think he ever believed it.

Another case was when I was at a cocktail party with John Van Norman, a very famous mathematician and theoretical physicist, asked me what I was doing. I said, "We have this very pure frequency of amplifying molecules." He said, "No, that can't be right. That's impossible. You're doing something wrong." Well, he went off to get another drink, and about 15 minutes later, he came back and said, "Hey, you're right!" Then he really wanted to talk about it and recognized that it was possible. Those were some of the doubts, you see.

Once the maser got going—I was building it for about 2½ years and a lot of people came in my lab and looked at it and said, "Oh, well, that's an interesting idea," but nobody was competing.

Nobody else tried it. When it was finally working, of course, a lot of people jumped into the field.

Well, I took a sabbatical at that point. I went off to Paris. I had been using ammonia molecules coming in the cavity and doing this amplification by stimulated emission. (Gesturing) You see, there are more molecules up here than down there, then the wave comes along and you make molecules give up their energy and exactly in phase with the oscillating. Well, that was a fixed frequency. I could use other molecules and get somewhat different frequencies, and my students and I had picked the name maser—microwave amplification by stimulated emission of radiation—stimulating molecules, you see. That's where the laser came from—light amplification by stimulated emission radiation. In fact, we even thought that maybe we could use iraser for infrared amplification, but that was already in use.

There was the maser, which goes up to one millimeter, and then there was the laser, which starts at one millimeter and goes shorter waves. It's really basically the same thing, but just different wavelengths.

There I was in Paris and one of my students was doing post doc research there with the French. They told me what they were doing. They were using electron spins in a magnetic field. I said, "Wait a minute! That would be very interesting from the point of view of masers because the electron spins—there are two levels and you put on a higher magnetic field as the levels split apart, you get higher and higher frequency—and lower magnetic field, you get lower and lower frequency, so we have a tonable maser. We decided to see if we could build one, and we got pretty far with it.

I heard later that Woody Steinberg at MIT had a somewhat similar idea of using electron spins. He gave a talk about it, but said he hadn't made one work. Nico Bloombergen from Harvard was in the audience and he said, "Why would you want to do that, anyhow?" Steinberg said, "It will give the best amplification. It's the most sensitive amplification to have."

Bloomberg went back home, and he had been working with electrons and crystal. Now, these can have three levels. You can have this level, and this one, and this one. He invented the idea of exciting electrons from here (bottom level) up to here (top level) and letting them fall back down to there (bottom level) and amplify.

Well, I went on to Tokyo as part of my sabbatical where I ran into a friend of mine, Francis Ryan a biologist from Columbia where I was at that time, and he was on sabbatical, too. I asked him what he was doing. He said, "I'm working on an equation trying to figure out how the number of cells can fluctuate—a number of individual biosystems can split. You take a microorganism and it can split and make two, or it can die. You have a batch of them, and some of them split in two and others of them die, and so what's the fluctuation in the number?

I said, "Hey, that's what I want. I've been trying to figure out the fluctuations in the maser amplifier." Oh, all I need to do is, as the photon comes along and makes two, that's like a cell splitting, and it comes along down here at the ground state and gets absorbed—that's like the cell

dying. Then the spontaneous emission where the atom and molecule falls down like that, you get spontaneous emission. Well, cells don't produce spontaneously.

After that, I said, "Well, let me see your equation." We had that one term and I went to a Japanese mathematician, Takahashi, to help me, and we solved it and worked out just what the fluctuations were in the amplifier and how good it would be. We knew it would be very good, and we showed that it was as good as basic physics would allow, and that's when you get down to amplifying a single quantum.

We published that, and afterward, a guy came up to me and said, "I've been working on parametric amplifiers. Do you think parametric amplifiers would do the same thing?" I thought about it and said, "Yes, oh yes! They can." In principle, they can give us good sensitivity. Now, even though masers give good sensitivity, parametric amplifiers are much cheaper and easier to build. This is trading ideas, you see.

I came on back home and everybody was busy with masers and everybody liked masers. It was a great field and people were jumping right into it. It was so popular and the *Physical Review* was receiving so many research papers on it that there wasn't anything someone hadn't done before. They decided to do something they'd never done before. They decided they weren't going to take any more papers on the maser. They said they had too many. Very unusual.

Well, masers were exciting. We worked on them for a couple of years, but I wanted to get on the short wavelength. That was the whole point. Nobody believed they could get down to a much shorter wavelength. At shorter wavelengths you've got too much energy exciting the atoms and they don't stay up there very long, too. No one believed it could be done, but that's what I wanted to do. I decided I was going to think of the best method I can and try to do it, so I sat down and wrote down all the equations to see how much energy it would take. I realized, hey, we're getting right down to light wave. Oh boy! Look at that!

Well, I knew if I said anything about it everyone would jump into the field because masers were so exciting then. I worked on it by myself for awhile. Then I was consulting for Bell Labs for awhile and my brother-in-law who was married to my kid sister, Arthur Schawlow, was with the lab, and I talked with him about it. I said, "Can I work with you?" and he said okay. We worked together and Art produced the additional idea of having two parallel mirrors, like this. I was going to make a cavity as we did in the microwave region, but a cavity in the optical region wasn't going to work, so we had that idea. We decided to publish the idea rather than try to make it work, because everyone would jump in and try to beat us to making the first one work.

We wrote it up and I said, "Take it to the Bell Labs patent lawyer first. Of course, we ought to give the patent to them and let them patent it." He did that and he called me up a couple days later and said, "The patent lawyer said they don't think they want to patent it. They said light has never been useful for communications and so they don't think they're interested. If you want it, you go ahead and patent it." I said, "Well, we mustn't cheat Bell Labs just because the lawyers don't understand. You go tell them yes, it can be used for communication." They said, "Well, okay. If you can show us how it could be used in communication, we'll patent it." We did, and

we wrote about infrared and optical masers and communication—now lasers and communication—so they patented it.

You see, new ideas are just not easy for people to recognize when they're really quite new. We wrote the paper and published it, then everybody jumped into the field. I wanted to build the first laser, of course, but I'd also been invited to go to Washington and help out the government, and I felt obligated to do that.

I went down to Washington, D.C., but some of my students were working on lasers, and the first one was really made by Ted Maiman at Hughes. Now, all the first lasers were built by industry instead of universities. You ask why in industry? Well, that's because industry had gotten interested. Yes, they were built in industry, but they were built by young students—young men who had been students in microwave and radio spectroscopy and they were hired to work in that field because industry realized that field was doing something.

The first one, Ted Maiman, had been a student of Willis Lamb at Stanford. He made the ruby laser. He did it with a pulse of light, exciting the ruby, and you got this red beam out of it. It was using a pulse of light that I hadn't thought about. With a pulse of light you can get more intensity and excite the ruby better.

The next laser was built by one of my students and one of Bloomberger's students at Harvard, and that was at IBM. Soroken and Stevenson built one in solid state, which was somewhat like ruby, but different. The next time, a gas laser was built at Bell Labs by one of my students, Ali Javan. Then Bennett, another of my students from Columbia who worked in the field, Ron Bennett and Donald Herriott [and Javan] built the next one. That was a gas discharge laser, and that's been a very, very popular one. Finally, another laser was invented at General Electric by Robert Hall, and that was a semiconductor laser.

You see, the interaction between basic research and industry and the necessity of people you train in the field. The main thing for me is, I had a good deal of experience in engineering during World War II at Bell Telephone Laboratories. I knew about oscillators, so I had this engineering background and mixed it with quantum mechanics. Engineers didn't know quantum mechanics, physicists weren't all that interested in oscillators. That's the kind of thing that did it.

There is no basic new idea in the maser or the laser. All the physics involved had been known before. Einstein discovered the stimulated emission back in 1918, and this kind of application could have been discovered 20 or 30 years earlier, but it was just bringing things together in the right way that made a difference.

What's happening now? Well, masers and lasers have also been found in space. They've been out there for billions of years. There are water masers out there that make pulses that are stronger than the total energy of the sun in one microwave line. Then, there are very powerful lasers. They, too, have been out there a long time. Anybody looking up in the sky in the 1930s—they were using microwaves back in the 30s—anybody looking up in the sky would have said, "What's that?" They might have figured it out.

Another thing I'd like to mention is that when masers came along, everybody said, "Well, that's interesting, but what can it do? It's a nice idea, but how can it help us?"

Well, I said there were many things it could do. I wanted to do science, and I wanted to do new kinds of science, which they have done. In fact, by now, they've won about 15 additional Nobel Prizes that were given to people who used masers or lasers as scientific tools, and I'm just delighted about that. I saw many applications, including cutting and welding, but I didn't see any of the biological or medical applications. One of the things that pleases me very much is that one of my friends came to me one day and told me, "The laser that saved my eye—reattached my detached retina." Well, I'd never heard of that, so I didn't recognize any applications in biology or medicine, but I did realize a couple of other applications, including communications, cutting, welding, science, but there were a lot more.

What are they doing now? Well, they run a whole range of wavelengths—from microwaves to x-rays. How much further can they go? Gamma rays maybe? Well, we'll see. They have short pulses, so we can get down to 10^{-16} second pulse length—they make very short pulses and it's amazing, it's very, very fast, and enormous power. There's one laser that puts out 10^{15} watts—a million billion watts. You can't afford to run that very constantly, it's just a pulse. There are very sensitive amplifiers. Then, positioning, you can position very accurately. For example, you can send a pulse to the moon and reflect it back, and we can measure it to a distance of about 10^{-4} centimeters. The distance to the moon is so large that this makes a precision of about something like a few parts in 10^{15} or 10 million billion. You can also measure things and control positions very accurately. With interferometry you can measure things very accurately.

Now on positioning, I'm doing interferometry in astronomy now using lasers. Lasers have built the field of stellar interferometry, and now, it's now a very fast-growing field. We can measure the shape and size of stars.

Now imaging… Now, people use x-ray lasers and focus down to about 150 atoms or 100 atoms in distance. That's very good imaging. Another really interesting thing about imaging is that now there's negative refraction. I think negative refraction is going to give us some very interesting imaging. I hope that gets developed. The future of imaging in negative refraction and shorter wavelengths, well who knows how far this will go.

Information transfer, as I said there are all kinds of applications for communications and computing. Nanotechnology imaging and noninvasive operations in medicine—I'm just very pleased it's used in medicine. Then there's fiber optics and doing operations with fiber optics. Laser TV will come along, and who knows what else.

We can predict some things, but the future is still unknown, but best wishes to all of you as you continue to produce in the future. Thank you.

Dr. Roderic Pettigrew
Dr. Townes, I hope you can feel from the warmth of the applause how much we appreciate you coming to share this event with us, and specifically, to enlighten us on the discovery of the laser and give us insight as to how such a tremendous technology occurs.

This Institute, as you heard today, is certainly focused on technological innovation. Lasers are a prime example, and to hear how this has happened, the extent to which it has changed the way health care has been practiced. Even you, the inventor, did not envision the extent of the applications that can be realized with such a technology is one of the reasons this Institute was created, which is to support technologies so that fundamental discoveries, fundamental information, and fundamental tools can be developed even when it is not necessarily clear at the moment what the application might be. We really appreciate you coming here. Once again, I think that we should all recognize you as a Nobel Laureate and thank you for coming here to share your experiences with us.

Our next presentation is on imaging molecules and the promise of preemptive medicine. The presenter is…actually, at the sake of embarrassing him…you know, I don't want to call him a father because we're probably about the same age, but I consider him to be one of the fathers of this field of molecular imaging. He's certainly one of the few people who started this in the country. In addition to being a creative and inventive mind, and one who has developed this new field of molecular imaging, he's also a practicing clinician.

I visited his laboratory about a year ago—he wasn't there at the time, so I got the real low down. The other scientists in his lab impressed me with how much Ralph, despite being a fundamental bench scientist, really enjoys being in the clinic interacting with patients. They said that he will move mountains to preserve his clinical time and his patient care time. I can think of no one that is better suited to enlighten us on this topic of where we're headed in our pursuit of imaging molecules and how technologies to realize that might help us to also realize this vision of preemptive medicine.

Ralph is Professor of Medicine at Harvard Medical School and also Director of their Center for Molecular Imaging.

Imaging Molecules: The Promise of Preemptive Medicine
Dr. Ralph Weissleder, Director, Center for Molecular Imaging Research, Massachusetts General Hospital, Harvard Medical School
Well, thank you very much for this very kind invitation. It's a pleasure to be here to celebrate the anniversary of NIBIB and in my opinion, an extraordinary Institute of the National Institutes.

It's a tough act to follow the discovery of lasers, so I decided to show some applications—some biomedical applications of lasers. Also, knowing we were going to talk about MR, show you some of the more recent examples of how we have used MR technologies, not for imaging, per se, but for biosensing.

Now, Rod asked me to put this into the context of molecular medicine. What is molecular medicine? Well, as Dr. Zerhouni mentioned earlier today, it embodies personalized, predictive, preventive, and preemptive medicines. Now, in order to get there, it has multiple different pillars, and with respect to NIBIB's mission, I would categorize them as follows:

Imaging and bioimaging, as well as quantitative systems analysis is certainly a pillar to get to molecular medicine. Also, the ability and the need to use chemical probes and to probe the entire

chemical space to ultimately allow visualization of molecular pathways essential to this. Another pillar, I believe, is this emerging field of nanotechnology and nanomaterials for sensing and is for many other biomedical applications. Finally, new technologies for genomic sequencing and individual genome sequencing. Collectively, these, as well as some other pillars, would form the basis for molecular medicine.

Now, what am I going to talk about? I'm going to talk a little bit about bioimaging, number one. All of you are familiar with the tremendous advances in anatopic type of imaging, which now allows us to fly through the human based on CT or MR imaging information. Now, I named this bioimaging because I believe that down the line, we have to get down to the cellular and subcellular level to image specific biological pathways and diseases in the body. Another way of looking at this and conceptualizing this is, it's not just a pretty tool, but it is the necessity ultimately to do *in vivo* pathology, because as we detect earlier and earlier lesions and more lesions in the clinic, we need to have ways of characterizing them. Finally, I think this is very important because ultimately, imaging at the true cellular level *in vivo* will allow us to unravel biology that we will never be able to unravel by *in vitro* technologies. As it turns out, a lot of biology is completely different in its true *in vivo* environment than it is in the test tube. The necessity to image from the macroscopic down to the microscopic and cellular scale, and to do this seamlessly, and in a clinical setting, to have the ability to go back and forth, I think, will be essential. I'll talk about some of those topics.

Then the second topic I'll talk about in the last 10 minutes or so of my presentation, I'll talk about the molecular nanolab based on the premise that there's a lot of information in blood and fluids and tissues that can be analyzed with new emerging nanotechnologies.

Now, the reason I've chosen those two specific examples is not only because they're important in my mind, but because they both enable dynamic data acquisition, and down the line, also quantitative data acquisition. I also chose them because much of the work I'm going to present has been funded by NIBIB. NIBIB has been instrumental in our laboratory; it's like a clock that makes our laboratory tick, so thank you very much for all the funding and support over the last five years.

Let's step into imaging. One of the biggest growth areas in imaging is a number of emerging optical technologies that, at the end of the day, all use the laser. They range all the way from microscopic imaging to macroscopic imaging, and from the research arena to the clinical arena. I'll just show you a couple of imaging systems that have been introduced in the last couple of years that now enable us to truly probe cellular and molecular phenomena *in vivo*. I will show you a couple of examples.

This is a kind of microscopic clinical whole-body imaging in mice. Let me start out with this technology. This is one of the technologies that people said it's not possible to do. We termed it FMT imaging, or Fluorescence Mediated Tomography; others also called it Optical PET imaging.

When we first started doing this about seven or eight years ago, the idea was, instead of using an isotope—radioisotopes, PET isotopes—to obtain specific molecular and cellular information,

and we could use near-infrared light. We built this system, and this is basically the chamber in which the animal sits, and in its early incarnation, it's filled with liquid. The lights are dimmed and the laser is turned on. The animal sits here and the laser is turned on at this spot and then it fluoresces and both images are recorded. The laser is then moved to the next spot over and the fluorescence is recorded. We repeat this hundreds, and ultimately, thousands of times, to reconstruct this type of information to obtain quantitative tomographic images.

To make a long story short, this methodology, after five or seven years of experimental tweaking, is entirely quantitative. This is measured fluorochrome deep inside the mouse, so one and 1.5 centimeters inside the mouse, measured versus true concentration. With a quantitation accuracy that's much better, detection threshold inside an animal is about a picomole and the spatial resolution is somewhere around 0.5 or less millimeters. This is one of the enabling tools with which to really quantitatively probe optical information *in vivo*.

Based on this development, we then said, well how can we use this? Being in a very multidisciplinary environment, some of the clever chemists in our laboratories had built probes that were highly sensitive for proteases, and we applied this to a genome profile and asked the question, if we had early lung cancer, what are the molecules that are highly upregulated, and can we develop chemical probes that can identify these very earliest lesions?

We worked together with Tyler Jack's lab and used this type of imaging to image one specific molecule—a patepsin—a cysteine protease that is highly upregulated in lung cancer development. This shows a 1.7 millimeter tumor, and color coded I have the protein expression levels of this cysteine protease. Importantly, this correlates directly with Western blotting. This was one of the first examples where we were actually able to show that the imaging information of the live mouse correlates with Western blotting protein profiles.

Recently, we have gone forward in building these combined FMT/CT imaging systems where we obtain both of these types of information, very similar to a PET/CT, and the ability to three-dimensionally reconstruct. You can start to see that down the line this will have tremendous implications for how we do biomedical research.

Another important aspect of end use of lasers in biomedicine was mentioned, and that was for intraoperative imaging. We also have a program in our laboratory, and we have used a mouse model of sarcoma, which was produced by injecting an adenovirus that expresses Cre recombinase into mice that have mutated Kras, and these animals developed these tremendous soft-tissue sarcomas. The question was, if we had molecular probe that was specific for sarcoma, could we use optical imaging to identify residual tumor cell left while a surgeon resected these. A number of our orthopedic surgeons have done prospective studies and intraoperative studies where they have resected whatever they can with their surgical skills, and then see if there's anything left. In this one in particular, there's still some color left indicating there was still tumor remaining. They're very excited to take this technology to the next level to patients to identify residual tumors during oncologic surgeries.

Another example of the type of imaging out there uses fiber optic approaches for real-time, microscopic imaging. Here's an example from Monokeya Technologies where they have

developed a confocal imaging system at the end of these fibers—these fibers are down to about 300 microns and can be introduced through an endoscope to achieve these types of images in live patients. That's down to the near microscopic level.

We have used this technology in mice to phenotype different tumor types that overexpress different angiogenic molecules and have been able to show that this type of quantitative information can be put together in order to quantify the microvascular phenotype of orthotopic tumors almost anywhere in the body, but also its response to angiogenesis inhibitors. Again, because this is translational, I believe there will be much more of this type of research that's going to happen.

You could argue this is not truly cellular resolution, and that's correct. In order to get down to the true cellular resolution *in vivo*, one probably needs to do multiphoton imaging, and we and others are currently in the process of building up a big program to put multiphoton microscopes at the end of fibers.

I'll show you some very exciting data that was recently published. I won't go into much detail. It was recently published in *Immunity*. It shows the power of imaging and how we were able to unravel biology that otherwise we would not have been able to decipher.

In this example, we were interested in how specifically cytotoxic T-lymphocytes are influenced in tumor-killing, bi-regulatory T-cells. To make a long story short, these cytotoxic T-lymphocytes (CTL) that express green fluorescent proteins are introduced into a live mouse, and here, we're imaging a lymph node. The red cells are the bad cells, the tumor cells that do not express certain tumor antigens. You can see, there are some green cells that come in and interact for about a minute or so with some of these red cells, and then they disengage and they don't kill them. They don't kill them because they haven't been primed for this antigen.

If we do the same experiment, but this time, express an antigen that these CTLs express, you can see that these killer cells really latch on to their target cells like Velcro, and then here, start to kill them in real time. This is one of the first examples where we are able to see these cytotoxic T-lymphocytes work in an *in vivo* environment.

Another area of tremendous interest to us in the translational arena is the ability to pair diagnostic information and therapeutic planning. I had shown you the ability, first of all, to do regular white-light imaging, and also near-infrared imaging using these near-infrared probes that target specific molecules that are upregulated in disease, for example, in this pre-cancer here, it's another cysteine protease that is upregulated, and by virtue of upregulation, we can detect it. However, there is some ambiguity in the live system because it may be a pre-cancer, or it may be a real cancer. Frequently we need to be able to go down to the true cellular level and have multiple different fluorochromes, and as a pathologist, having multiple different colors we ask questions like what is happening in this lesion. This stains all the cells. This one here is another protease and this is for microvascularity, but being able to image all three different processes at the same time is a powerful diagnostic adjunct.

Now, importantly, as we detect something like this, it characterizes *in vivo* what we want to be able to zap it or kill this type of tissue right there. One program in our laboratory has now started creating platforms where we use in the near infrared in the far right, and then in the near infrared, these nanoplatforms where we use one wavelength as a reference channel, so we can quantitate the amount of the fluorochrome, then use two channels out there around the 800 or 850 nanometers as diagnostic biomarkers and use one of the channels here as a therapeutic channel so we can…If a lesion turns out to be malignant, we can therapeutically zap it.

Most recently, we have made some of these agents. These early ones are targeted so we have different flavors. These are targeting tumor cells or tumor host cells, and so you can easily see them and zap them in a different wavelength. Most importantly, the first generation of these materials are currently 100 fold better than the best photodynamic agent out there. They're much, much better because they're based on nanoplatforms, so we're now adding amplifying concepts of targeting, of amplification, and so on. One can completely eradicate tumors or other specific cell types with these materials. Also, by virtue of using light locally, one can selectively ablate cell types and tissues. Down the line, we believe this will be a huge advance in biomedicine.

Let me focus a little bit more on these imaging agents on these probes. I said at the beginning that they're essential, but at the same time, it's also very clear that to date, we have only scraped the surface. Most of us have used some antibodies and antibody fragments, and maybe peptides. What we really need to do as a community is, using evolutionary libraries, as well as chemical libraries, and systematically probe the chemical space for potential affinity ligands. I'll show you a couple of examples.

The use of antibodies and antibody fragments alone will not be sufficient. Or at least, this traditional approach will be too slow to comply with the NIH guidelines of eliminating all sorts of diseases by next year. Anyway, I'll show you one example where we've used a diversity-oriented synthesis library method… No, actually I'll show you another example where we used a phage display library method to crack an important problem, and that is pancreatic cancer.

Currently, there are no imaging agents that could be injected intravenously and used to highlight precursors to very aggressive forms of pancreatic cancer. What we did was, we teamed up with a number of mouse modelers and molecular biologists around town, and used their mouse models and isolated these pancreatic ductile adenocarcinomas, but also isolated normal pancreatic cells and used iterative phage display to identify a number of hits. We found about 50 hits, some of which matched with known targets of pancreatic cancer, but we were not interested in those. We were interested in the ones that were not known because we'd tested all the known ones before and they didn't really work.

One of these, it turns out, is this peptide sequence here that targets a novel cell surface receptor, which is actually an intracytoplasmic protein that in pancreatic cancer, gets put onto the cell surface. You can see, this peptide sequence here separates quite well between normal cells and tumor cells.

We took this peptide sequence, put it on our nanoparticle platform, then asked the question, if we inject this into a mouse that has pancreatic intraepithelial neoplasias—so precursors to pancreatic

ductile adenocarcinomas in the pancreas—which one cannot see with the naked eye, could we detect these? Remember that these nanoparticles were fluorescent, so as we switch I'm going to show you a blow up of this region here. As we switch to fluorescent channel and go back and forth between the white-light image and the fluorescent channel, we start seeing these punctuate lesions in here. They all turned out to be interepithelial neoplasia of foci where cancers will develop within the pancreas. This is a very, very powerful process for identifying affinity ligands for pre-neoplasia. Now, if one mirrors this with the ability to treat them, you can see that this could be done laparoscopically through minimally invasive approaches.

Another way of getting similar information is to use some of these nanotechnologies, but also marrying it with chemical libraries. One experiment that I did two years ago—and it's an experiment that never should have been done because the paradigm was at that time, well, you have a nanoparticle and you inject a nanoparticle, then it winds up in macrophages and goes to the liver, so don't waste your time. My hypothesis at that time was, if we take nanoparticles and decorate their surface with certain small molecules, after IV administration, we would be able to change their pharmacokinetic properties and be able to target them.

We made some of these, and I won't go into detail because some of this work was published, and we then screened them. By the way, we had also developed some quick chemistry of putting these DOS chemical libraries on them, we're talking about libraries of several thousand compounds that we put in spatially confined ways onto these nanoparticles.

We took all of these nanoparticles and screened them against different cell types with the question being, are there unique nanomaterials out there that identify or highlight and differentiate either different cell states or different cell types or disease processes? Without going into any specifics here, we were able to identify a number of different compounds, and in this paper that we published, one of them we identified targets pancreatic ductile adenocarcinoma, but there were also a number of other ones that are currently in publications.

In the last five minutes or so, I want to switch to another area that is currently of tremendous interest to us in the laboratory, and that is nanoscale sensing. It's based on the premise that blood is a window into disease and that serum proteins and metabolites correlate with molecular abnormalities deep in organs. However, there are a number of different challenges. This type of technology has to be much more sensitive than it currently is, and it has to be simple scalable. Ideally, we have to be able to detect DNA, protein, metabolites, drugs, and so on, all at the same time, and it has to be multiplexed, fast, and cheap in order to have an impact in clinical medicine or in biotechnology.

Some of the current examples out there do some of these things better than others, but there are very, very few examples of nanotechnology that do all of them. We believe that we have stumbled across one of these technologies, and that is NMR.

Let me go back one step and explain to you what we're doing, and what we're not doing. We're not using NMR to do chemical NMR, and we're not doing MRI imaging either. What we're doing is, we're using a nanoparticle proximity assay to measure the T2 relaxation times of water proteins around magnetic nanoparticles. Now, this is based on an observation that we had about

five years ago that when one has monodisbursed nanoparticles in solution, *versus* a cluster of these nanoparticles, they have different effects on the surrounding water and one can measure these effects.

For example, if I have nanoparticles that have a DNA sequence on them, and then hybridize them with a matching DNA sequence, we can create these clusters and start with these clusters to cleave them through proteolytic enzymes as enzyme sensors and go this way. Either way, measuring the water T2 relaxation times, means that we have an inherent amplification built in because each of these nanoparticle clusters exerts its effects onto billions and billions of water molecules that we ultimately measure. Also, by virtue of NMR, where we can do these measures in whole blood, tissue samples, in sputum, in stool samples, and there is no purification that is needed. Also, we have devised a number of assays going this way or this way or having reversible assays to sense DNA, RNA, proteins, small molecules, or even bugs.

How do we sense this? Well, early on, we used this—$2M machines, which were certainly not practical, and we were kicked off the magnet at odd hours. Then a couple of years ago, there was this technology that came on the market [that were] these hand-held mouse NMR imaging systems or benchtop relaxometers, but none of this is really practical. What we really need at the end of the day is a hand-held imaging system or a little chip. We went ahead and created one of the first NMR machines on a chip. These are currently being fabricated at a cost of about $5—well, I don't want to say this at NIBIB. Ultimately it may cost around $5, but this is around $500,000.

This is conceptually what the first iteration of this system looks like. It's a little chip that is about three centimeters across here, and there's a little hand-held magnet back here. This magnet is about $100 and we bought that in a toy store. We have lithographed on here little NMR microcoils. This is our entire NMR machine that generates the pulses and allows us to read the signals that we get back. This is a blow up of the microcoils up here, on top of this we have meandering microfluidic networks so we can actually draw blood in here. It mixes the blood with the nanoparticles onto these chambers back there for measurements.

Let me show you some very, very exciting examples. One of the first applications after we built this little gadget was, we asked if we could measure bacteria. Someone earlier mentioned today that it's important to identify bacteria in blood, sputum and so on. What we did was, we made nanoparticles that recognize bacteria, and this particular example is *S. aureus*. We did this by a very simple trick. We conjugated vancomycin, an antibiotic, onto these nanoparticles. As you can see, these nanoparticles actually cluster upon the surface of these bugs, as shown by this iron trace EDS (electronic data system). Because these nanoparticles cluster here on the surface, they exert a tremendous T2 shortening of all the water that's around these bugs, and this can be detected in these types of assays. We were able to detect bacteria; this is the control experiment. I should also point out that these are tremendous T2 changes.

The next question was, how many bacteria can be detected in the system? With this particular example, we were down to close to 10 bacteria per 10 µL, so one bacteria per microliter—that's the current detection threshold, and this is exactly what the WHO (World Health Organization) mandates for anything being used for field testing. It's very, very, very sensitive.

We then asked the question, if we detect bugs, can we detect mammalian cells? What is the detection sensitivity? Because we needed to use this ultimately to identify rare cells in circulating blood. This is one of those early calibration curves, and again, we're able to detect about one cell in a blood sample that's put onto this chip. It could be a stem cell, and in this example, it was a circulating cancer cell.

Not only that, but we have been able to use this assay, and having a multiplexed chip, to take these cells and ask questions like: What is the new status of these cells? What's the EGFR status, the VEG-F, AFP, Ca125, glucose, or folic acid in the plasma? Because the technology can be miniaturized, it becomes possible to ask all of these questions. I don't want to make this too long, but we were able to actually phenotype these very rare cells in real time. The concept would ultimately be that we would take a drop of blood, put it on the sensor, and then get a readout of all these different markers. I should also say that this technology is very fast and measurement takes less than a minute to get profiles. This is very, very exciting.

Another exciting thing of the future is that these systems can also be constructed to become implantable devices and that we can leave them behind in tumor beds or inject them through hollow needles. For example, if we would encapsulate some of these nanoparticles in semipermiable membranes, analide would diffuse through, and by diffusion through this semipermiable membrane would cause clustering. We believe that this type of clustering can be detected in implantable sensors. One would, for example, leave this here at a tumor site to sense locally.

I'm going to conclude here and I hope to have shown you some of the recent advances in bioimaging and nanotechnology in our lab, which we hope that together with other technologies, will help ultimately realize molecular medicine.

Finally, I want to thank the many PIs in our center, as well as the many, many current and former postdocs in our center, as well as members of another lab I direct, the Center for Systems Biology at Massachusetts General Hospital, as well as all the different collaborators who have contributed to some of the work that I've shown today. Finally, and most importantly, to NIBIB for funding some of this work. Thank you very much.

Dr. Roderic Pettigrew
Thank you, Ralph, for that very futuristic talk. I anticipated something imaginative, but I didn't know that you had advanced quite to that level. I must admit, even as a person who looks for the inventive and far-reaching, I'm impressed by what you showed us. It appears as though our funding is being very well spent.

At this time, I'm happy to inform the audience that we can take a brief break. Please return at 2:45 p.m. when we will begin our final and concluding session on the future of interdisciplinary science.

SESSION III: THE FUTURE OF INTERDISCIPLINARY RESEARCH

Dr. Roderic Pettigrew
We have another outstanding scientist and educator who will open this session with a presentation on training the interdisciplinary scientists of tomorrow. This presentation will be given by Dr. Shirley Ann Jackson. Dr. Jackson is exceedingly well known to both the research and education communities. At the current time, she is the 18th President of the Rensselaer Polytechnic Institute where she has led a miraculous renaissance at the Institute. I saw some of the data on the increase in fundamental research and funding at RPI since Dr. Jackson has taken the reigns of that university, and it is pretty outstanding, I would say. If I remember correctly, Shirley, I think it was a 600 percent increase, or something of that nature. I would say that's pretty revolutionary.

Dr. Jackson is also the past President of the American Association for the Advancement of Science. She was previously Chairman of the U.S. Nuclear Regulatory Commission from 1995 to 1999. Among her many great honors, which include some 40 or so honorary doctorates, is an honor that she received just this year from the National Science Foundation, the Vannevar Bush Award, which was given to her based on, and I quote, "…her lifetime of achievements in scientific, education, and public policy." She is clearly extremely well suited to speak to us on what we can expect in training the scientists of tomorrow. Dr. Jackson…

Training the Interdisciplinary Scientists of Tomorrow
Dr. Shirley Ann Jackson, President, Rensselaer Polytechnic Institute
Good afternoon! It is a privilege to speak on this landmark 5th Anniversary of the establishment of the National Institute of Biomedical Imaging and Bioengineering, or NIBIB here at NIH. NIBIB is a pivotal initiative of the NIH because it indicates the critical linkage of engineering and physical and computational sciences to the life sciences and biomedical research, in general, and it highlights the promise that interdisciplinary and multidisciplinary research hold.

Educating the next generations of scientists and engineers in the novel and promising research approaches requires that we reach beyond the traditional disciplinary fundamentals and that we develop capacities for innovation and provide exposures for students to experiences not always associated with traditional science. This afternoon, I will address this unique and growing challenge, but I always like to begin with the big picture.

Over time, some of the traditional sciences have become increasingly reductivist as sectors grow progressively more specialized, and therefore, more narrow. Yet as science advances, important problems are often found where the disciplines overlap and diverse approaches intersect. In fact, one may draw a corresponding parallel from the world in which we live, because our world is evermore integrated and flat, but it is also asymmetrical with differences and unstable.

On the one side, we've made great strides globally since the 1960s with average life expectancy increased from 37 to 67 years. Child mortality rates have decreased. Diseases such as small pox and polio are largely eradicated or greatly reduced. Fertility rates have been reduced so that today there are 3.5 births per woman in developing countries rather than the six births in the 1960s. Science has improved crop growth so that grain production has tripled. There have been

advances in transportation and communications technology that have expanded trade and financial markets. Corporate enterprises have formed collaborations, and there has been the overall movement of technology and information and ideas around the globe.

These things have offered nations, commercial enterprises, and even individuals, access to, and interaction with, one another such that the playing field is leveled as never before—a playing field in which nearly anyone with ingenuity and motivation can compete and participate regardless of ideology, ethnicity, gender or geographic location. That actually forms a kind of framework. Even though the focus this afternoon is primarily scientific, it is a framework that lays out where and how many problems are addressed.

This interlinked planet has led to great change, but on the other side, the world is more asymmetrical than ever before, and the imbalances are as threatening as any pandemic. The population grew in 50 years from 1950 from 2.5 billion to 6 billion. Water use has tripled, the demand for seafood is five-fold over what it used to be, and I won't even talk about the ten-fold increase in automobiles and the environmental impact on the planet. These real opponents that in the sense of biomedical advancement that we're dealing with relate to asymmetry of nations, peoples, and cultures. We can measure it in many ways: the relative public health, degree of poverty or comparative GDP, literacy levels, access to energy, access to clean drinking water, and food.

Today, the wealthiest ten countries are 50 times richer than the poorest. Two hundred and fifty years ago at the outset of the industrial revolution, it was a factor of three. Global imbalances have been with us for all time, but they are more acute because of the degree of difference today and because communications and global media make them highly visible everywhere by more people.

I believe that we understand, as Dr. Satcher mentioned last night, that the asymmetries, whether within a society or globally, if not addressed, will always come back to haunt us. Addressing global asymmetries, especially in health care, does require new interdisciplinary approaches and new tools—tools that are in evidence within the NIBIB research mission. New interdisciplinary fields such as nanotechnology, computational biology, and bioinformatics offer great promise.

I serve on the board of a medical technology company, Medtronic, which develops and manufactures biomedical products and therapies emphasizing a continuum of care to prevent, diagnose, and monitor chronic conditions. For some of my examples, I'm very grateful to Dr. Steven Osterly, who is the Senior Vice President for Medicine and Technology at Medtronic.

Within Medtronic laboratories, is an array of fundamental research at the nanometer scale. For example, Dr. Osterly's laboratory is developing nanostructured surfaces, multiple substrates, and multiple form factors, and his work has enabled what is referred to as nanostructure-assisted laser desorption and ionization, which allows sample analysis without an interfering matrix background.

In another Medtronic example, nanofibers grown on top of a particle could be used as a drug delivery vehicle. A structure such as a bioresorbable polymer shell over a high surface area—

something called Gecko bioadhesive nanofiber—could create a feature to improve bioavailability through improved residence time of drug substances, more targeted drug delivery, and improved membrane diffusion. Nanotechnology is revolutionizing multiple industries as it advances and improves biomedical technologies across a broad spectrum.

As you know, nanotechnology permits the rational observation and manipulation of the electronic, optical, and magnetic properties of a material at the molecular and atomic levels, enabling researchers to study and exploit unique biological, chemical, and physical mechanisms, which manifest only at that scale. Nanotechnology is not merely small, it is different because it is small.

Nanometer scales move us, and I know this as a physicist, to fundamental limits in terms of our current understanding of the physical, biological, and chemical mechanisms and processes at that level. At the same time, as you've heard from others, nanotechnology is enabling the development of new structures and systems heretofore unattainable.

At Rensselaer Polytechnic Institute, we're taking a similar approach because our historic background is in engineering, and our approach comes from marrying our traditional strengths in engineering, computation and information technology, modeling and simulation, and nanotechnology, with the life sciences.

Two and one-half years ago, we opened a new facility: the Center for Biotechnology and Interdisciplinary Studies. The work of that center is built broadly around four of what we call "constellations" or critical masses of faculty in biocatalysis and metabolic engineering systems biology, in tissue engineering and regenerative medicine, in computational biology, and bioinformatics. We have also hired faculty across a broad spectrum in biology, biochemistry, biophysics, biomedical engineering, and chemical and biological engineering, all of whom work together.

An example of the work coming out of this initiative, one of our faculty is studying, through simulation, protein aggregation, which as you know, can kill nerve cells in neurodegenerative diseases like Alzheimer's or Parkinson's. A protein which aggregates in Alzheimer's disease, known as an amyloid beta, is paired down in his studies to a peptide one sixth the size of the natural protein—the essential segment responsible for clumping.

Alone, amyloid beta can adopt a variety of different conformations, but when more molecules are added, they aggregate, making the shape less flexible. With a hexamer, for example—a clump of six peptide chains—only a few configurations are possible.

Now, to study the protein behavior and to watch it react to different scenarios and conditions, multiple frames of atomic-level description are required. Then a computer helps to predict what happens next, although in very slow motion. Each step of computation represents two femtoseconds. Based on the size and charge of individual amino acids and on interactions with the surrounding media, a kind of jockeying occurs and the protein assumes a three-dimensional shape. In simulation, the progress of knowledge comes from a balance between theory, computation, and experiments. Predicting the shape in the protein folding problem is a challenge.

Another Rensselaer research team, in conjunction with the Wadsworth Center of the New York State Department of Health, is working to describe a mechanism to explain how intein, a type of protein found in a single-celled organisms and bacteria, cuts itself out of the host's protein and reconnects the two remaining strands. The intein breaks a protein sequence at two points—first at what's called the N-terminal and then the C-terminal. Because the protein cuts itself and joins the pieces together in a predictable way, the research team hopes to harness the complex biological reaction to develop a nanoswitch because of the speed and size of the reaction, which could be used for applications from targeted drug delivery and the ability to control it, to genomics and proteomics, to sensors. Because the reaction may be sensitive to environmental stimuli—and people believe that it is—the process could be more than just a two-way switch between off and on. A separate Rensselaer team previously found that the reaction at one terminal, the C-terminal, speeds up in an acidic environment. To control the reaction and use it as a nanoswitch, better understanding of the mechanism behind this reaction is needed.

Now, the researchers revealed the details of the reaction mechanism by applying the principles of quantum mechanics, which really comes out of physics and is a mathematical framework that describes the behavior of the smallest known particles. Until recently, scientists could not apply quantum mechanics to biological systems because of the huge numbers of atoms involved. The latest generation of supercomputers, along with the development of efficient mathematical algorithms to solve quantum mechanical equations, is making such calculations possible.

Typically, for instance, quantum mechanics has been applied to condense metaphysics problems, which typically involve a large number of atoms, as well. They've been able to apply them because of symmetries in physical systems make the calculations simpler and easier. That is the kind of work that I spend quite a bit of time doing.

As one goes down to the nanoscales, there is nothing different physically between a carbon atom in a protein, and a carbon atom in a nanotube, and even though a protein is an asymmetric, complex system, at the quantum level, atoms are just atoms. It doesn't matter if strange things are happening with carbon or nitrogen or hydrogen or oxygen. Quantum mechanics allows researchers to do things that cannot be done in classical studies, such as modeling the way chemical bonds break and form, and how what is known as protein tunneling occurs—which is a mechanism that allows proteins to move through energy barriers that normal logic would deem impossible.

For this project, researchers use computing facilities at what is known as the Rensselaer Scientific Computation Research Center, and the National Center for Supercomputing Applications at the University of Illinois at Urbana-Champaign. In these calculations, as I implied in my earlier example, speed is often the limiting factor. Systems shrink in size and as nanotechnology enables revolutionary scientific manipulation and investigations at that scale, the computational demands and the need for sophisticated simulations dramatically increases. Additional computing power would allow researchers to model complex biological systems with ever greater accuracy. Rensselaer researchers and others are excited at the prospect of now actually simulating the molecular dynamics of an entire cell, for example.

I'm telling you about this because one talks a lot about nanotechnology as something that *is*—or rather, the ability to image at that level. That's very important, but people are increasingly very interested in understanding the dynamics of living systems at that level and wishing to bring new techniques into the ability to model at that level using the kinds of computational tools that heretofore physical scientists and engineers used more heavily than those in the life sciences. I've chosen this particular example, as opposed to an imaging example, because it has implications for what the education of the next generation of interdisciplinary scientists has to be.

This spring, we opened a new computational center for nanotechnology innovations, which today is one of the world's most powerful university-based supercomputing centers. It's one of the top ten computing centers of any kind in the world. We did it in partnership—a partnership between IBM, New York State, and Rensselaer. This will operate what are known as heterogeneous supercomputing centers that involve technologies from IBM Blue Gene, Linux Clusters, and AMD Processors.

The point is, the diversity and scale of this setup will allow large-scale, leading-edge computational research in both scientific and technological arenas. I'm not going to tell you what the teraflops (FLOPS being floating point operations per second - measures computing power, teraflops being 10^{12} flops) are, but the important point is that the center will have the power and speed to enable academic and industry researchers to conduct a wide range of computational studies along a continuum from basic research to commercial application, and in areas that range from new device fabrication to new biomedical technologies and treatment modalities, to new fundamental studies in the basic biology of complex systems.

It will integrate computational simulations with other cornerstones of scientific inquiry, including theory and observation through bioimaging techniques, opening new discovery possibilities. This will be the kind of combination of platforms to support investigations at the nexus of multiple disciplines and sectors—bioengineering, medicine, information technology, and experimental media, both as a tool in and of itself and as a research area. The possibilities multiply exponentially.

Already research is taking place on carbon nanotubes, on biomaterials, polymer chains, and more. In fact, there are simulation techniques that people are already using to help us better understand, for instance, what happens when we develop devices using what are called virtual patients and the imaging techniques that allow us to do that for drug delivery systems and what happens with stents or transdermal patches and inhalers.

These new tools and the interdisciplinary approaches that they both allow and imply, and what you might glean from the research examples—although the research examples are in many ways limited to what people have done to date. They all highlight our need to reformulate how we educate tomorrow's scientists and those who would work in an interdisciplinary arena.

Again, I might begin with the broader view, but in the end, what I would say is that what we ought to focus on are a variety of principles, which taken together, engender what I refer to as globally-focused—globally-focused because many of the problems are global; globally-focused

because more and more researchers are working simultaneously around the world; interdisciplinary because that is our focus and need here, and what I call diversity-enhanced education. Let me talk about that for a moment, because first, I mean diversity of approach, which begins with disciplinary fundamentals, but students must also acquire the vision, the motivation, and the capacity to work across, between, and at the intersection of multiple disciplines and sectors.

As education has evolved—and indeed, there is considerably more knowledge to acquire to achieve mastery in anything—we've moved away from a basic integration of knowledge into distinct, and often isolated specialties, and possibly to the detriment of the ability to solve the most complex problems and detriment to the understanding of the complexities of the world.

Basic science is the springboard for advances in technologies which enhance our lives. Education, as well, has tended to separate the study of science too quickly from the humanities, arts, and social sciences. Now, why do I bring that up? I bring that up because our new generation of scientists—our young people—have to be prepared to operate in a world that will expect them to reason, question, analyze, evaluate, and assess in a way that will require greater intellectual agility and the ability to see connections across a broad intellectual milieu.

What does that mean to how we teach them? It means it requires diversity of pedagogy. That, in turn, means that education itself has to be enhanced and expanded through the utilization of the very new tools that we talk about using in research and through a variety of new media that are available. Educators then have to devise ways of organizing pedagogy to reach students and to develop their skills and perspectives using new technologies, such as those that allow the simulation of physical and biological phenomena; gaming technology; and technologies that allow us to visualize in real-time that we don't always today. The technologies of telepresses that allow the researcher and student to be in the middle of what he or she is studying, as well as telemersion, which allows collaboration in real time across geographies.

I think that means that we really have to start earlier. Even as we educate our students from a disciplinary base at the undergraduate level, undergraduate research experiences need to fall into these categories to habituate students to the kinds of tools available and the ability to use to them to maximum effect.

The third principle is diversity of outlook . That really requires students to be exposed to diverse cultures and lifestyles and to experience and absorb associated differences in the thought approach and practice, including the approach to medicine and differences in thought about the source of disease. Differences in approach from a multicultural perspective that requires them to marry the latest and highest level technological capabilities with traditional thoughts about medicine. That means they have to operate within a broader context and collaborate across borders—literal borders, and borders of fields—because the challenges that all of us will face are global and interconnected.

I believe this will reinforce their analytical abilities, their awareness of complexity, and their ability to be critical analyzers and consumers of information. People are actually working today, looking at the issue of how one does so-called meta tagging of data as it gets expressed and

appears through the internet to allow people to bring that type of information in real time and to given investigations and computations that they're doing.

All of this says that 21st-century challenges are seldom simple or seldom born of a single issue. They may involve science or engineering. They may have a direct clinical or medical component, but they may have an aspect of international law, diplomacy, or geopolitics and ethics. Again, this requires early exposure to research and to problem solving, which goes beyond particular disciplines, and which requires teamwork.

Finally, there is diversity. All young people who aspire to research careers of diverse backgrounds are encouraged to achieve to their highest levels. Because we have a lot of untapped talent, and if we don't tap it all—if we're just talking to ourselves—then we are going to miss the opportunity that they represent as a hope for a better future. Universities need to shift their traditional approaches to encompass these broad-based principles in their undergraduate and graduate education programs.

Faculty, of course, are the agents and interpreters of the exponentially increasing available and retrievable information. You say, what happens to discipline-based faculty? Discipline-based faculty are there to help students acquire problem-solving skills and to guide them in identifying and understanding which problems are important to solve, and then to help them interpret the results. Again, a critical component in the career continuum, is entry into basic and clinical research that forces students into interdisciplinary problems and which must then be supported by Federal research entities like NIBIB that provide the advanced interdisciplinary research training for clinical and basic investigators.

I understand that NIBIB has strategies and objectives in place to build a cadre of biomedical imaging and bioengineering researchers to lead the advancement in this field. NIBIB is also building flexible opportunities to fill critical gaps in the career continuum, which also means enhancing participation of underrepresented populations, including research experience for clinical residents and fellows, and postdoctoral support for interdisciplinary training for individual fellows. This is just the right place for you to be.

I'm not going to talk that much about what has happened to Federal funding for basic research. A lot of it has been driven by increases over a decade in biomedical research, and at the same time, support for research in the physical sciences has fallen off. I know that NIH's own funding has plateaued in recent years, but since we know that many of the most important advances are inherently interdisciplinary, support for research and development has to be across a broad spectrum of fields. I would find it very interesting if an institute at NIH, like NIBIB, could be allowed and have the motivation to think about the ability to sponsor unique projects coming from the life sciences side here, with an entity like the NSF coming from the physical sciences and engineering, to really think about the kinds of projects that will push the frontiers and allow the physical scientists to come together with their knowledge and computational abilities with life scientists and their knowledge of living systems.

I'm glad to see that the U.S. House and Senate recently put in some increases in the budgets for NIH, NSF and other agencies, and we need to continue to enhance the NIH budget, especially in

areas supported by NIBIB. In the end, a lot of it is going to depend upon how that money is going to get used.

The last thing is that we all have to be engaged and worried about the drop off in our own talent base, even as our government has not made it easy for really talented individuals to come from abroad and to stay here for their basic training. We have to look across the whole spectrum to make that happen.

Addressing the great challenges that face not only this country, but the interlinked global community—whether we're talking human health, which is the focus here, clean water, food production and energy security—all of these require innovation based largely on interdisciplinary and collaborative research, and of course upon necessary human talent; we have to tap the talent pool.

I would again challenge you to think even more broadly about what interdisciplinary research really means, and while biomedical imaging is a very critical tool. We think we know what bioengineering is, but I think it is an evolving definition. There is much beyond even what we know about today that is going to have to be brought to bear. That's why I brought in the specific computational approaches—to really be able to model living systems in real-time and to understand how the introduction of their interventional therapies will play out, whether we're talking about drug therapies, physical interventional therapies, or ones that take a more genetically-based approach. What's happening in the human body is not static. What's happening in living systems is not static. We're a long way from being able to model what's happening in living tissues as a system, and that's going to take the bringing together of fields that traditionally have been separated. Bringing them together not only using the tools we've talked about, but tools beyond that. Thank you very much.

Dr. Roderic Pettigrew
Thank you, Dr. Jackson, for that very scholarly presentation and perspective on the challenges and opportunities for educating the next generation of scientists.

If the panel will come up and take their seats… We certainly do appreciate the importance and value of modeling so we can be more intelligent about the way we design both approaches to diagnosing disease and also therapeutic approaches. Systems modeling is a critical component of being able to achieve that.

For the next period we have a bit of a change of pace. We have a panel of young investigators—just the type of people Dr. Jackson was referring to. These are all individuals—there are four of them—who have received just their first NIH grant from NIBIB.

The two moderators are Drs. Norbert Pelc and Dan Sodickson. Norbert was a member of the inaugural National Advisory Council of NIBIB. Norbert and I have known each other for many years. Norbert is a consummate scientist himself. He was eluded to earlier this morning by Walter Hinshaw about his background in industry. He is known throughout the imaging community as one of the most outstanding physicists in the field of medical imaging physics, and

that is no exaggeration. Norbert is Professor of Radiology at Stanford and has been there for about a decade or so, actually more than two decades now, he tells me.

Dan Sodickson—I have often referred to him as a wunderkind. As my former Chairman of Radiology told me after I had been at Emory for about ten years—he said, "Rod, you used to be a young turk, and you may still be a turk, but you're not so young anymore." I don't think you've quite reached that stage yet, but I think Dan represents a transitional phase as a junior-level scientist, I would say, but nonetheless distinguished now from the truly young, new investigator stage. Formerly at Harvard University and MIT, and now, having been recruited to head the NMR research effort at New York University.

They will lead this discussion. We are interested in hearing the perspectives from this panel of four young investigators who have received the Nagy award that we mentioned earlier today and was also described by Stan Baum.

At this point, I will turn it over to Norbert and Dan Sodickson.

Nagy Awardees Panel: Experiences of Young Investigators at the Interface of the Life and Physical Sciences
Moderators:
Dr. Norbert Pelc, Stanford University
Dr. Daniel Sodickson, New York University School of Medicine

Participants:
Dr. Jennifer Elisseeff, Johns Hopkins University
Dr. Elisa Konofagu, Columbia University
Dr. Garry Gold, Stanford University
Dr. Joe Tien, Boston University

Dr. Norbert Pelc
Thank you, Rod. I'd like to start with some introductory comments.

It's been mentioned repeatedly that this field we're in is highly interdisciplinary and has been so. The history of device development, including the imaging systems and their clinical application, has involved multiple disciplines—mechanical and electrical engineering, physics, mathematics, anatomy, physiology. The field is increasingly interdisciplinary, and now we talk about things like molecular biology and genetics, computational sciences, material sciences being needed. The people we need to train, and the new scientists that need to come into this field, need to be exposed and conversant in a wide range of disciplines.

Dr. Schmitt said yesterday how important it is to train the next generation of scientists—those that are unafraid to go into areas that would be truly revolutionary, and what we will be discussing is how do we train, and more importantly, nurture the career of young investigators in this increasingly interdisciplinary field at the interface of the life and physical sciences?

It's impossible for me to talk about nurturing the career of young investigators in this field without thinking about the Whitaker Foundation. I think it also needs to be mentioned that, today we celebrate the 5th anniversary of this Institute and also its great successes. I think that the great success in this short time was facilitated by the fact that the Whitaker Foundation trained a generation of engineers and scientists with an appreciation of clinical problems who were ready to jump into this field that we're in.

Peter Katona is here, and I'd like to suggest a round of applause for the Whitaker Foundation and the last president of the Foundation. Peter, please stand up.

The topic we're discussing is how to train and nurture the career of the young investigators. The way we'll do this is, each of us will introduce ourselves very briefly. Given the celebration of the science that the Institute has enabled, we'll also talk a for few seconds about the projects that we're involved in. We'll concentrate on the young investigators and their career paths and life experiences thus far.

A brief introduction of myself… I received my bachelors in applied mathematics, engineering and physics at the University of Wisconsin, then did my graduate training at Harvard in medical radiological physics. I'll come back to that in a moment.

The project that I'm involved in right now funded by NIBIB is to explore a radically different kind of computer tomography scanner, that instead of having a single source and a large array of detectors, it has a two-dimensional array of x-ray emitters and a small, two-dimensional array of fast photon-counting detectors. The goal of our project is to actually go ahead and mount this on a gantry and go as far as possible in initial testing of this and animals and humans. The benefits of this inverse geometry CT system, as we call it, is that it should be able to image an arbitrarily wide volume in a single, fast rotation with improved image quality, such as no cone beam artifacts even though we're imaging a large volume, with very high and uniform spatial resolution throughout that volume, and in fact, with lower radiation dose per subject than current systems. Among the applications it should enable is very fast volumetric, dynamic computed tomography imaging.

Back to my training, as you see, even my undergraduate degree was interdisciplinary and that was by virtue of being lucky enough to be at the University of Wisconsin, which had this program. That luck was even more important because at that time, the University of Wisconsin was one of the nexuses of the application of physics to medicine, one of the first medical physics programs was there, and I had the good luck of running into John Cameron as an undergraduate who encouraged me to go into this field. I was able to find this field that was at the interface between the life and physical sciences as an undergraduate, and then to continue that as a graduate student, and as you can see, my graduate training is in medical radiological physics.

Even with that luck, looking back I'd have to say that the interdisciplinary training that I was able to get at that time was inadequate. Although the physics training that I received was certainly good enough for me to have gone on to my career, in terms of my appreciation of the medical problems, clinical applications, the ability to interact with physicians and colleagues

really didn't come until I was out in the workforce and interacting with collaborators. My training, per se, was inadequate to do that.

Hopefully, we will hear from the young investigators today that this has changed. Part of what we should do is judge the degree to which that has changed, and if so, whether or not it needs improvement.

At this point, I'll turn it over to Dan…

Dr. Daniel Sodickson
Well, thank you. I'd like to join Norbert in welcoming you to this panel. I'm going to change the perspective a little to the point of the young investigator and frame the question before us today from that perspective, which is really how we get from here—and I've drawn a little circle around my depiction of the young investigator—to here, which is the Principal Investigator who is well established.

In addition to moderating, I've been charged with getting the conversation going by surveying my own path. I'll try to do that very quickly in order to give the others as much time as possible. Just quickly, here it is.

I did my undergraduate training at Yale in physics and humanities. Then, I was lucky enough to stumble upon the Harvard-MIT Division of Health Sciences and Technology at MIT, and I'll get into that in a second. Then, I was seduced into the M.D. Since then, for the last ten years, I've been at Beth Israel Deaconess Medical Center working my way up in research and a little bit of administration. As Rod mentioned, I've just been recruited to NYU to head the relatively young, but promising, Center for Biomedical Imaging, which has been a lot of fun.

Thinking about the education of a young investigator, my mind sort of wandered to these words… "Upon three Seals is the mind of young impressed—upon the 'yea', upon the 'nay', and at the last, upon 'perhaps'." (Samuel Bowditch) Interpreting this quite freely, I associate the "nay" with the principal of guidance, and as any parent will know, saying no is the first way to teach what cannot and should not be done. After that, the "yea" is in support, which is encouragement, and specifically, funding. Then there is "perhaps," which is the encouragement of new ideas. I think these three themes will all be visited at one point or another.

In terms of education and guidance, as I said, I was lucky enough to find Harvard-MIT Division of Science and Technology (HST). I won't say much for lack of time other than that this is the mission of the HST: Integrating science, engineering and medicine to solve problems in human health; and training clinically-informed scientists and scientifically-informed clinicians. This almost completely overlaps the mission of the NIBIB. I hope, Norbert, that there are some measures that are improving interdisciplinary education.

I have one slide for research aimed at the questions I was asking as I came out of my training. In April 1996, I was doing a preceptorship in cardiac MRI with Warren Manning at Beth Israel Deaconess. He asked me to take a look through the literature and decide in what areas I might want to work, which is a provocative question, but not necessarily a very precise question. As I

read, I kept thinking, why can't we image faster with MR, which is an important issue for cardiac MRI. The answer eventually came to me, that we were always imaging one point in one line of information at a time and getting data in a sequential fashion, much like a fax machine. Then I remembered a paper I read about, which used arrays of the detectors. I started wondering what the information of those arrays was, and in fact, whether they could be used to encode spatial information. Then, a few doodles on paper later, my career was essentially formed. It was really a great stroke of luck.

What I've been focusing on for a long while now is parallel MRI. Parallel MRI can be defined in an analogy with multi-detector row CT. Rather than gathering one slice of an image at a time, we can now array detectors around the body to see different pieces of the image, combine that with the usual encoding of MRI, and get many data points at once. This started out as a highly engineering and mathematically intensive area, but has broadened out into a number of clinical areas. It's relatively routine on just about all modern MR scanners, but of course, the challenge was getting this funded at the very beginning, because this was a very preliminary approach based largely in physics and engineering, which brings me to the topic of support.

Of course, there are many kinds of support. Family support is absolutely crucial. Then there's this kind of support from my first mentor, Warren, to the group of people that I work with now. I refer specifically now to monetary support. As Norbert mentioned, the Whitaker Foundation came to the rescue here, and that was my first grant. After that was the NIH R29, the first mechanism, which has since been discontinued, but I might argue that there is a lot of merit to it. It certainly helped me along. Next to the rescue—and I've had a lot of rescuers over the years—came the NIBIB just perfectly timed for these two R01 grants.

I won't belabor this since we all know the mission and the success of NIBIB, because that's been amply documented today. Just one or two thoughts about guiding future scientists and I'll turn it over to our panel. For me, that beginning question—why can't we? Why can't we image faster with MR? This was the genesis of my career to date, and what I'm still pursuing. In fact, this general kind of question—why can't we do that which we would very much like to do? What can't we do that we would like to? I think this is a crucial aspect of the education of the young investigator. Often we're taught about what has been done and what can be done. We talk about the benefits at scientific conferences, but we don't spend as much time talking about what we've failed at miserably. In fact, I think this is one area that could be very helpful in the MR field. The ISMRM (International Society for Magnetic Resonance in Medicine) started an initiative to try to list these areas and try to provide it to young investigators. I think it has to ultimately bridge academia, industry and funding organizations to be successful.

With that, I'll just leave you with a variety of questions that perhaps the panelists can pick up and come back to in the area of guidance, promoting interdisciplinary education without losing disciplinary rigor, and how to share information about unsolved problems. For support, one I'll highlight here that I think the Whitaker Foundation did very well is an interesting area to consider, is how to use current grants to prepare young investigators for their next grants and how to bring them together, perhaps at a yearly meeting, and inform them on how they're going to get the next one. I think I've already taken more than enough time. Let me turn to our next panelist.

Dr. Jennifer Elisseeff
Thank you very much. It's quite an honor to be here today to celebrate NIBIB. I'm very happy to give a background of why I'm here today. I started out in chemistry. Why chemistry? Well, first of all, I didn't have a biomedical engineering department yet. I think you could minor in it, but it wasn't a major quite yet. I actually started out in biology, but I gave up when I hit the fact that you had to take physical chemistry for biology majors. I thought, why can't I take the real physical chemistry? Then I wanted to take quantum mechanics, too. Chemistry seemed like the middle of the road where I could take biology and physics and it didn't seem too abnormal.

Then I went to a real interdisciplinary program, as was mentioned, at the Harvard MIT Division of Health Sciences and Technology and there I started in the realm of tissue engineering. On day one, I realized some of the fun aspects of interdisciplinary research; that being the different cultures that are brought together. The first day, there was a joint group meeting with surgeons and engineers. Since it was my first day, I made sure I was there right on time, and I noticed that it was only surgeons that were there right on time. Nine o'clock in the morning for a group meeting was mid-afternoon for them. Then, slowly, ten or 15 minutes later, the engineers dragged in. There was also an apparel difference. The surgeons were in their suits and the engineers were in their jeans and a little bit disheveled looking. From the beginning, I saw there was a difference and that it wasn't just mixing the science, the different backgrounds and fundamentals, there was also a mixing of different cultures together.

There I did some work using the chemistry, but started to apply it to medical problems. I realized that things were still in a little bit of a black box. Trying to grow tissues, we put cells on scaffolds and biomaterials together and see what comes out. It seemed too much of a black box. I came here to NIH to try to learn some biology and to try to apply these principles of developmental biology to a more rational design of tissue engineering systems. Since then, I've been close by at Johns Hopkins since 2001.

This slide is just to show how engineering functional tissues that we heard about this morning is a very multidisciplinary field. We have to worry about biomaterials. How are we going to design these systems? What's the chemistry? What's the processing? We also need to think about what cell we're going to put there and all the complications of the relative choices of stem cells that we have. The biology that I mentioned… If we don't even understand how the cells work, how can we rationally design the materials to help induce those cells to do something that we want them to do? That's another discipline you have to put together.

There are a lot of *in vitro* technologies, such a bioreactor that can be used to help induce tissue formation. Another big gap is the jump to preclinical models. We're really trying to translate these technologies, but there's a very big difference between the dish and an operating room, so we need to put together either the surgeons or even veterinary surgeons and push these technologies forward.

The grant I have that is funded by NIBIB is looking at rebuilding cartilage tissue. I want to show here the connection between technology and medical problems. We're not just making new technologies, we're designing these new technologies in conjunction with a medical problem.

This is knee cartilage with a big hole in it. This is not going to repair itself naturally, and even worse, will lead to further degeneration in the whole joint. We're taking a lot of different approaches to different pieces. In the previous slide, what cell are we going to look at? You notice these cells are flat, but we need them to be three-dimensional. There's a big difference. How can we build organized tissues with many layers, and how do cells talk to each other? With a little bit of biology and a little bit of chemistry.

Then when we want to move this into a real person, or in our case initially, into a large animal, how are you going to get these things to stick in place? How are you going to get these cells and these materials to stay in this very challenging environment? Well, that's when we put the chemist and the surgeon together. Together, they designed this adhesive that we apply to the tissue that can serve as a bridge between the material we put in and the tissue. This is a lot like the way that a primer will help bind the paint to the wall surface. It's always provides entertainment putting the surgeons and chemists together. How does the chemist survive in the operating room the first time, and how does the surgeon learn what "clean" is from a biological perspective and a not surgical perspective? We have an interdisciplinary group.

This is the most recent picture of my lab. We're always on the road, but we always have a surgical resident working full time in the laboratory. We've had them from ENT (Ear, Nose and Throat), from plastic surgery, from orthopedic surgery, and then we have the chemists and biologists trying to mix them all up.

I also want to mention that out of this research came a startup company called Cartilix. I was really happy to hear today two cases where industry was responsible for building the first MRI and the first laser because we hear too much today how industry can be harmful for basic research. Whereas here, industry has really helped us translate research. That's the case for these technologies where there's no way an academic laboratory can manufacture a product and be ready for clinical trials. We're actually approved, we're manufactured, and we'll be starting clinical trials as soon as the first patient volunteers in Europe. I'm very thankful for the funding and support. I'm thankful for the senior mentors who are out in this audience who have been supportive during my progression. Thank you for the opportunity to be here today.

Dr. Elisa Konofagou
Good afternoon. My name is Elisa Konofagou. I am also very honored to be invited to the 5th anniversary of NIBIB. My journey also started by interdisciplinary area in chemistry and physics on the other side of the Atlantic in Paris, but my accent is Greek. I'm from Greece originally. I always wanted to study biomedical engineering. I got "the bug" when my mother was doing a Ph.D. in economics at Harvard back in 1984 and she said, "You should look into MIT and see what kind of programs they have there." Sure enough, there was a biomedical engineering that stuck out on the page and I thought, "Yes, that's what I want to study."

I went back to Greece, and there was no such thing, and there is still no such thing at the undergraduate level. There was biophysics, which was interesting mix of the biology and physics that I wanted to combine together. There was the biophysics in Chemical Physics Department at the University of Paris, and they had an excellent program. I actually went there and after looking at Raman spectroscopy and NMR spectroscopy, I got interested in for interaction of

porphyrin molecules with DNA strands and into analyzing the actual signals and images. Very serendipitously, there was a new Masters program launched at Imperial College that year. I managed to get in and really got exposed to electrical engineering... That was a heavy year, but it really exposed me to medical imaging, and I really had “the bug” from then on. We did so much that connects for segmentation of prenatal echocardiograms, and I also got the bug for ultrasound, which I’m going to talk about a little bit today.

I did my Ph.D. at the University of Houston looking at the novel approach—not just looking at anatomical information, but looking at the actual elastic properties of tissues. Why do we want to look at elastic properties? Well, that’s a very good question.

It turns out that a lot of the pathology, and especially for cancer, and this is very intuitive to all of us. The cancer itself, when it forms, there is a change in mechanical properties. That’s why physicians can tell by palpitation and examination, they can feel for something superficial—some kind of hard nodule. The idea was to try to image that—actually image the hardness that the physician would feel, or might not feel if there was a tumor a little bit deeper seated. The new method was called elastography, which actually did start in ultrasound back in the late 1980s. It would show differences between benign and malignant tissue. This is a clinical study by my Ph.D. advisor, Jonathan Ophir, which was funded by the NCI. Last year, a study was presented at the RSNA showing that the sonogram and elastogram together, comparing the two modalities, from the size, you were actually able to differentiate one hundred percent of breast lumps. Then we got some phone calls from different patients asking to come to our lab for a scan. They were scared and didn’t want to undergo biopsy, which is understandable, but of course, we couldn’t do that any time soon.

The idea is you use two sonograms and compress a little bit, and look at the difference, you create a new image. Just from ultrasound, we can actually get information from the speckle. The speckle is the granular pattern, which is the salt and pepper noise that physician sees on the ultrasound, but in fact, it contains information on the underlying scattering.

We took this further for the heart. This is a much more difficult problem. Instead of compressing the tissue, you actually utilize the inherent contraction of the heart. Here is a theoretical model from the UC San Diego group. On the left is a homogeneous heart—a normal heart—all the same stiffness. There is a deposition of collagen when you have an infarct, which is in the region that you see here in blue, and this collagen starts hardening very fast. In fact, in the course of 2 weeks after an infarction, you would get a 10x stiffer region.

You have a pretty good mechanical contrast that we aim at imaging. Here we’re comparing with the gold standard of tagging that has been around for more than 25 years. We’re also comparing two-dimensional strain measurements from ultrasound that is actually unprecedented. Normally, you do it in the axial direction, but we have also achieved lateral estimation, as well. These are displacements through systole, and the strains, as well, and we also compare with the theoretical model. The lower the strain, the higher the stiffness of the muscle. We have pretty good correlation and preliminary data for the normal control case, and also for the infarcted patient with reperfused myocardium where we see the anterior wall, which has a much lower strain than the posterior wall that compensates for it.

I'm going to switch gears and this is the last topic I'm going to talk about. We're also looking at the blood brain barrier, which is a rate-limiting factor for brain drug delivery. It defends the brain and makes sure that the molecules that are harmful to the brain are not diffusing into the brain. However, when you have a part of the brain that has a disease, such as Parkinson's or Alzheimer's the drugs don't go through the blood-brain barrier. That's a very important problem right now, because only 5 percent of the drugs cross the blood brain barrier. You can use ultrasound for therapeutic applications, as well. The way that you would focus electromagnetic light waves through a lens and burn a piece of paper, you can also use it to burn tissues. We don't really want to burn tissues, we actually want to go completely non-invasively, and use this skill on a live mouse to cause localized opening.

This is a series of MRI images using a model drug where we aim for the posterior cerebral artery, and we also aim for the hippocampus, which is this swirl region here. This is actually affecting the Alzheimer's through the amyloid beta plaques. As you can see, in the course of 45 minutes after the ultrasound procedures, you can open the entire region of the hippocampus and treat it.

The good thing is that this is at the lower pressure, and this is what is used in diagnostic levels, so we know it's pretty safe. You can also see over here that if you scan again after a day, the blood brain barrier has recovered, so hopefully, it's safe.

I want to say a big thank you to NIBIB. This study has been funded by an R01 that we got last year, and we have also been enjoying some funding by the Coulter Foundation, which is also essential for translational research. Thank you again, and also my collaborators—clinicians, students, and also engineers and biologists that we have to bring together. Thank you very much.

Dr. Garry Gold
Thank you, first of all, for inviting me. My name is Garry Gold. I'm an Associate Professor of Radiology at Stanford. I think I serve as the token clinical person on this panel of young investigators.

What you see up on the screen describes a little of the brief history of my career path to where I am right now. It's not strictly complete in the sense that I took a sort of iterative approach to reaching biomedical engineering or bioengineering or imaging as my ultimate career. All during my bachelor's degree at Stanford in electrical engineering, I was taking premedical coursework and thinking I might go to medical school or that I might stay in engineering; there was no bioengineering program at Stanford at the time. Right after I received my bachelor's degree, I worked making mass spectrometers in Silicon Valley for awhile. Then I ultimately decided to go to medical school. I went to medical school for a year, which was a very clinically-oriented program without any opportunities for research for medical students that I could determine.

After a year there, I left and I was very dissatisfied with the way medical education was done at that point in time at that particular institution. I came back to Stanford to finish my Masters degree in electrical engineering, once again going to the other side of interdisciplinary line between the two specialties. Ultimately went back for an M.D. at Stanford doing a radiology

residency and doing research during my radiology residency, including an NIH postdoctoral fellowship.

The key points in my research career during this iterative approach… I think that the first key point was meeting Al Macovski at Stanford, who is the Director of the Magnetic Resonance Systems Research Laboratory. Al has served as a mentor for me over the last 20 years. Very inspirational, he's a Ph.D., I'm an M.D.—I don't think that matters. As was said, you often don't pick your mentors, it just happens. Al really inspired me to go into biomedical imaging. Ultimately, I decided to take it from the radiologic end rather than the engineering end.

During my radiology residency, I came to the NIH for a research festival. I was very impressed by the scope and the nature of the research that was going on here, and that led me to push during my residency to create a pathway that didn't really exist—to do research during my radiology residency *via* a postdoctoral fellowship sponsored by NCI. I did a clinical fellowship in musculoskeletal imaging in San Diego (primarily because I was interested in MRI and sports) with Donald Resnick, who is a leader in that clinical area. Then I joined the Stanford faculty in 2000.

I should mention that a key part of what happened to me since then is that my Chair in my department believed in me enough to give me the necessary research time to develop a research program and write grants. Along with that initially was a Whitaker grant, which I also consider to be absolutely crucial to the development of my career. I thank Dr. Katona and the Foundation, the conferences were excellent. Meeting other investigators, and the inspiration there in that sort of career-development program, is something I think we're missing a little bit of for clinical people these days. I also received a Career Development award from the VA, and subsequently received my first NIH grant from the NIBIB in Rapid MRI of Osteoarthritis, and then subsequently my second grant. I'm going to touch on those briefly.

My first grant was the Rapid MRI of Osteoarthritis and we're looking at improving the speed and sensitivity of MR imaging of articular cartilage and the degeneration of articular cartilage. It's a very prevalent disease that is going to be more prevalent as people age. These are some 7 Tesla with sodium images of articular cartilage highlighting the differences between an otherwise healthy-appearing 65-year-old and a healthy-appearing 35-year-old. I think for those of us who no longer fall in the "young" category, it's somewhat discouraging that the sodium or proteoglycan content may go down with age.

This grant was interdisciplinary in nature in that it involved radiology and electrical engineering, but it didn't really involve many of the larger biological specialties. My second project, which was also recently funded by NIBIB… The success of my first project enabled me to explore a little more, in this case, form relationships with the biomechanics people at Stanford, and ultimately combine MRI with biomechanics to look at the problem of a dynamic disease process in young people called patellofemoral pain.

Anterior knee pain often occurs while you're climbing stairs or walking or running. It's very difficult to diagnose by our traditional methods because it doesn't show up on routine MRIs. We're looking at this project to combine upright weight-bearing MRI, real-time MRI, and finite

element modeling to really look at cartilage stress in a dynamic environment to explain and stratify patients for the right kind of therapy. I would say that in this process, the support of NIBIB has been crucial. The timing of my grant from NIBIB couldn't have been better for me in terms of just when my Whitaker award was coming to a close, the NIBIB was forming and the first RFAs were coming out. That enabled me to get a great start on a research career. I thank you.

Dr. Joe Tien
Hi. My name is Joe Tien. I'm an Assistant Professor of biomedical engineering at Boston University.

I came into this field as an elementary particle theorist. For those of you who don't know what that is, it's in physics. I thought I would show you my first paper. This was published over 14 years ago and is called *Energy levels of quark atoms.* I would bet that most of you don't know what a quark atom is, so let me tell you.

All of our protons and neutrons contain three quarks each, and it turns out that if each of these triplicates were to break apart and become doublets, then these might have unusual properties. We study these particles because we thought they might be useful for nuclear fusion and generate a lot of energy. That's great, except that these particles don't exist in nature, so I spent a year of my life studying the properties of things that don't exist.

At the time, that didn't really bother me; this was in '93. When I went to graduate school over at Harvard in the Department of Physics, it did start to bother me and I did want to work on things that did actually exist. I made a transition—and you're probably thinking that this is where I went from physics to biomedical engineering—but no, this is where I went from being a theorist to an experimentalist. What I did was join the lab of George Whitesides in the Department of Chemistry, where I started analyzing problems that had to do with self-assembly. I went to the lab and got my hands wet and realized that I enjoyed this sort of work.

Over the span of my graduate career, I've found that there was a particular type of problem that was appealing. It was the sort of problem where you build something, but at the same time, it has a mathematical basis. It also needs to have a geometrical basis. There's something about fitting together forms in three dimensions that really appeals to me.

When I graduated in '99, I had to pick a field to go into. I knew I wanted to go into biological work, partly because the problems of biology were very difficult. At the time, my only formal training in biology was as a freshman in high school. I had to go learn some cell biology, and I did that in a postdoc where I worked with Chris Chen—we've heard about some of his work today. When he was still at Johns Hopkins, I was in the Biomedical Engineering Department there. His lab is really more of a cell biology lab using bioengineering tools to study cell biology. We did that and looked at mechanotransduction in cells.

That ended at around 2001 or 2002 when I went to join the faculty at Boston University where I had to again pick a field I wanted to work in. I thought that working on single cells was interesting from an academic point of view, but it may not have that sort of relevance that I was

looking for in terms of potential impact on health-related fields. I wanted to pick a problem that was more geometric and mathematical, so my group started moving toward the field of tissue engineering.

In tissue engineering, in 2002 and even now, the field is generally dominated by ideas of chemistry. You create a new type of scaffold or a new polymer and that's going to induce some additional type of functionality to your object. The concepts that we've been trying to put forth is that if you build a 3-dimensional form or a geometric form that looks like a particular type of tissue, then maybe you can induce that particular tissue function in the construct that you make.

We first proposed these ideas to NHLBI, but they rejected it, and it was probably for good reason because the way the proposal was crafted, it didn't have the mechanistic background that NHLBI was looking for. Luckily, the Whitaker Foundation found enough promise in these ideas that they funded us, and later when Whitaker closed up, NIBIB stepped in and saved us from financial ruin. NIBIB has funded us ever since.

I now have a group of interdisciplinary people; a biologist, a geneticist, a physicist, a chemical engineer, a mechanical engineer, and we've been able to validate this idea that if you take a scaffold that has a particular 3-dimensional form that mimics that of a particular tissue, then you can actually get something that is functional.

What sort of role did NIBIB play in all of this? I can think of three things that were critical for this whole endeavor to succeed. The first is obviously money, and money always helps. I think NIBIB is more willing to find high-risk work in interdisciplinary fields than—well, NHLBI, and I don't know about other agencies.

The second thing is that NIBIB was able to bring together this group of individuals, and I don't want to underestimate the impact of that. As a business is coming into the fields of biology and physiology oftentimes gets pigeonholed into being—well, the physicist and engineer don't know anything about biology. I don't think that's true, but at the same time, it's a good idea to have study sections that are devoted to, or filled with, people who do actually understand what you're talking about and are more receptive to these interdisciplinary ideas.

The third thing is, I found out that NIBIB is very open in how it treats its new investigators. What I mean is that in the study sections, they have been willing to take on Assistant Professors on study sections, and I think that's kind of rare. For me, I know, sitting in on those study sections really allowed me to tailor what it is that we want to do to the interests of the medical community and find some common ground.

I just want to conclude there. Thank you very much for this opportunity to be here and talk about something that really has nothing to do with science. I also want to say that, I don't know that the future has in store for NIBIB, but as long as it retains its willingness to take chances on unconventional approaches, and in particular, physical insights into biomedical problems, then I think it will do just fine. Thank you.

A question and answer period follow with the panelists.

Audience participant
How does your research help you treat patients?

Dr. Garry Gold
I do a lot of research on articular cartilage, and I also read MRIs of people who have problems with their articular cartilage. There's nothing that quite focuses your attention and your knowledge of the literature as to have to write an R01 on articular cartilage. You go into the reading room and go, "Oh! That's what I read about in this paper, and the chances are this lesion really represents this." I think that I've been fortunate in that the research and the clinical work have been able to inform each other. The clinical work often presents problems that are potential research areas.

On the bigger level, I think it's very important that clinical people be aware of how research is performed, and not only the limitations and the benefits, but be able to read the literature and interpret it in a critical way to assess what the best therapies may be for their patients. I think that's true for all clinicians, and all clinicians need at least that basic level of exposure.

Dr. Daniel Sodickson
I'll answer a kind of inverse question to yours. As a nonpracticing M.D., the question I often get is, "Was going to medical school worthwhile? You're not practicing. You're not using it. Was it a waste of valuable years?" Of course, the answer is a resounding no. I think in much the same way as Gary was saying in that I think the research informs the clinical perspectives. I think the clinical perspective to which I was exposed informs my research day to day. It's sort of a clinical conscience hovering over me in the background encouraging attention to problems patients will care about. I think it works in both ways.

Audience participant
I was impressed with Jennifer Elisseeff's photo—of your laboratory. You were not in it, but you pointed out that it was your team and that a surgical resident was part of your team. You are at Hopkins, and certainly, the Department of Surgery at Hopkins, as do departments of surgery in all the prestigious universities, require their trainees to spend time in a research laboratory. I'm not sure if I were to see pictures of the labs that any of the young investigators have, that you would find radiology residents as part of that operation. I've been saying for a very, very long time, that certainly the prestigious, the institutions that have the resources, if they require their trainees to spend time in a laboratory as part of their training, then I think we would have many more people sitting up front.

Dr. Norbert Pelc
If I could amplify on that comment, if you would look at a picture of Al Macovski's lab circa 19-whatever, you would see Garry Gold there, and even more recent pictures of the lab would have Garry there. One of the things that caused that to happen was the fact that Garry was able to get a funding mechanism to put him in that lab for research training. I commend NIBIB for coming up with that mechanism, but we need to find other ways of encouraging and being able to fund radiology residents and other trainees to spend time in the laboratory.

Audience participant
I think the question is, why and how do departments of surgery, neurology, internal medicine, etc., find the resources to allow their trainees to spend time in a research lab?

Dr. Jennifer Elisseeff
Just from my experience, my first resident when I started the lab was a plastic surgery resident, and there, the department Chair put the funds there to have that time. From their practice, they had the money to do that. The ENT residents that I've had, and the residents that I will have in the next two years have training grants to help support that. In other departments, even within Hopkins, there's no mechanism there and it's hard to find people. It really varies from department to department.

Dr. Elisa Konofagu
I also want to add very quickly that, according to the NIH roadmap, Columbia has received a CTSA grant (i.e., Institutional Clinical and Translational Science Award). That's for five years and it exactly addresses this problem. One thing is that having clinical fellows be able to have time in the lab and on the bench, and it also sponsors translational research, so those are identified already as two areas that need to be addressed.

Dr. Roderic Pettigrew
Okay, we want to thank our panel of investigators and the moderators. That was stimulating. We could continue that for some time, but we do want to get out by 5 p.m.

For the final presentation, the Deputy Director of the National Institute of Biomedical Imaging and Bioengineering will make the introductions. Dr. Belinda Seto…

Dr. Belinda Seto, Deputy Director, NIBIB
Good afternoon. I'm very pleased to have the pleasure of introducing the last two speakers for this afternoon. Indeed, they are the dynamic duo who were the first grantees of the NIBIB. They personify the theme that we have talked about today; the interdisciplinary research and the team science.

Dr. Dennis Spencer is the Harvey and Kate Cushing Professor and Chief of the Neurosurgery Department at the Yale School of Medicine. He pioneered the surgical method of doing surgery for epileptic patients to conserve and spare the neocortical areas to preserve essential functions. Dr. James Duncan is a Professor of Biomedical Engineering, Diagnostic Radiology, and Electrical Engineering also at Yale University. His expertise is in the area of computer visualization, image processing, and medical image analysis. It is indeed my pleasure to close this very, very exciting day with a talk on image-guided interventions. Thank you.

The Impact of Team Science on Health Care: Experiences and Perspectives on the Future
Dr. Dennis Spencer, Harvey and Kate Cushing Professor of Neurosurgery, Chief of Neurosurgery, Yale University

Dr. James Duncan, Professor of Biomedical Engineering, Diagnostic Radiology, and Electrical Engineering; Chair, Biomedical Engineering Program; Director of Undergraduate Studies, Biomedical Engineering Program, Yale University

Dr. Dennis Spencer
Thank you very much, Belinda. I want to congratulate the Institute on its anniversary. Jim and I want to thank you very much for inviting us to come today and speak about our research passions and the interactions of multidisciplinary teams.

I think I am the token clinician in this group today. I am a clinician and clinical researcher, and have spent my career investigating humans with epilepsy and have done this by applying basic science tools to human investigation.

As members and leaders of laboratories usually end their talks by acknowledging the members of their lab, I'd like to start this way by acknowledging all the members of the Yale epilepsy group. I do this because the way that we have begun and culminated our team research concept actually was team clinical care. In the late 1970s, when we began to investigate those difficult-to-manage patients with epilepsy, it took a team to get our arms around that complex disease entity. It then merged, and as we brought in clinical investigators and basic researchers into our laboratories, we now represent individuals from every department at Yale University.

You'll see later on that Jim will present his diagram of the imaging team, and it is that overlap today that we are going to speak about. It has been very fruitful in the last five years, I think, because of NIBIB.

I'm going to pose this very practical part of the discussion… We're going to do a little team trade off here, and the practical part is to outline for you our problem. Our problem is epilepsy, which is recurrent seizures, and the prevalence is fairly high. It's five to ten per thousand, not only in North America, but in the world. Unfortunately, almost half of those patients are refractory to medical management.

Now, of those patients who are refractory to medical management, we know from many statistics, that they have a very poor quality of life. They have trouble getting work, they have trouble completing education and socializing, there's risk of physical injury, and in fact, the risk of death is very high; almost 30 percent in somebody who lives their life with refractory epilepsy. Sudden death in epilepsy, status epilepticus—falls, automobile accidents… We also know that about 50 percent of those patients who have localization-related epilepsy are potential surgical candidates, meaning that they may have a region in the brain that we can identify and then resect without cognitive or neurological problems in order to help their epilepsy.

Surgery, however, obviously requires a very tight special resolution. Historically, this has depended upon the old standard of electrophysiology. Electrophysiology is still very much the

gold standard, however, historically there has been great change over the last generation or in the last 20 years.

In the 70s, we used EEG coupled with audiovisual monitoring to first classify the epilepsies. Then two institutions, UCLA and Yale began to put in intracranial electrodes in the 1970s. This aided the classification from lobar classifications of localization-related epilepsy to sub-lobar, such as medial temporal lobe epilepsy.

The 1980s was a revolution. The anatomical abnormalities that we knew were probably there as the origin of localization-related epilepsies were now beginning to be seen, whereas they were not imaged by angiography or CT scans in the 60s and 70s. It became clear toward the mid-1980s that with MR and its application to this particular disease, that not only was medicine and neurosurgery particularly, but epilepsy was being revolutionized by a concept that all localization-related epilepsies had substrates—a pathophysiology plus an anatomical localization. Of course, we are familiar with the common substrates of epilepsy now. Sclerosis, which is neuronal loss and gliosis, the most common example being medial temporal epilepsy, with hippocampal neuronal loss and glial scarring. Trauma, of course, has the same kind of neuronal loss and gliosis. Tumors represent about 15 percent; these are probably developmental tumors of medically intractable epilepsy.

Developmental abnormalities became increasingly more evident as we began to hone in on cortical thicknesses and look at patients with, for example, cortical dysplasia. In the vascular realm, cavernomas seen by CT or angiography because they are low-flow state vascular lesions, but they were the most common vascular abnormality responsible for epilepsy. The idiopathic category is now dissolving slowly and most of the idiopathic group is moving up into the developmental realm.

Now, what's interesting and relevant to our discussion and Jim's elaboration of the last several years of imaging research is the substrate characteristics. Almost all of these substrates have fairly common characteristics, including hypometabolism, which was measured before any other measurement using PET scanning; hypoenergetics, measured by MR spectroscopy; measuring phosphocreatine and N-acetylaspartate looking at mitochondrial dysfunction; and general dysfunction, measured cognitively by neuropsychology testing. We also know a very peculiar paradox. These hypoenergetic or hypometabolic states—much like non-linear physics—biological phenomena, avalanches, or volcanoes, have this ability to immediately or suddenly change from in their critical state to one of sudden hyperexcitability, and then, to resolve again. This hyperexcitability is distributed as a network, and again, it's measured electrophysiologically, and it seemingly has a destiny to repeat this circuit over again.

Our present and past evaluation has been to search for definitions, and we are using imaging as a tool to understand the path of physiology and localize areas of the brain for therapy. Just one example of how we have, in the past, used separate imaging to look at this disease: This is the substrate of medial temporal lobe epilepsy. We see the anatomical static representation of hippocampal atrophy in the left temporal lobe of this patient. The MR spectroscopy demonstrates a diminished N-acetylaspartate indicating mitochondrial dysfunction more prominently in the left anterior temporal lobe, but also seen in the contralateral temporal lobe. Contralateral too, in the

epilogenic region, the PET scan shows hypometabolism in that temporal lobe, and then if one injects HMPO SPECT material at the beginning of a seizure, we see the explosion of the seizure and blood flow coming out of that left temporal lobe. Now these are all individual measurements. What do they have in common? How can we put this together to learn more from each of them? Each are major questions that we are certainly trying to answer.

At the present, and in the past ten to 20 years, we would begin our evaluation of patients the very same way with a history and physical; monitoring the patient with scalp EEG in units specially designed to do audiovisual monitoring; we would do static imaging and neuropsychology testing; and then if a patient had concordance and every particular test lined up to one particular substrate, the patient might be able to go on to surgery. However, 50 percent or more of these patients—either their MR is negative or they do not have concordance of the data, and in that case, we use all of the metabolic and functional imaging to help us then take the patient to the operating room where electrodes are implanted in a search for the region that is responsible for seizures..

The second problem in which we learn more about each individual imaging device is how to put this together in the universe of the operating room so it can be utilized effectively. We have a tremendous opportunity here as neurosurgeons because we have the opportunity to interface with a patient's open brain tissues to look at outcomes. With this loop in mind—imaging, the operating room, and outcomes—Dr. Duncan will continue the discussion.

Dr. James Duncan
It's in this context that we began our work about five or six years ago with NIBIB funding on a project titled [Bioimaging and Intervention in Localization-Related Epilepsy]. I also want to also congratulate Rod for a job well done in the last five years. We recently got the grant renewed, and that's perhaps even more of an accomplishment in the current state of things.

We're working in a kind of loop where we're trying to study the disease epilepsy, then plan an intervention, then navigate and help intervene, and then perhaps go back and reevaluate the disease. It's this loop that we're working in.

Here's an engineer's viewpoint of the epilepsy surgery. He first sees a variety of structural and functional image information that's acquired preoperatively. Then it needs to be mapped or registered in the operating room so there's structural features segmented using automatic strategies in the commercial equipment. We work with a company called BrainLAB; BrainLAB and Medtronics dominate this market. Then using laser ranging probes on the commercial system, this is coregistered, a kind of light striping technique, in order to bring an integrated set of 3-dimensional, structure, function, and ultimately, metabolic information mapped into the OR. This helps guide the surgeries.

There's a first-stage, or what I call a first-stage surgery, of performing a ten centimeter craniotomy, attaching electrode grids that Dennis and his team does, and ultimately then, coming back after monitoring where the seizures are happening with this electrode grid and resecting a piece of brain tissue.

A few years ago, myself and one of Dennis' colleagues and a patient went to a congressional caucus, and it's amazing. The patient you see there is doing quite well and really functioning quite nicely.

The critical path technologies we worked on to improve the technology and further develop the investigational tools were basically the first… This is an MR-centric grant, so we used MR structural and functional imaging, then MR spectroscopic imaging to do the investigations and the intervention development. As you'll see, there's a host of quantitative mathematical analysis developments made mainly to register and map the information.

One of the key problems is that during the surgery, after the systems are registered, the preoperative image data and the intraoperative environment, after the craniotomy, the brain deforms and shifts inside. I'll point to this as an example of some of the work and go into detail just briefly. Then there's problems of visualizing the electrodes bringing those into the imaging environment, and then getting signals in and out of the commercial system in order to do a variety of image-based research.

When all this is pulled together, we'll be looking then to do image-based investigation to help improve the interventional process and the actual study process just looking first at regions in our first set of funding, and then regional relationships as we move forward in the second part, then we'll also be looking at additional alternative therapies to surgical resection.

Here's the complimentary block diagram to Dennis'. By the way, I forgot to mention that this is a bioengineering research partnership (BRP) funding mechanism, something particularly nice that I encourage investigators to look into. It was the NIBIB team that brought that to bear. It's an integration of partners in neurology, neurosurgery, and MR technology and acquisition, MR spectroscopy and MRI imaging processing analysis at Yale; commercial partners in BrainLAB, the image-guided surgery company; and now NeuroPace, which you'll hear a little more about later in terms of the response of neurostimulation that we're looking into; and a new partner, Richard Leahy, who's in electrical engineering at USC—a friend of mine and colleague who we'll bring into this later.

The first level work was an issue with Tommy Vaughn at the University of Minnesota, and then Hoby Heatherington who has now moved to Yale who developed high-field phased array technology to do volumetric acquisitions with high SNR and actively decoupled surface coils, then active shimming technology developed at Yale by Robin de Graaf and Doug Rothman. We put this all together to get pretty good N-acetylaspartate NAA spectra that we could begin to look at biochemical changes in the brain related to neuronal depletion.

The image analysis piece was an interesting problem. We didn't have an intraoperative MR machine, but we needed to watch this as we provided information to this mapped image and the OR system into the commercial system, because the brain can move up to one centimeter due to gravity and brain swelling and loss of CSF and different pressures.

If you could actually image before and after, you'd see some sort of shift like that (referring to image on screen) if you look at the craniotomy on the left and the points dropping in the segment

on the right. We went about it by mounting stereo cameras in the OR to look at the exposed surface and then segment the brain from the MR anatomical images and categorize what we knew from the literature as compliance properties in the brain, and used the stereo cameras to reconstruct and expose the forming surface. Ultimately, with the idea of pushing on this biomechanical model from the reconstructed surface information from the stereo cameras, so it's an interesting mix of optical camera technology from computer vision with biomechanical models developed from the structural MR information.

This is a recently completed Ph.D. thesis. Chrissy De Lorenzo in my lab worked on this. The first part of it was looking through the cameras in matching intensity and then sulcal feature information. I'll play it back in order to register these camera images and then estimate to less than one millimeter of accuracy the surface patch at the bottom.

Interestingly, though, there are a couple of problems with trying to estimate a collection of displacement parameters while simultaneously making sure that the cameras are related to each other properly and calibrated. A simultaneous calibration displacement estimation problem was the challenge.

I show this as an interesting piece of applied mathematics and computational technology that was a key part of some of the work on this grant. Instead of mixing together a mathematical objective function that completely mushed things together to solve for calibration and displacement, we felt that it was better and more robust to a variety of tuning parameters to leave these as two objective modules—one seeking to find displacements from the image information and the stereo cameras, and another looking for camera calibration parameters.

It turns out that if you put these two together, you have a large objective with level curves that seek an optimum. If you leave them separate, you have two sort of level functions, each of which might seek its own optimum, but if you allow them to talk to each other in this modular environment, they move along each module seeking to find a rational decision trying to find the right displacement parameters or find the right calibration parameters by knowing information from the other module.

It turns out that these things move along certain curves known as reaction curves to the other module's information, and together, in a sense, they play a game—an non-cooperative game, but if they were merged together it would be a cooperative game. The point they seek as an equilibrium point is the most rational compromise between these two parameter setups. If any of you saw the movie *The Beautiful Mind,* this is about John Nash who won the Nobel Prize out of the economics literature. It's his ability to play a non-cooperative game in these reasoning modules and seek a very stable, robust, and interestingly, not parameter-sensitive equilibrium point.

We ran this in our prototype system on a variety of patients and got displacements for brain shift for about 7½ to down around under a millimeter. Here you see a slice through the deforming model carrying the grayscale information along. It starts at time one here. The red points are a set of markers that were put in at the OR at 2 hours, and then yellow markers at 3¼ hours after this deformation process, showing that in the region at the surface, it was quite accurate in predicting

the deformation from this combined modeling and surface information. The error increases as you go away from that, but we're mainly looking at information near there as one of the key pieces.

There is a variety of image registration, both rigid and non-rigid, that is used to bring this information together, but to do this on a routine basis you really need a data structure and an image structure organization in order to interact and bring these pieces of functional, structural, and metabolic information together, the registrations of the images, the brain shift correction…

A person who started as a postdoc and is now an Assistant Professor in our group, Bob Dimitris, developed part of this BRP, which is a bioimage suite developed to organize all this. Interestingly, since then, he's built on it and now has a new grant that's making this more robust and we're using it in other environments. NIBIB is, through one of its special mechanisms, is further funding the robust development of this.

Another key piece of the issue was to move information in and out of a commercial system—a commercial image guidance system. In partnership with BrainLAB, who calls their system Vector Vision, we worked with them to develop a research interface now known as Vector Vision Link, which they are now including in their product. It allows these three normal windows—here you see an electrode array that we visualized and have models for, integrated with the structural MR image information. Here you see piped into that a window from our Bioimage Suite software and the research work station. We can pass control signals in and out of the commercial system and pipe our own research interface into it. As Dennis might tell you later, one of the younger neurosurgeons, Ken Vivas, is particularly thrilled about using this.

All this information is brought together to further study epilepsy and move toward possibly less invasive interventions at some point where surgery might not be needed. The question is, can we look at biochemical or MR spectroscopic imaging and relate it to the electrode firings and seizure activity from these attached electrodes? Work from Hoby Hetherington and Julie Pan has now begun to show this. Looking at NAA to creatinine ratios and deviations from normal data sets in a set of ten patients, a paper that's been published I believe in *Neurology,* was able to show that seizure-involved intercranial EEG electrode positions where seizure activity was happening was shown to be concordant with most deviations of NAA depletion, a marker for neuronal loss in these sets of patients.

However, as we move forward, this isn't the only story. If you start to use these 3-D volumes of neuronal loss and damage as places to perhaps guide an intervention, you also want to know what functional activity is going on in that region so that if you resect that or perform an intervention you don't destroy that.

It turns out that this is a very complex issue. In these same regions here—the bottom row is MR spectroscopy images mapped onto anatomy, and these are fMRI images responding to auditory language and then motor tasks. In regions where you see NAA depletion, you see fairly normal language activity, so it's easy to say, "Well, we better not resect that or we'll lose some critical function." We have to be careful how we make those decisions, and that integration of this information is critical for surgical and interventional planning, in general.

That's the first round of the work we've been doing over the past five years or so, which has been more individual region based. Now, Hoby Hetherington and Julie Pan in collaboration with Yale investigators and Dennis have now found, as perhaps many of you who are involved in the neuroscience area studying the brain, that there are lots of interrelationships in this system and it's very complex, even as you look at abnormal situations. They studied key structures in the hippocampi and the thalami and looked at deviations in the depletion from normal to show that these regions were abnormal in a set of 18, and in this case, medial temporal lobe epilepsy patients. Also, the hippocampus and thalamus depletion on the side of the seizure, and even across the seizure, started to form interrelationships that you can think of almost as an epileptogenic networks that could be a key part of future thinking about interventions.

Similarly, in the normal brain, functional connectivity is a bigger and bigger issue as you look at fMRI studies, you're not looking at isolated regions anymore, but trying to think about how information is connected and processed. Even in the resting state brain, as you go to reading tasks, you begin to recruit other regions like the thalami, in order to perform normal tasks and see how the brain functions. As we move forward, we're thinking about these interrelationships in both normal and abnormal networks.

Finally, back to our cartoon, this is how I envisioned it; bringing all this information together in the OR in a stage one and stage two resective surgery. Now, as we move forward, we're thinking that maybe these volumetric maps from MR spectroscopic imaging and NAA depletion might guide other interventions, like targeted probes being developed by our drug delivery group and Mark Salzman, where protected from glial cells might ultimately deliver stem cells or gene vectors or some kind of drug.

Additionally, we're looking at a new technology, responsive neurostimulation, through this collaboration with NeuroPace where basically neural pacemakers sense seizure activity and then deliver small electrical impulses, brief and mild stimulation, to try to arrest the seizure. These are FDA approved and are being implanted already. We're trying to understand and put people in the magnet that have these. There are some challenges here about doing passive shimming of the device itself, and then developing non-ferromagnetic batteries so that we could put somebody in a magnet. NeuroPace has finally done that.

Now, with the goal that we can model the brain and understand things about conductivity that are already in the literature, like Richard Leahy has been working on, and put it together with maps of white and grey matter, and then potentially map out stimulation and where it might go in the brain, and know if it is really interrupting and being delivered to epileptogenic zones.

We're setting out in this next round of work to isolate regions in different ways and regions related to NAA depletion and the electrode analysis of where seizures are occurring, even hypothetical plans of where electrical activity might be delivered by looking at conductance modeling. We're looking at before and after both surgical interventions and this response to this neurostimulation therapy and map out how we're going to do this.

Of course, the earliest work is really very simple showing studies done at one time point of 34 days, and 100 days later, and then 146 days later. This shows that we can get the same

spectroscopic information through simple rigid registration of datasets. Now as we move toward intervention, we want to accurately compare this information in a variety of ways to see if our therapies are working effectively or not.

We'll finish by tag teaming back to Dennis. Thank you again for the invitation.

Dr. Dennis Spencer
Thanks, Jim. I wanted to conclude our part of the symposium by actually discussing two aspects: One is the practical application of what we've been doing for the past five years to a patient and patient problem. Secondly, I want to briefly outline where the new granting period is going to take us in terms of information and patient observation.

J.S. is a 40-year-old, right-handed male whose seizures began at age 8. He would actually arouse in the middle of the night with what he thought was a nightmare of a raven picking at the ring finger of his right hand. He would awaken and feel the pain, and the finger would then twitch a bit, and he would understand that it was over then and he could go back to sleep and the raven would not visit him further that night. This continued on almost every night for a few years.

Finally, this happened before he went to bed and progressed to arms and legs shaking, and then a full-blown secondary generalized seizure, and it was clear at that point that he had epilepsy. He was treated with phenytoin, and for many years, was always balanced between phenytoin toxicity at a very high level to control his seizures, or putting up with the more minor focal seizures of his ring finger.

He was very bright. He did continue his education and became a journalist in his home town, but he never told anybody. He never socialized a lot. He only told his mother and father about his epilepsy, and finally, this conflict brought him to our epilepsy surgery program.

I illustrate this with his face because, well 20 years isn't a long time, but it's the middle of the 19th century when neurology was all about physiognomy—the study of faces. Harvey Cushing, the father of neurosurgery, photographed everybody because all he had was the face to tell him the state of the disease he was treating; most of those were pituitary patients.

We obviously want to see through the face in to the brain, and we have the luxury of doing that. J.S.'s brain, however—his MR was normal. We saw nothing. We could do functional and metabolic testing to look at the function of his hand area where we thought the seizures should be coming from, and overlapping that with the paradigms created by the imaging analysis laboratories so that we could study the relationship of the hand motor area to hypometabolic regions confirmed by the MR spectroscopy and by SPECT scanning showing decreased blood flow in regions surrounding this.

Having a fairly tight constraint considering where we were going to treat him and not knowing necessarily that the seizures were not coming from an area close to his motorsensory area and projecting first into there to cause his seizures, we could then construct a grid. We had a special grid made that would cover this area with a tight 5 mm electrode array, and could then monitor the patient in the audiovisual monitoring unit over a period of time to record his seizures. Doing

that, we could identify that even interictally, between seizures, bursts of activity were coming from, unfortunately, right over the motorsensory region of his brain. We confirmed that with an electrode array stimulation identifying his forearm, his hypothenar region, and his hands in relationship to those metabolic changes.

We decided that while we were monitoring him, he would not be a candidate for resection, but that we could engage him in the NeuroPace neurostimulation trial if it seemed he was responding. While he was in the unit, he had stimulation upon detection of the half-wave forms that occurred before he had the behavioral seizure, and when those occurred, the computer would stimulate this area. He didn't tolerate motor stimulation, but the areas of hypometabolism and some of the sensory areas were tolerated well with stimulation. In fact, during this time, he had no seizures, so he went on to have a NeuroPace implant and he is now in phase one of that study.

That's where we've been for the past five years in using information coming out of the imaging laboratory, but now, having a better handle on our neurometabolic imaging—having Hoby Hetherington's ability to give us a tight localization of the hippocampus, we will now be able to change our targets from anatomical targets and electrophysiological targets to the neurometabolic targets and can place our electrodes specifically in those areas that we would anticipate will have the most chemical abnormalities.

This means that new areas unfold for research, and just one glimpse of what is happening there… Our craniotomies physically are less. We're using smaller craniotomies, but we're putting in more electrodes because we're learning more about the networks involved in epilepsy and we're learning out more from those networks leading to changes in monitoring our patients. That's possible because we can now image precisely where each electrode is on each gyrus.

This has led to an interesting phenomenon. This is a graph from my wife who co-directs the epilepsy unit with me and our computational electrophysiologist. This looks at spikes in a patient who is implanted with electrodes. This is what we would consider the stable state; the patient has been implanted, they're still on their drugs. We begin to withdraw their drugs over a two-day period of time and create that critical state—that unstable state—which occurs just before the patient erupts into their seizures.

Now, here's what happens. This is a graph counting all of the individual spikes of the 250 contacts in this patient's brain. If we count these spikes, they should be increasing as the brain becomes more unstable. However, paradoxically, the spikes go down, and the measurement of Teager energy, which is an analysis that goes along with the spikes, also decreases. Because of our ability to image this now, we can look at the relationship of the network. This is the seizure generating area in this patient, which almost simultaneously occurs here and in the first synapse into the inferior parietal lobule in an area of hypometabolism coincides with that region of seizure onset.

Besides being able to look at the electrophysiology of this network and preoperative metabolism, for the last 15 years, we have been looking at neurotransmitters and chemicals. Neurometabolism is my particular interest in epilepsy at the present time, and we collect data using microdialysis catheters that accompany our depth electrodes. Of course, now with the ability to have both good

quantification of neurotransmitters, we're particularly interested in glutamate. Adel Chavez, who is an Assistant Professor in Psychiatry, but who is also the hands-on person in the microdialysis laboratory, measures the neurotransmitters, and they (catheters) are implanted in particular areas of interest with our electrode strips, grids, and depth electrodes.

In fact, that has led to the conclusion that in this particular patient, whose 3-D brain you've seen before during our presentation, this region of seizure onset is accompanied also by seizure onset in these electrodes, hypometabolism, and decreased energetics on MR spectroscopy. Glutamate also is at basal high level when we put it into an epileptogenic region—it is sometimes four or five times higher than normal, but it also decreases along with the spikes, which is an observation we never could have made without this appropriate imaging.

I'd like to just conclude by emphasizing the obvious from today's wonderful experience. It is technology enabling science, and science and technology are merging into the same. Just one observation—it's so important for our clinicians and our clinical research people to have interaction with the imaging and bioengineering group because imaging has become a common language for all of us. We can sit and talk to each other, and our interest may be metabolism or may be in viruses carrying genes, but we can talk using imaging as a common language. The conversation that I had with Jim six years ago which was naively coming into his lab and saying, "Is there somehow we can look at how the brain deforms in the operating room when I'm putting in electrodes?" has led to an incredibly wide array of different kinds of discovery. Now we're going from brain shift to networks, which is a very exciting place to go; networks defined metabolically by blood flow, electrophysiology, and function, and from that, we know that new therapies are soon to follow.

Thank you very much for inviting us to come.

Dr. Roderic Pettigrew
Thank you Dennis and Jim for that overview of your work. As we mentioned several times, we wanted to conclude with you, not only because you were the first grantee of the NIBIB, but because your research really exemplifies what the Institute is about, and that is, team science and impacting people's lives in a positive way.

One of the things that I was struck by in an earlier conversation with Dennis when we talked about the results of his research, were a couple of concrete end points. He mentioned that with the utilization of the kinds of technology that Jim showed in the operating room, he's been able to reduce his operating time by about 90 minutes when performing the typical epilepsy surgery procedure. In addition to that, he has virtually eliminated neurologic deficits as a consequence of neurosurgery. I think those two end points are really remarkable.

At the design of this symposium, we had two principal goals in mind: We wanted to highlight some of the achievements of researchers that were supported by the Institute, and illustrate both the breadth and the depth of the research that NIBIB has supported over the past five years. I certainly think we've done that, and we wanted to inform the public on the impact that the type of technological innovation we're leading at the Institute is having on the delivery of health care, and I think we've done that, as well.

I want to thank all of the speakers, those who came from both near and far. Many of them changed their schedules in order to join us on this landmark occasion. I'd like to thank the attendees, and I would like to have all the members of the National Institute of Biomedical Imaging and Bioengineering stand. These are the people that have made all this research possible and happen. Please stand so you can be recognized by the audience.

I want to particularly thank my Deputy, Dr. Seto, who has been a tremendous help since she arrived on the scene about three years ago.

I had a concluding slide that I think is lost for follow up. I was going to recognize all the people who put in so many hours to make this symposium happen. As you might well imagine, there is a lot of work that happens behind the scenes to pull something together like this with as many guests as we have from far and wide. I do see a few of them here. Cheryl Fee, who is back in the corner, spent many hours day and night over the last several months; Colleen Guay-Broder; Karen Peterson; Lillian Ashley, who is probably back in the office trying to take care of my 100 emails right now; Dr. Seto; Dr. Heetderks also contributed heavily; and Anthony Demsey, as well, put in significant effort in making this happen. Other members of the Institute put in time, contributions, and ideas into the construct of this program. Thank you very much. Here is the complete list of all the people who were involved behind the scenes in making today a reality.

Without further adieu, at the hour of 5: 10 p.m., on Friday afternoon, I will draw this symposium to a close. Thank you all again for your attention and your attendance.