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The Second Best Thing About Payday

nih record

ABOVE • *Drs. John Niederhuber (l) and Hugh Auchincloss, Jr., smile after a round of putt-putt at a CFC golf event. See p. 7.*

features

departments

The NIH Record is recyclable as office white paper.

Change Is Coming

Grand Rounds Spotlights Patient-Doc Communication

By Belle Waring

A guy walks into the doctor's office. "Listen, doc," he says. "I got this terrible pain." That's the setup for an old gag with a million punchlines. But when a physician has only 15 minutes per patient visit, time spent listening may seem like a luxury, if not impossible. And that's no joke.

A change is coming, says Harvard Medical School's Dr. Elizabeth Rider, who recently traveled to NIH for Clinical Fellows' Grand Rounds. In "Difficult Conversations: Evidence-Based Methods for Improving Outcomes," she made the case for enhancing communication skills in medical encounters.

Dr. Elizabeth Rider argues for better patient-doc talk.

"Why do we care?" she asked the audience in Lipsett Amphitheater. "It's not cell receptor communications. It's interpersonal."

And now it's regulatory. Residents must demonstrate and document interpersonal

SEE **COMMUNICATION**, PAGE 6

Reverse Animal Model

NICHD Scientists Discover Mouse Disorder, Search for Human Analog

By Robert Bock

Dr. Tracey Rouault

Traditionally, researchers have developed animal models in hopes of gaining insight into human disorders. Dr. Tracey Rouault has reversed this approach. She has developed a strain of mice with a fatal disorder of iron metabolism. She is now searching for people with the human version of the mouse disorder.

"We know which gene is affected," Rouault said. "We have a treatment that would likely be beneficial. Now we need to find out if anyone has it."

Animal models—long a research mainstay—are lab animals that have been altered in some way to develop a condition resembling

SEE **REVERSE MODEL**, PAGE 4

Grantee, Alumnus O'Malley Wins National Medal of Science

By Joan Chamberlain

Dr. Bert O'Malley, former NCI section chief and a long-term grantee of NIDDK and NICHD, has won a National Medal of Science for his outstanding contributions to knowledge in the biological sciences. On Sept. 29, President Bush presented the award recognizing "his pioneering work on the molecular mechanisms of steroid hormone action and hormone receptors and coactivators, which has had a profound impact on our knowledge of steroid hormones in normal development and in diseases, including cancer."

O'Malley, chair of Baylor College of Medicine's department of molecular and cellular biology, is the first scientist in the field of molecular endocrinology to receive the medal, considered the highest national honor in biological sciences.

"Bert O'Malley has creatively and persistently wrestled with some of the biggest questions in biology. His discoveries have not only clarified

SEE **O'MALLEY**, PAGE 8

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briefs

FAES Holds Insurance Open Season

The FAES Health Insurance Program is conducting Open Season from Nov. 3-26. The program is open to those who work for or at NIH in full-time positions but are not eligible for government plans. This includes NIH fellows, exchange scientists, special volunteers, guest researchers, contractors and full-time temporary personnel. The minimum enrollment period is 3 months. Benefits take effect Jan. 1, 2009.

Open Season is for those who did not enroll when first eligible and for current subscribers who want to make changes. FAES offers CareFirst BC/BS Blue Preferred PPO for medical coverage and Cigna HMO and PPO for voluntary dental coverage.

For more information visit www.faes.org, email faesinsurance@mail.nih.gov or call (301) 496-8063. FAES is open Monday-Friday from 8:30 a.m. to 4 p.m.

Manchester Quartet Returns for 20th Year

The Manchester String Quartet has begun its 20th season of free performances at NIH. Concerts begin at 12:30 p.m. in Masur Auditorium, Bldg. 10. Future concert dates, all Mondays, are: Nov. 10, Dec. 8, Jan. 12, 2009, Feb. 9, Mar. 2, Apr. 13, May 11.

The series is made possible by a grant from the Merck Company Foundation. For reasonable accommodation needs, contact Sharon Greenwell, NIH Visitor Information Center, (301) 496-4713 or email sg115f@nih.gov.

Use or Lose Reminder

Don't forget to officially schedule your "use or lose" annual leave no later than Saturday, Nov. 22. Questions about "use or lose" leave should be directed to your administrative officer.

NIDA Announces 'DrugPubs,' A New Research Dissemination Center

Anyone interested in receiving the latest scientific information about drug abuse and addiction has a new number to call: 1-877-NIDA-NIH. The National Institute on Drug Abuse has launched DrugPubs, its new Research Dissemination Center designed to distribute materials and information on drug abuse and addiction to virtually all audiences: drug abuse researchers, health professionals, teachers, advocacy groups, teenagers and the public. Callers can receive scientific information on drug abuse in a timely and effective manner. NIDA supports most of the world's research on the health aspects of drug abuse and addiction and views information dissemination as a key part of its public mission.

DrugPubs distributes a wide range of free or low-cost materials including fact sheets, brochures, pamphlets, posters and videotapes on a variety of drug abuse topics. To order publications in English or Spanish, call the number above or 1-240-645-0228 (TDD). Order requests can also be emailed to drugpubs@nida.nih.gov.

NIDA formerly distributed its research information and science education materials via the Substance Abuse and Mental Health Services Administration National Clearinghouse for Alcohol and Drug Information. Callers to the clearinghouse who are requesting information relating to the science of drug abuse and addiction will now be referred to the NIDA DrugPubs phone number and the NIDA web site www.drugabuse.gov.

Olden To Found New School of Public Health

NIEHS director emeritus and principal investigator Dr. Ken Olden has left NIH to set up the new School of Public Health on the Hunter College campus of the City University of New York (CUNY). It will be the first such program designed with an urban focus and it offers Olden the natural next step in his career in the environmental health sciences.

Shown at Harvard University during his 2007 sabbatical, Dr. Ken Olden remained active in public health venues even after he returned to the bench in 2005. (Photo courtesy of Harvard University)

During his tenure as NIEHS director from 1991 to 2005, he placed a strong emphasis on public health, community-based participatory research, children's health and environmental justice programs.

Accepting his appointment, Olden described his vision for the program. "The goal of CUNY's School of Public Health is to train interdisciplinary urban public health researchers and practitioners capable of working across all levels of analysis, disciplines and social sectors—such as health, education, the environment and criminal justice—to address complex urban public health problems."

After his retirement as director, Olden continued to pursue his interests in public health while also serving as a PI in NIEHS's Laboratory of Molecular Carcinogenesis metastasis group.

Grantees Win Nobel Prize in Chemistry

The 2008 Nobel Prize in chemistry is shared by two NIH grantees, Dr. Martin Chalfie of Columbia University and Dr. Roger Y. Tsien of the University of California at San Diego. The two researchers share the award with a former NIH grantee, Dr. Osamu Shimomura of the Marine Biology Laboratory in Woods Hole, Mass. The three researchers are honored for discovering green fluorescent protein (GFP) in a colorful jellyfish and developing it into a key tool for observing previously invisible processes such as the development of nerve cells in the brain or how cancer cells spread.

By using DNA technology, researchers can now connect GFP to other interesting but otherwise invisible proteins. This glowing marker allows them to watch the movements, positions and interactions of the targeted proteins.

"I am glad that these seminal discoveries were recognized by the Nobel committee. It is imperative for researchers to map and understand the role of different proteins and their interactions real time in the body," said NIH director Dr. Elias Zerhouni. "Understanding how this protein machinery malfunctions will increase our knowledge about potential causes of illness and disease and perhaps lead to better treatments."

The National Institute of General Medical Sciences began supporting the work of Shimomura in 1979 and Chalfie and Tsien in 1982. Over the years, NIGMS has provided more than $18 million in support of the three scientists. In addition, the National Institute of Neurological Disorders and Stroke has provided more than $8 million to support the research of Tsien, who received NINDS's Javits Award for the work cited by the Nobel committee. Tsien has also received support from the National Eye Institute. Chalfie has also received support from the National Institute of Allergy and Infectious Diseases and the National Institute on Aging. NIH has provided a total of more than $29 million to the three researchers.

"The discovery and development of GFP was literally a green light for biological research, enabling scientists to quickly visualize gene expression, protein movement and other critical processes with great clarity in living cells," said NIGMS director Dr. Jeremy Berg. "GFP rapidly became an essential piece of the scientific toolbox, paving the way for an explosion of groundbreaking studies that significantly advanced our understanding of health and disease. It is impossible to understate the impact of these investigators' work on scientific progress."

Shimomura first isolated GFP from the jellyfish *Aequorea victoria*, which drifts with the currents off the west coast of North America. He discovered that this protein glowed bright green under ultraviolet light.

Chalfie demonstrated the value of GFP as a luminous genetic tag for various biological phenomena. In one of his first experiments, he colored six individual cells in the transparent roundworm *Caenorhabditis elegans* with the aid of GFP.

Tsien contributed to our general understanding of how GFP fluoresces. He also extended the color palette beyond green, allowing researchers to give various proteins and cells different colors. This enables scientists to follow several different biological processes at the same time.

Four From NIH Named to IOM

Three scientists from the National Cancer Institute and one recently departed researcher from the National Institute of Mental Health were among 65 new members and five foreign associates elected to the Institute of Medicine of the National Academies at its annual meeting on Oct. 13.

***Clockwise, from top l**:*
New IOM members are Dr. John Niederhuber, Dr. Elaine Jaffe, Dr. W. Marston Linehan and Dr. Husseini K. Manji.

The new members are Dr. John Niederhuber, NCI director; Dr. Elaine Jaffe, chief, hematopathology section, and acting chief, Laboratory of Pathology, Center for Cancer Research, NCI; Dr. W. Marston Linehan, chief, Urologic Oncology Branch, NCI; and Dr. Husseini K. Manji, who until recently was director of NIMH's mood and anxiety disorders research program. He is now at Johnson & Johnson Pharmaceutical Research and Development, but continues to be a special volunteer for NIMH.

The new members also include three prominent alumni of NIH: Dr. Maria Freire, who used to lead the Office of Technology Transfer and is now president of the Albert and Mary Lasker Foundation; Dr. Naomi Lynn Gerber, the longtime chief of the Clinical Center's rehabilitation medicine department, who is now at George Mason University; and Dr. Barbara Rimer, formerly a top NCI official, now at the University of North Carolina.

Membership in IOM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service. Current active members elect new members from among candidates nominated for their accomplishments and contributions to the advancement of the medical sciences, health care and public health.

The Institute of Medicine is unique for its structure as both an honorific membership organization and an advisory organization on matters of health and science policy. Established in 1970 as a component of the National Academy of Sciences, IOM has become recognized as a national resource for independent, scientifically informed analysis and recommendations on health issues.

REVERSE MODEL

CONTINUED FROM PAGE 1

a human illness. But because the human disorders are sometimes not well understood, the animal models often only approximate the human disorders. For example, mice designed to mimic amyotrophic lateral sclerosis may correspond to only a minority of cases. Similarly, a mouse model for Alzheimer's disease develops some of the brain changes seen in the disorder, but doesn't develop the memory loss and dementia characteristic of that condition.

Mice lacking the gene for iron regulatory protein 2 develop tremors, weakness in the limbs and a form of anemia that cannot be treated. People with a mutation in this gene may have been misdiagnosed as having Parkinson's disease or some other neurological disorder.

NICHD researcher Rouault disabled a mouse gene for iron metabolism. She and her colleagues in the section on human iron metabolism have found that mice lacking the gene develop a progressive, and ultimately fatal, neurological condition. Moreover, her team has even discovered how to treat the condition.

The mouse disorder affects the nervous system, causing tremors, weakness in the limbs and a form of anemia that cannot be treated. The disorder results from disabling the gene for iron regulatory protein 2 (IRP2), which regulates how much iron is in a cell. Human beings with a mutation in this gene might have been incorrectly diagnosed as having Parkinson's disease or some other neurological disorder that causes tremors and impairs movement.

In 2001, Rouault and her colleagues discovered that mice lacking the gene for IRP2 developed iron deposits in the brain, tremors and weakness in the limbs. In 2005, the researchers discovered that the mice had anemia and other blood abnormalities.

In a study published online recently in the *Proceedings of the National Academy of Sciences*, Rouault and her coworkers reported that the antioxidant compound Tempol can restore normal iron metabolism to the animals. If given early enough, Tempol can arrest the nervous system deterioration and prevent symptoms from getting worse.

The researchers are also studying whether treatment with Tempol can reverse nervous system damage that has already occurred.

Tempol works by activating iron regulatory protein 1 (IRP1). Rouault said that IRP1 and IRP2 have the same function—both proteins regulate how much iron is in a cell. Although iron is a nutrient, too much can be toxic. For this reason, cells have intricate biochemical machinery to prevent iron from building up to lethal levels. IRP1 and IRP2 govern the actions of various other proteins involved in iron metabolism.

Normally, IRP2 fulfills this regulatory function unassisted and the gene for IRP1 remains dormant. Tempol, however, activates IRP1 so that it too can regulate iron in the cell.

When IRP2 is disabled, all of the iron is taken up by a cellular protein known as ferritin. Normally, ferritin stores iron temporarily, releasing it when it is needed. But mice lacking IRP2 manufacture too much ferritin. Consequently, the cell is deprived of the iron it needs to carry out biological function.

IRP1 is bound to a chemical compound—known as an iron sulfur cluster—that keeps the gene inactive. Tempol chemically removes the iron sulfur cluster and allows IRP1 to regulate iron metabolism. When given to mice that can't produce IRP2, Tempol stimulates the activity of IRP1. The activated IRP1 reduces ferritin production to normal levels and prevents the nervous system damage that results from reduced levels of iron.

In their article, Rouault and her coworkers noted the location of the corresponding human gene for IRP2 in a particular area of chromosome 15 (15q25). She said the location may assist researchers studying neurological disorders. It's possible that some research teams have collected samples of genetic material from families with neurological conditions. An analysis of these samples may lead to the identification of people with mutations in IRP2.

Patients with generalized neurological impairment and anemia that doesn't respond to treatment may have their physicians contact Rouault at Rouault@mail.nih.gov or write her at the Molecular Medicine Program, NICHD, Bldg. 18T, Rm. 101, Bethesda, MD 20892.

Brady Receives Presidential Honor for Scientific Achievement

By Shannon E. Garnett

NINDS scientist emeritus Dr. Roscoe O. Brady recently received the National Medal of Technology and Innovation—the highest honor for achievement in science and technology bestowed by the President of the United States.

The medal recognizes individuals, teams or companies for their outstanding contributions to the nation's economic, environmental and social well-being through the development and commercialization of technology products, processes and concepts; technological innovation; and development of the nation's technological manpower. The award was established in 1980 and is administered by the U.S. Department of Commerce.

For more than 50 years, Brady has conducted pioneering research on hereditary metabolic storage diseases, also called lipid or lysosomal storage disorders (LSDs) such as Gaucher disease, Niemann-Pick disease, Fabry disease and Tay-Sachs disease. His work has defined much of what is known about the biochemistry, enzymatic bases and metabolic defects of these disorders. Also, he has inspired colleagues throughout the world to define the causes of many other related disorders and to pursue further investigations in this field.

While there is a great deal of research on the LSDs today, there was virtually none before Brady's investigations at NIH. In addition to identifying the enzymatic bases, he and his research team developed methods to diagnose individuals with these conditions and detect carriers, and methods for the prenatal detection of these disorders that provided the basis for genetic counseling to at-risk families. In 1991, they established the first effective treatment—enzyme replacement therapy—for Gaucher disease.

"As soon as we identified the missing enzymes in Gaucher disease and in Niemann-Pick disease, I thought about enzyme replacement therapy," said Brady. "Although it took many years to bring enzyme therapy to fruition, the ultimate benefit was amazing. It showed the way enzyme replacement therapy can work for human diseases."

Brady's studies on Gaucher disease and success with enzyme replacement therapy led to breakthroughs in other areas of LSD research, including a treatment for Fabry disease and the identification of new types of LSDs.

"This work would have been extremely difficult, if not impossible, to do anywhere other than at NIH," said Brady. "There were years during which we had no appreciable progress. When we first developed the enzyme replacement therapy, we couldn't produce a sufficient amount of the enzyme. Finally we figured out how to make a large quantity of it. Then we didn't do the first clinical test right. But the NINDS board of scientific counselors said 'just keep trying.' I believe this is why NIH was created, to support difficult, high-risk, time-consuming research. People told us enzyme replacement therapy would not and could not work and now it's helping countless patients."

NINDS scientist emeritus Dr. Roscoe O. Brady (l) received the National Medal of Technology and Innovation from President George W. Bush at a ceremony held in the East Room of the White House on Sept. 29.

Brady and his team brought enormous relief to patients who, without treatment, suffer from a wide range of symptoms including liver and spleen enlargement, severe anemia, thrombocytopenia (low blood platelet count) and painful skeletal deformities. "People now on enzyme replacement therapy can live a normal life," he said.

Brady officially retired in 2006. He is now scientist emeritus at NINDS. His work continues and is focused on finding other ways to treat LSDs. "We are looking at molecular chaperone therapy, which provides a template to guide and stabilize the abnormal enzyme, and, of course, gene therapy because we want to permanently cure these patients," he said.

Throughout his career, Brady has received numerous accolades and honors. His work is also featured in an exhibit on the NIH Office of History web site at www.history.nih.gov/exhibits/gaucher/index.html.

Brady received the National Medal of Technology and Innovation at a special ceremony held in the East Room of the White House on Sept. 29.

COMMUNICATION

CONTINUED FROM PAGE 1

Enhanced communication can affect patient decisions to participate in clinical trials, Rider said.

and communication skills, deemed a core competency by the Accreditation Council for Graduate Medical Education as well as the Joint Commission on the Accreditation of Healthcare Organizations, various medical schools, fellowship programs, specialty and licensing boards.

Here's the background. Studies show that when physicians interact with patients:

• They prevent patients from completing their opening statements around 75 percent of the time.

• They respond to patients' cues less than half of the time in both surgery and primary care.

• They fail to elicit over half of patients' complaints.

• They use jargon.

Studies also show that enhanced communication improves health care outcomes, symptom resolution, patient adherence and compliance and both patient and physician satisfaction.

It also builds a sense of alliance, a factor affecting patients' decisions to participate in clinical trials.

Meanwhile, in malpractice suits, ineffective communication is a factor.

"Hundreds of studies," Rider said, "show that [effective communication] is not just being supportive." And it's a mistake to assume you'll automatically learn it effectively as you go along.

Video clips offered several takes of doctor-patient duos in role-played conversations. The audience was invited to critique each version.

Depending on the culture and institution, Rider noted, there are many paradigms for communicating with patients and families. She offered two evidence-based models for physicians to use or adapt in their work.

In the Kalamazoo Consensus Statement framework, now implemented at Harvard Medical School, the physician completes 7 essential elements and 23 sub-competencies, including:

1) Build a relationship ("show interest in the patient as a person").

2) Open the discussion ("allow patient to complete opening statement without interruption").

3) Gather information ("begin with patient's story using open-ended questions").

4) Understand the patient's perspective ("elicit patient's beliefs, concerns and expectations").

5) Share information ("explain using words that are easy for patient to understand").

6) Reach agreement ("ask about patient's ability to follow treatment plans").

7) Provide closure ("ask if patient has questions").

The Four Habits model is more compact: 1) invest in beginning/set the agenda; 2) elicit patient perspective; 3) demonstrate empathy; 4) invest in the end.

Eliciting the patient perspective can be surprising. To illustrate, Rider showed a slide of a bear up a tree—in closeup.

What is the bear's perspective? What's he up to? Looking for honey?

Next slide: a wider shot of the same bear, clinging to the branch, while at the foot of the tree stands a stroppy orange cat with a major attitude.

"This was a news item," Rider said. The cat, a domestic shorthair, had treed the bear, which now seemed somewhat...less than fierce.

So now what's the bear's perspective? The moral of the story: Take time to see things from the patient's point of view.

The audience had questions. Isn't writing a prescription often the most efficient way of ending an interaction with a patient?

You still have to communicate, Rider said. She described the real-world scenarios where parents request an antibiotic prescription, even when their child just has a cold. (Viruses don't respond to antibiotics). You need to be flexible, communicative and to use your "differential self," as she called it. "You respond differently with different patients" depending on the patient's needs.

Now a pediatrician and communication specialist, Rider began her career as a clinical social worker and therapist, where the focus is interpersonal relations. She acknowledged that while there's "a large and useful literature" on communication in social work and nursing, the physician has additional responsibilities and "physicians use [their own] clear models."

For an M.D., she admitted, it's tough to find the time to communicate fully with patients and their families. But it's worth it.

"It will make people happier," said Rider. "It's better care and more efficient."

NCI director Dr. John Niederhuber (l) congratulates putting contest winner Dr. Hugh Auchincloss, Jr., NIAID deputy director. NCI Executive Officer Larry Ray looks on.

NIAID Wins CFC Director's Golf Challenge

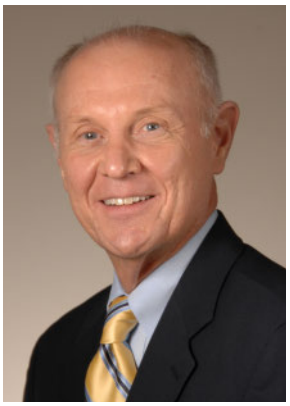
There is a history at NIH of having the director of the institute that spearheads a particular year's Combined Federal Campaign challenge the other directors to do some task. Last year it was Dancing with the Stars, and the year before that it was making basketball free throw shots. On Oct. 16, the challenge was the NIH Directors Classic—Sink a Putt for CFC! Once again, the weather cooperated as NIH'ers gathered to cheer on their IC in front of Bldg. 1.

The parking lot turned into a mini-golf course complete with Arnold Palmer drinks (lemonade mixed with iced tea) served at the 19th hole. Bleachers were filled with fans waving pom-poms.

NEI Executive Officer Dave Whitmer came with his own putter and shirt. The players supported each other with high-fives and cheers. The best score of the match was posted by Dr. Hugh Auchincloss, Jr., deputy director of NIAID, followed by Dr. Peter Sheridan, NIMH health scientist administrator, and Dr. Roger Glass, FIC director, who tied for second. Dr. Walter Koroshetz, NINDS deputy director, Dr. Joni Rutter, NIDA associate director for population and applied genetics, and Dr. Michael Gottesman, NIH deputy director for intramural research, tied for fourth. In addition to bragging rights, Auchincloss won a basket of motivational tools to help inspire NIAID CFC giving.

The CFC is off to a great start this season, but still needs your help. For more than 40 years, the CFC has enabled thousands of federal employees to improve the quality of people's lives locally, nationally and internationally. The organizations that receive funding through CFC provide many services, including helping abused and neglected children, feeding the hungry, searching for cures to diseases, preserving our natural resources and giving help and hope to those in need.

NIH has raised $10.5 million since 2002, which is both a source of pride and an inspiration to overachieve again this year. The next CFC event will be Nov. 6 at Rockledge. For more information, visit http://cfc.nih.gov.


NIH Presidential Rank Awardees are (from l) Colleen Barros, Don Christoferson and Maureen Gormley.

Three NIH'ers Earn Presidential Rank Awards

NIH Deputy Director for Management Colleen Barros has received the Distinguished Executive Award, and NHLBI Associate Director for Administrative Management Don Christoferson and Clinical Center Chief Operating Officer Maureen Gormley both received the Meritorious Executive Award. They are among more than 350 career federal executives recognized Sept. 30 by President Bush for their outstanding leadership and longtime service to government.

"Winners of the prestigious Presidential Rank Award represent the cream of the crop within the federal executive ranks," said Michael Hager, acting director of the Office of Personnel Management. "Their professional dedication and commitment to excellence is helping to advance President Bush's agenda for enhancing federal government performance and creating a more effective civil service."

NIAID's Germain Named EMBO Associate Member

Dr. Ronald N. Germain, deputy chief of NIAID's Laboratory of Immunology, was recently named an associate member of the European Molecular Biology Organization (EMBO). The honor recognizes proven excellence in research. Membership is a life-long honor, with new members nominated and elected annually by existing members. EMBO members hail from all fields of molecular life sciences ranging from developmental biology, genomics, molecular medicine, neuroscience and plant biology to systems biology. Forty-eight scientists from the EMBO membership have received the Nobel Prize and many others are recipients of prestigious international awards. The new members will be welcomed at the EMBO meeting held in Amsterdam next summer.

O'MALLEY

CONTINUED FROM PAGE 1

how hormones work, a stubborn mystery several decades ago, but they have also illuminated the causes and treatment of diseases as diverse as cancer, diabetes and reproductive disorders," said NIH director Dr. Elias Zerhouni.

In 1965, O'Malley joined NCI as a clinical associate. Two years later, he was appointed head of the molecular biology section in NCI's Endocrine Branch. There he developed a model system—the chick oviduct—to study the effects of the steroid hormones estrogen and progesterone in this highly responsive tissue. Those studies led to an unexpected observation of the hormones' effect on activities inside the cell nucleus.

From 1969 to 1973, he directed the Reproductive Biology Center at Vanderbilt University School of Medicine. In 1973, he joined Baylor University's School of Medicine as chair of the cell biology department and director of the Baylor Center for Reproductive Biology. Today the Baylor Center is part of NICHD's Specialized Cooperative Centers Program in Reproduction and Infertility Research.

Much of O'Malley's early work focused on the steroid hormones—glucocorticoids, mineralocorticoids, androgens, estrogens and progestagens—that regulate reproduction and basic metabolism. He used the tools of physiology and biochemistry to study the hormones' role in reproduction and developmental diseases and was one of the first to apply new methods as they were introduced.

"The challenges in those days were immense, considering that scientists had not yet found the receptors for these hormones nor had they yet discovered that they all belonged to a common family," said Dr. Ronald Margolis, NIDDK senior advisor for molecular endocrinology.

In the 1980s, evidence was growing that receptors for steroid hormones had unique structural properties and belonged to a common family of receptors. Instead of attaching to receptors on the cell surface, these hormones linked up with receptors in the cell and its nucleus and acted as transcription factors to change the expression of genes. After the first nuclear receptor was cloned, scientists went on to find 49 more, including those for steroid hormones, thyroid hormones, certain vitamins and receptors for hormones that were still unknown. These "orphan receptors" also turned out to have profound effects on cells.

"Bert was one of the first to create an *in vitro* transcription assay, or a test tube system, that could recapitulate what happened inside a cell to study

***Right**:*
Dr. Bert O'Malley (l), former NCI section chief and a long-term grantee of NIDDK and NICHD who recently won a National Medal of Science, is applauded by President Bush.

PHOTO: RYAN K. MORRIS/NSTMF

the changes in gene expression. His assay stimulated much research that led to an even greater understanding of hormone action because scientists could use the method to study their favorite hormone and receptor," said Margolis.

"O'Malley's discoveries led to the development of selective steroid receptor modulators, a class of new drugs that can selectively target one tissue while leaving other tissues unaffected. His findings also laid the groundwork for the development of two important drugs: a progestin compound that prevents preterm birth in certain cases and raloxifene, which prevents osteoporosis," added Dr. Louis De Paolo, chief of NICHD's Reproductive Sciences Branch.

In 1995, O'Malley and others discovered a group of nuclear receptor coregulators, molecules in the nucleus that control how nuclear receptors work. Coregulators, he found, helped turn on and off transcription factors such as nuclear receptors, which in turn helped to orchestrate the expression of many other genes. Probing deeper, he identified a subset of coregulators, called coactivators, which are required for hormone action. Other researchers soon found corepressors, which silence transcription.

"Hormones control almost all cellular physiology," O'Malley explains. "Receptors for steroid hormones, the most important class of hormones, are activated by the hormone, then they go into the cell's DNA and search out and find the target genes to be turned on or off. In the final step, they recruit complexes of coregulators, including coactivators, that perform all the functions to turn the genes on. In a sense, these coactivators are master genes because they can activate different transcription factors at the same time, so you get a coordinated physiologic outcome."

Forging ahead, O'Malley and colleagues came to a stunning conclusion: nuclear receptor coregulators control physiologic processes as basic as cell

O'Malley at work at NIH in 1967

growth, metabolism, inflammation and reproduction. And if defective, these "little molecules with big goals" can lead to disease. "When the activities of these master genes are compromised, cellular processes can quickly deteriorate," says O'Malley. In overdrive, some can spur the uncontrolled growth of cancer cells.

For example, the steroid receptor coactivator SRC-3 fuels the growth of most prostate tumors and 65 percent of breast tumors. Another coactivator, SRC-2, controls sugar production by the liver. When it is defective, a form of glycogen storage disease develops. Other SRCs influence fat cells, energy balance and carbohydrate metabolism.

O'Malley is principal investigator of the Nuclear Receptor Signaling Atlas (www.nursa.org/), a trans-NIH consortium that provides a central source of information on hormones, nuclear receptors and coregulators. To date, 300 coregulators for 49 nuclear receptors have been found and 165 coregulators have been linked to disease.

"O'Malley's prodigious career is a tribute to the importance of basic research," says Dr. Griffin Rodgers, NIDDK director. "His research revolutionized the understanding of hormone action and the molecular regulation of processes as basic as metabolism and reproduction. By studying the mechanisms of hormone action, he unexpectedly found molecular pathways that lead to a number of diseases. Some therapies that capitalize on his findings are already in clinical trials."

"Basic research is our fountain of knowledge," says O'Malley. "I always felt that if I knew how things work in normal cells, I'd have much better insight how to fix them when they go wrong in disease. If you open the hood of a car, you don't know how to fix it if you don't know how the motor works."

Sex and Gender Research: Pain

ORWH Seminar Looks at a Sensitive Issue

Three perspectives on the response of the gastrointestinal tract to pain and stress were presented in the recent Women's Health Seminar Series: Sex and Gender Research—Pain.

Dr. Lin Chang, professor of medicine at UCLA's David Geffen School of Medicine, discussed sex differences in visceral pain in irritable bowel syndrome (IBS). "In the United States, about 7 to 10 percent of individuals meet criteria for IBS," she said. "What you should know is that the majority of individuals that meet criteria for IBS don't seek health care."

Chang said the prevalence of IBS according to age peaks around 30 to 40, then decreases after 50. IBS is also more likely to occur in women than in men; and women are more likely to be diagnosed and treated. When presenting with IBS, women are more likely to experience symptoms of abdominal pain, bloating with distension, urinary urgency, muscle stiffness and altered taste or smell. Chang noted that fluctuation in ovarian hormones also adversely affects IBS symptoms for women.

In addition, Chang said, stress plays a role. "It's been shown that chronic stress may be associated with increased vulnerability for individuals at risk for developing chronic pain disorders such as IBS," she said. "The number one chronic stress is a change in the role in your life." She also noted that a greater proportion of IBS patients have reported childhood, physical, verbal or sexual abuse.

Dr. Jennifer Labus, adjunct assistant professor of psychiatry and biobehavioral sciences at UCLA, talked about sex differences in brain responses in IBS. She described a study where patients were placed in a scanner and had their brains monitored while experiencing experimental stimuli, which caused different active areas in the brain to light up. "Research has shown response to IBS symptom-like stressors suggests that females may show a greater engagement of known emotional-arousal regions," she said.

Labus noted significant sex differences were demonstrated in the connectivity of brain regions. "There are differences in visceral pain in autonomic functioning between men and women with IBS," she said. In particular, women experienced enhanced responsiveness when expecting increased stress or pain. She said results of the study were "consistent with reduced feedback inhibition of an emotional-arousal circuit in women with IBS."

Dr. Muriel Larauche, postdoctoral fellow at the Center for Neurobiology of Stress, spoke on sex differences in responses of the gastrointestinal tract to stress and the implication of corticotropin releasing factor (CRF)-signaling pathways.

She said women have a 50 percent higher rate of CRF, a hormone involved in the stress response, in the colon than men. This higher rate of CRF can have an increased effect on IBS. "Increased expression of CRF in response to stress is much higher in females, by 70 percent, compared to males, who have only a 40 percent increase," Larauche said.

She also said reactions in the gastrointestinal tract and colon are modulated by sex steroids, such as estrogen. This finding may have implications for the treatment of IBS in women.

digest

Timing Key for Families in Life-Support Decisions

Whether to stop life support measures all at once or discontinue them one at a time can affect how surviving family members rate care in the intensive care unit, according to a paper in the Oct. 15 issue of the *American Journal of Respiratory and Critical Care Medicine*. ICU clinicians often care for patients who are on several life-support measures at once. When such patients are dying and the decision is reached to withdraw life support, these clinicians must balance the complex needs of the patient and the patient's family. A study funded by NINR found sequential withdrawal may have a varying impact on the family's satisfaction with ICU care. Researchers looked at the life-support withdrawal process for 584 patients who died in the ICU. Family members were asked their perceptions of the care provided. Included in the study were such life-support measures as mechanical ventilation, tube feedings and dialysis. Family members of patients who had a short ICU stay reported lower satisfaction with the ICU care if the withdrawal process was extended over more than 1 day. However, for family members of patients who had a long ICU stay (8 days or more), satisfaction with care increased with a more extended withdrawal. Investigators had theorized extending the process would lower satisfaction among all families: drawing out the process is unlikely to help the patient, because it prolongs non-beneficial and sometimes painful therapies.

Whether to stop life support measures all at once or discontinue them one at a time can affect how surviving family members rate care in the intensive care unit.

Paralyzed Limbs Move via Artificial Brain-Muscle Connections

Researchers with funding from NINDS and NCRR have shown for the first time that a direct artificial connection from the brain to muscles can restore voluntary movement in monkeys whose arms have been temporarily anesthetized. The results, published online Oct. 15 in *Nature*, may hold promise for people affected by spinal cord injuries and paralyzing neurological diseases, although clinical applications are years away. In the study, investigators trained monkeys to control the activity of single nerve cells in the motor cortex, an area of the brain responsible for voluntary movements. Neuronal activity was detected using a type of brain-computer interface. In this case, electrodes implanted in the motor cortex were connected via external circuitry to a computer. The neural activity led to movements of a cursor as monkeys played a target-practice game. After each monkey mastered control of the cursor, researchers temporarily paralyzed the monkey's wrist muscles using a local anesthetic to block nerve conduction. Next, scientists converted the activity in the monkey's brain to electrical stimulation delivered to the paralyzed wrist muscles. The monkeys continued to play the game—only now cursor movements were driven by actual wrist movements—demonstrating they had regained the ability to control the otherwise paralyzed wrist.

More Effective Treatment Identified for Common Childhood Vision Disorder

Scientists have found a more effective treatment for a common childhood eye muscle coordination problem called convergence insufficiency (CI). For words on a page to appear in focus, a child's eyes must turn inward, or converge. In CI, the eyes do not converge easily and as a result additional muscular effort must be used to make the eyes turn in. While the majority of eye care professionals treat children diagnosed with CI using some form of home-based therapy, a new study concludes that office-based treatment by a trained therapist along with at-home reinforcement is more effective. The research, reported in the Oct. 13 issue of *Archives of Ophthalmology*, was funded by NEI. The 12-week study found that approximately 75 percent of those who received in-office therapy by a trained therapist plus at-home treatment reported fewer and less-severe symptoms related to reading and other near work.

New Genes Linked to Gout

Researchers have identified two new genes—and confirmed the role of a third gene—associated with increased risk of higher levels of uric acid in the blood, which can lead to gout, a common, painful form of arthritis. Combined, the three genetic variations were associated with up to a 40-fold increased risk in developing gout. The findings suggest that genetic testing could one day be used to identify individuals at risk for gout before symptoms develop, as well as determine who might benefit from medications to prevent gout's development. Published Sept. 30 online in *The Lancet*, the study was supported by NHLBI, NCRR and the NIH Roadmap for Medical Research.—**compiled by Carla Garnett**

volunteers

The phone numbers for more information about the studies below are 1-866-444-2214 (TTY 1-866-411-1010) unless otherwise noted.

Allergies in Children

NIH Pediatric Clinic offers allergy and asthma care (ages 6 months to 18 years) and is also conducting an allergy and asthma study. Refer to study 05-I-0084.

Smart Pill

Healthy adults 18-60 are asked to consider participating in an NIH study testing a new method to measure gastric acid output. Compensation is provided. Refer to study 08-DK-0138.

Pelvic Pain

Healthy women ages 30-50 are needed for a study that investigates the role of hormones and genes in pelvic pain and explore better approaches to treatment. Compensation is provided. Refer to study 04-CH-0056.

Twins Study

NIH is seeking same-sex fraternal twins 5-20 years old to participate in a study of children's brain development. Compensation is provided. Refer to study 89-M-0006.

Iron Overload

Do you have iron overload? Participate in an NIH research study. Compensation is provided. Refer to study 08-DK-0157.

Heart Disease Risk Factors Study Recruits

Healthy black African volunteers are needed for a study investigating the relationship of obesity to heart disease risk factors. Volunteers must be born in Africa, non-diabetic and between ages 18-49. There will be three outpatient visits to NIH. Compensation is provided. Call (301) 402-7119 for information. Refer to protocol 99-DK-0002.

Study of Pre-Menopausal African-American, Caucasian Women

Healthy African-American and Caucasian women volunteers are needed for a study investigating the effect of the American diet on vascular disease risk. The study will look at the effect of fat in the blood before and after a meal. Volunteers must be non-diabetic, pre-menopausal women between the ages of 18-49 years. The study requires three outpatient visits followed by a week of daily visits to NIH for breakfast, weight measurement and meal pick-up. Compensation is provided. For information call (301) 402-7119 and refer to protocol 07-DK-0163.

NINR director Dr. Patricia Grady (third from l) welcomes new council members (from l) Dr. Diana Lake, Dr. Stanley Finkelstein, Dr. Marla Salmon, Dr. Marion Broome and Capt. Maggie Richard.

NINR Welcomes New Council Members

Five new members recently joined the National Advisory Council for Nursing Research. They are:

Dr. Marion E. Broome, dean of Indiana University School of Nursing, as well as a distinguished professor in the school's department of family health nursing. She is a widely published expert in pediatric nursing research and practice.

Dr. Stanley Finkelstein, professor of laboratory medicine and pathology in the Medical School at the University of Minnesota. He is also director of the Schmitt Center for Home Telehealth, a fellow of the American Institute of Medical and Biological Engineering and a member of the editorial board of the journal *IEEE Transactions on Information Technology in Biomedicine*.

Dr. Diana E. Lake, a medical oncologist at Memorial Sloan-Kettering Cancer Center in New York City. Her practice is devoted to the care of breast cancer patients and she is involved in clinical trials to develop better hormonal therapies and improved approaches to cancer treatment before surgery.

Capt. Maggie L. Richard, director of the human research protection program in the Bureau of Medicine and Surgery, Department of the Navy. She has served over 20 years in the Navy Nurse Corps and is former head of the nursing research service at Bethesda National Naval Medical Center.

Dr. Marla E. Salmon, dean of the University of Washington School of Nursing. She is a member of the Institute of Medicine and the nursing commission for the Joint Commission on Healthcare Accreditation.

seen

Fungus Among Us

'Mushrooms' Flourish on Campus This Fall

Fall is a good time to spot mushrooms on campus; some are so exotic-looking as to suggest Halloween horror. Among the species visible is "chicken of the woods" or *Laetiporus sulphureus*, says Lynn Mueller, landscape architect for the Office of Research Services. "The campus is literally covered with hundreds of varieties of fungi," he said. "We generally call them mushrooms. Mushrooms are just one type or form of fungi. Others include molds, yeasts and mildew. Some fungi are beneficial to plants and some are not.

"Fungi help to decompose and recycle dead organic matter into reusable matter for other plants to use for growth," Mueller continued.

Often seen on the campus during warmer and damp weather, he said, are "fairy ring toadstools," jelly fungi, mildew on roses, flowerpot mushrooms, various "turkey tails" and chicken of the woods.

"Most are not edible," he warned. "Only the morel, 'shaggy mane' and chicken of the woods [provided it is cooked properly] are edible but they can easily be confused with other like-shaped and colored mushrooms like the false or 'beefsteak morel.' Another very toxic one is the Death Angel. For the sake of your health, do not pick or eat any mushrooms found on the campus. Gather your button and shiitake mushrooms only at the grocery store."

PHOTOS: MAGGIE BARTLETT

Campus trees this fall are costumed in fungi of various kinds, including "chicken of the woods" (middle, l) a species that can be eaten if properly cooked and which, unsurprisingly, is said to taste like chicken. "The campus is literally covered with hundreds of varities of fungi," said Lynn Mueller, landcape architect. Don't eat any, he warns. The only safe mushroom is a store-bought one.