

ABOVE · NIH'ers took their sons and daughters to work on Apr. 28. See more photos on pages 8-9.

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Treatment in	Children	

Passion Went Into Building of the Safra Lodge; Tour Date Offered

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NINDS DVD Wins CINE Award

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# nihrecord

Developing 'Happily Ever Afters'

## **Pediatric Cancer Progress Slow, But Steady**

**P** or the legion of youngsters clamoring to have designer jeans and other high-priced trendy items, there is also a smaller, no less vocal group pushing on behalf of kids for other expensive, but much more crucial, tailor-made products—designer drugs. It's the growing trend toward individualized medicine no more evident than in research on childhood cancers—that presents both promise and problems in efforts against the disease, according to scientists at an Apr. 26 NCI/Children's Inn seminar.



"How do we get further?" asked Dr. Alan Wayne, clinical director of the Pediatric Oncology Branch at NCI's Center for Cancer

Research. "As with any big complex problem in our complex society, we do it in a multifaceted, collaborative way. More and more it takes collaboration from government, private industry, philanthropic organizations and regulatory bodies like the FDA, as

SEE PEDIATRIC CANCER, PAGE 10

#### Haase To Discuss AIDS Virus in Hill Memorial Lecture, May 26

HIV reputedly causes a chronic infection that can fester for years before it manifests itself in the form of AIDS-related symptoms. But according to Dr. Ashley T. Haase—a leading investigator in the pathogenesis of HIV and other slow-progressing retroviruses called lentiviruses—this perception belies an intensely fast-paced series of events that take place during the first few weeks following transmission. These events—including a brief window during which the virus is at its most vulnerable will be the focus of his discussion as he gives the NIAID James C. Hill Memorial Lecture on Thursday, May 26, at 2 p.m. in Lipsett Amphitheater, Bldg. 10. The lecture is titled "The Critically Important Fast Phase of the Slow Infections Caused by Immunodeficiency Viruses."

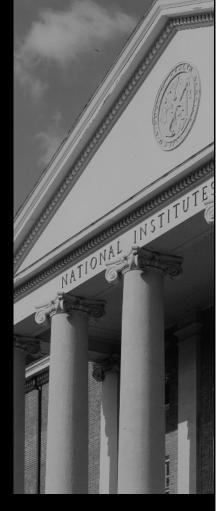
"With HIV and its close relative in monkeys, simian immunodeficiency virus, so many really interesting developments happen immediately after transmission," says Haase, a Regents' professor and head of the department of microbiology at the University of Minnesota. "In order to better understand the virus and its ability to outmaneuver the body's immune



To say that science is hard is an understatement. But it can also be fun, especially when scientists get to show children what they do at NIH. In the debut of a new "mini-curriculum," researchers from the National Human Genome Research Institute and children of NIH staff had "Fun with DNA" during Take Your Daughters and Sons to Work Day on Apr. 28.

The Human Genome Project and genet-

SEE KIDS AT WORK, PAGE 8



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**\$** The **NIH Record** is recyclable as office white paper.



## briefs

#### **Lecture Honors NCI's Ihde**

The first annual Dr. Daniel Ihde Memorial Lecture will be held at the National Naval Medical Center in Clark Auditorium, first floor, off the main lobby of the hospital, on Friday, June 3 at noon. The speaker will be Dr. John Minna, former chief of the NCI-Navy Medical Oncology Branch. His topic will be "Molecular Pathogenesis of Lung Cancer with Translation to the Clinic."

Ihde served from 1981 to 1991 as deputy director of the NCI-Navy Medical Oncology Branch and from 1991 to 1994 as deputy director of NCI.

#### **CIVIL Addresses Violence at NIH**

Are you or someone you know having difficulty managing anger at the worksite? Are you concerned about how to respond to behavior at work that is less than civil, and possibly even intimidating, harassing, or verbally or physically threatening? Are family or other personal disputes affecting your ability to think clearly and be productive at work, or are you worried that family members or others with hostile attitudes or behavior may make unwanted visits to the worksite to see you?

If the answer to any of these questions is yes, you may want to call CIVIL, the NIH team of experts that promotes civil behavior in the NIH workplace. The phone number is (301) 40-C-I-V-I-L, or 402-4845; TTY (301) 402-9499. Anyone can call. CIVIL will help you sort through the issues, determine the next steps toward solving problems and work to promote a safe and productive work environment. To learn more about CIVIL, call or check out the web site at civil.nih.gov.

If you believe that you or others are in immediate danger, you should always call 911 first, if on campus, and 9-911, if off-campus.

#### **Heritage Month Celebrated in Two Parts**

Everyone is invited to "Progress with Diversity," NIH's 33rd anniversary observance of Asian/Pacific Islander American Heritage Month.

Dr. Morgan Sheng, Menicon professor of neuroscience at MIT, will present a lecture titled "Molecular Mechanisms of Brain Plasticity," on Thursday, May 26 at 11 a.m. in Lipsett Amphitheater, Bldg. 10. The lecture is jointly sponsored by the NIH-FDA Chinese American Association and the Asian American and Pacific Islander employment committee of NIH's Office of Equal Opportunity and Diversity Management. Sheng is a fellow of the American Association

for the Advancement of Science and an expert on excitatory synapses in the brain at cell-cell junctions specialized for rapid chemical signaling via the neurotransmitter glutamate. He will present his recent studies that focus on the structure-function of glutamate receptors and associated scaffold proteins of the excitatory synapses, ranging from structure of single molecules to *in vivo* roles in learning and memory behavior.

On Friday, May 27 from 11:30 a.m. to 1 p.m. in Masur Auditorium, Bldg. 10, the cultural program will feature Chinese, Indian, Korean and Indonesian dances and music performances by the Washington Jin Ling Chinese Dance Academy, Pushpanjali School of Dance, Washington Korean Dance Company and the Seni Budaya Theater Dance Association. Dr. Richard Nakamura, NIMH deputy director, will present the keynote address. Immediately following the program, a reception will be held in the old Visitor Information Center exhibit gallery; guests can meet the performers and sample Asian pastries.

#### **Conference on Biology of Manual Therapies**

Have you had a massage lately? Seen the chiropractor? How about the physical therapist? You might be hoping to improve your back pain, relieve your headaches or remedy another ailment. But do you ever wonder how these various forms of manual therapies might work?

On June 9-10, attendees at a multidisciplinary conference titled "The Biology of Manual Therapies," will address this issue. The conference, to be held in Natcher Conference Center, will assess current knowledge of the underlying biology supporting manual therapies and identify opportunities for further research.

Manual therapies include a host of techniques that focus primarily on bones and joints, the soft tissues, and the circulatory and lymphatic systems. There is increasing evidence that manual therapies may trigger a cascade of cellular, biomechanical, neural, and/or extracellular events as the body adapts to the external stress.

The conference will cover three primary topics: neuroscience, immunology and endocrinology, and biomechanics and imaging.

NCCAM, NINDS, NIAMS, NICHD and NIBIB will partner with the Canadian Institutes of Health Research to sponsor this conference.

For more information visit www.nccam.nih.gov or contact Erika Gundersen at (202) 973-8734 or ManualTherapies@courtesyassoc.com.

#### Opening in June

#### **Safra Lodge Stirs Passionate Commitment**

It's rare for professionals involved in a construction project to speak of passion, but that is the word everyone involved with the Edmond J. Safra Family Lodge uses when they talk about the building. Jan Weymouth, executive director of the lodge, says the entire group had the same "passionate goal to get this built. We all knew this was a very special place."

The 26,500-square-foot, 34-room building that opens June 1 was conceived to meet the emotional and spiritual needs of adult Clinical Center patients and their families. Converting the concept into a comfortable home-away-from-home presented a number of challenges for the project team. Project Officer Shah Saleh of the Office of Research Facilities was assigned in 1999 to manage design and construction. The lodge had to meet an array of safety, security and environmental requirements, coordinate its schedule with the CRC opening, and be easy and cost-effective to maintain and operate.

The challenges began with design. The lodge needed not only to create a sense of warm hospitality, but also needed to fit into the more institutional look of most campus buildings. It needed to allow patients plenty of privacy, but give them places where they could choose to socialize. Early members of the project group saw presentations by eight architectural firms before selecting a collaborative proposal from LSY Architects and Weinstein Associates. They envisioned the lodge as more of a large home than an apartment building.

"We all worked together as a team, and as a result, everyone involved is happy with the final product," says Saleh. "We all have reason to be very proud of our work."

The project teams met regularly to resolve challenges that arose in the course of construction, including heavy rains that saturated the worksite, scheduling conflicts with neighboring construction projects, and a change to custom designs for all interior and exterior light fixtures 3 months into the construction process, which required re-evaluation of the electrical system. Construction of a tunnel to bring campus utilities to the project site was another challenge. Through close cooperation of partnering group members and Dan Moses in the Utilities Operations Branch, ORF, the tunnel extension brought utilities to the lodge within days of the building being ready to accept them, without interrupting power to existing buildings, and without interference in nearby projects such as

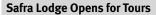
the CRC and the perimeter fence.

"There was an emotional commitment to this project, beyond the feeling of another day at NIH," says Weymouth.

To complete the transformation of the lodge into a home, interior

designers had to attend to far more detail in the furnishings than is typical in an NIH office or lab building. Many of the furnishings were custom produced by multiple vendors. Inez Austin, the lodge decorator, said, "This is the most positive effort I've been involved with. The personal attachment everyone formed for the project caused them all to work well beyond what was technically required."

Creation of a "healing garden" at the lodge is a separate project endowed by the Safra family and is scheduled for completion in the spring.



The Edmond J. Safra Family Lodge at NIH, conceived as a house of refuge for loved ones of patients receiving care at the Clinical Center, will open on June 1.

NIH'ers who would like a tour of the new lodge and its gardens may visit Tuesday, May 31, between 11 a.m. and 1 p.m. The lodge is located a short walk west of the CRC. "The May 31 tour is the only chance for the general NIH public to see the lodge," said Jan Weymouth, executive director. "Once it is open for guests, general tours will not be available, to protect the privacy and safety of registered guests."

Dedication and opening ceremonies will take place May 26. Because of space limitations, attendance is by invitation only.

Construction on the lodge began in 2003. A \$4.5 million donation to NIH from the Edmond J. Safra Philanthropic Foundation allowed building to begin, along with the design and creation of a garden. Other contributors include the Merck Co. Foundation, the Bristol-Myers Squibb Foundation, GlaxoSmith-Kline, the Harry and Jeanette Weinberg Foundation and many more corporations, foundations and individuals.

For more information on the lodge, call (301) 496-6500 or email cc-familylodge@nih.gov.



The Edmond J. Safra Family Lodge opens on June 1, and will be officially dedicated during a ceremony on Thursday, May 26.

#### **HILL LECTURE**

CONTINUED FROM PAGE 1

system, we need to examine the processes that are unfolding over the first few weeks."

Haase will describe key events that occur in female monkeys immediately after simian immunodeficiency virus (SIV) crosses the vagina's mucosal barrier—the protective lining of

the respiratory, reproductive and gastrointestinal tracts that helps the body fight off disease-causing microbes. He'll delve into the changes that occur with memory helper T cells—immune cells that the body produces to help fight a subsequent infection, and the very cells that SIV, and HIV, preferentially first infect because of their availability. According to Haase, the virus hijacks memory helper T cells so that it can make copies of itself while catching a ride to the lymph nodes and lymph organs, enabling the virus to spread throughout the body. At the same time, it triggers the large-scale destruction of memory T cells in the gut, one of the

largest reservoirs of infection-fighting cells. As the virus multiplies and immune cells plummet, the virus quickly overpowers the body's ability to fight it.

For these reasons, Haase suggests that the critical time to attack HIV is within the first few days of transmission, when the virus is at its lowest numbers after having passed through the mucosal barrier.

"The mucosal barrier does an effective job at keeping the virus out, and very few viral particles make it across," he says. For him, the most promising means of HIV prevention would be an HIV-killing gel that can bolster the effectiveness of the mucosal barrier, allowing even fewer viral particles through, or a robust vaccine that can quickly build up the numbers of HIV-destroying killer T cells at the mucosal surface.

Haase's work on the prototypic lentivirus in sheep, called visna, has been awarded the Sen. Jacob Javits Award in Neurosciences from the National Institute of Neurological Disorders and Stroke. He is also a two-time recipient of NIH's MERIT (Method to Extend Research in Time) Award for his work on HIV and SIV, and is a member of the National Academy of Sciences' Institute of Medicine and American Academy of Microbiology.

The lecture is dedicated to the memory of Dr. James C. Hill who, as former NIAID deputy director, helped build the institute's HIV/AIDS research program during the early years of the epidemic.

A reception outside of Lipsett Amphitheater will be held following the lecture. •

#### **NIEHS Recycled 75 Percent of Waste**

NIEHS successfully diverted 75 percent of its waste stream into recycling in the past year, said Dick Sloane, resource recovery expert. That is a total of 848,048 pounds of paper, cardboard, glass, plastic, pallets, metal and other recyclable material. Animal bedding is also recycled, adding it to compost that is used on flower beds at the Research Triangle Park, N.C., campus.

Here are totals for the year, in pounds: white paper—58,430; other paper—134,646; cardboard—70,296; glass—7,296; plastics—15,915; animal boxes—9,745; disposable clothing from the animal area—10,905; wooden pallets—7,290; metal—74,960; construction and demolition waste—238,834; animal bedding—209,959.

In addition, NIEHS recycled the pavement it replaced during that time period, adding a whopping 2.9 million pounds to the total.



Dr. Ashley T. Haase of the University of Minnesota will give the Hill Lecture on May 26 in Lipsett.

#### **NIAID Program Builds Diversity**

Recently, 24 undergraduate, graduate and medical students from diverse backgrounds, and equally diverse goals, were invited to NIH as part of the third annual Intramural NIAID Research Opportunities (INRO) program. Begun in 2003, the program is the backbone of NIAID's effort to increase intramural research program diversity.

Students from across the country spent 5 days learning about training for biomedical research careers, attending scientific lectures and touring. The event culminates with students interviewing scientists who most interest them.

The program traditionally begins on a Sunday. Current NIAID research trainees are on hand to address visitors. This year, postbaccalaureate trainee and INRO alumni David Reynoso of the Laboratory of Malaria and Vector Research, spoke about the hands-on approach of his mentor and the gradual fostering of independence as he became more comfortable with his research. He also offered useful tips on how to find affordable housing in the Washington metropolitan area. Dr. Frank De Silva, Laboratory of Viral Diseases, provided insight into challenges faced by minority researchers, emphasizing the importance of strong mentorship.

Dr. Wendy Fibison, associate director, Office of Training and Special Emphasis Programs, guides the INRO program. She has current OTSEP-sponsored trainees spend the entire week with the visitors, offering their insights.

"The visiting students connect most with people at their own level, people who have recently struggled with the same questions they are now asking," said Fibison. "And, the trainees remember so well their own struggles."

Dr. Thomas Kindt, NIAID scientific director, has strongly supported the program since it began. He has no doubt that "the diversity of the workforce offers significant advances in biomedical research at NIAID and throughout the NIH."

Since its inception, INRO has grown. Begun as a 3-day program with 11 participants chosen from a pool of 18 applicants, it has evolved to a 5-day session hosting 24 students selected from more than 120 applicants. More than 40 NIAID researchers requested interviews with one or more of the INRO students during the visit.

Although the program is formally over for the year, students will receive regular mailings from OTSEP informing them of new research advances, events of interest and the latest information about training opportunities.

Ultimately, the success of the program is measured by how many INRO participants actually receive offers to participate in a traineeship within the intramural research program.

To date, seven INRO 2005 students have accepted offers to return and 11 more are talking about it. Before the students boarded planes to go home, they took INRO 2006 promotional cards for their colleagues and friends, assur-

## 1960s-Era Scientific Instruments on Display

The Stetten Museum and the Office of NIH History announce two new exhibits of 1960s-era scientific instruments on campus. Each highlights the instrument's history at NIH and explains its use to visitors and staff.

The Varian A-60 NMR (nuclear magnetic resonance) spectrophotometer in the Natcher Bldg. showcases NIMH researcher Dr. Jay Giedd's MRI (magnetic resonance imaging) study of the youthful human brain and NIDDK scientist Dr. Ad Bax's use of NMR to visualize large proteins. In Bldg. 50, visitors can get up close to a Siemens 1-A electron microscope used by NIAID's Dr. Albert Kapikian for more than 30 years of research on viral diseases. With it, he was the first American to visualize human rotavirus and the first ever to visualize Norwalk virus and hepatitis C.

Two seminars will be presented about the instruments. Dr. Edwin Becker, NIDDK, will speak about the history of NMR at NIH on Tuesday, May 24 at 1 p.m. in the Natcher balcony A conference room. Kapikian will describe his research on Tuesday, June 28 at 1 p.m. in the Bldg. 50 lobby conference room.

The exhibits, sponsored by OD's Office of Communications and Public Liaison, remind viewers of the groundbreaking work of NIH scientists by introducing the scientific tools that made the work possible. ③





The Kapikian Electron Microscope (top) is on dislpay in Bldg. 50 and the Varian A-60 NMR Spectrophotometer is in the Natcher Bldg.

'Women Change America'

#### **NIH Marks Women's History Month**

"Critical Thinking." That's how women at NIH change America, according to organizers of the 2005 Women's History Month celebration, who adapted the occasion's national theme—"Women Change America"—for the NIH audience.

cation artist, performed the one-woman play, Off the Wall: The Life and Works of Charlotte Perkins Gilman. Author in 1892 of The Yellow Wallpaper, a semi-autobiographical account of a woman's struggle with depression, Gilman was a pundit and lecturer on equal rights for wom-Economics, which was critically acclaimed and subsequently translated into seven languages.

Following the performance, Timmons took questions from the audience about parallels between the skills Gilman used to promote change in her society and the skills employed by women at NIH who are involved in the scientific community. The audience was invited to take part in a critical thinking workshop after the program.

A mentoring seminar concluded the month's celebration. Held in the Stone House, the seminar recognized four outstanding NIH women Women's Program." The honorees were Joan Brogan, OEODM deputy director; Dr. Vivian Pinn, NIH associate director for research on

Leading off the celebration, sponsored by NIH's Office of Equal Opportunity and Diversity Management on Mar. 9, Ann Timmons, a communien. In 1898, she published the book Women and

as "great mentors and champions of the Federal



Ahove.

NIH deputy director Dr. Raynard Kington congratulates "great mentors" (from 1) Dr. Vivian Pinn, Dr. Ruth Kirschstein, Joan Brogan and Dr. Joan Schwartz.

Right center:

Glenda Keen, Federal Women's Program assistant, greets Justin Hayes, a representative of Maryland Sen. Barbara Mikulski, who sent remarks for the occasion.

Right bottom:

Cheryl Kelley of FDA offers the keynote address.





women's health; Dr. Ruth Kirschstein. senior advisor to the NIH director; and Dr. Joan Schwartz, assistant director of the NIH Office of Intramural Research.

Cheryl Kelley, special emphasis pro-

gram manager at the Food and Drug Administration, gave the keynote address.

The primary goal of the Federal Women's Program, and other special emphasis efforts at NIH, is to identify and eliminate barriers to a model equal employment opportunity program at NIH, at the department and throughout the nation's workforce, according to Rose Pruitt, NIH Federal Women's Program manager, OEODM. Career development at various levels, and a quarterly review of recruitment, hiring and promotion of women are merely two objectives NIH has identified to accomplish its goal.

"With women accounting for more than 50 percent of the U.S. workforce, women are America," Pruitt said.



Below and top right:

PHOTOS: JANET STEPHENS

Perkins Gilman

Ann Timmons, a communication

artist, performed a one-woman play

about equal rights pioneer Charlotte

#### **Real College Students Get Depression Too**

The University of Michigan launched its own Real Men Real Depression (RMRD) campaign recently, becoming the first university to customize and implement NIMH's national educational outreach program. Almost every part of the university participated in developing the campus-wide effort, including the Office of the Dean of Students, the U-M Depression Center, the Division of Student Affairs, the University Health Service, University Housing and student groups.

The NIMH/Michigan collaboration began a year ago, following NIMH's presentation of the campaign at an annual conference in Ann Arbor. Over several months, the two organizations designed a plan to bring the materials and the message, "It Takes Courage To Ask for Help," to campus. The university ran ads in campus shuttles; aired public service announcements on the campus cable station; displayed posters in central, high-traffic areas; distributed booklets and co-branded trifolds throughout campus; and blanketed dining areas in residence halls with campaign tent cards.

Michigan has created a sophisticated evaluation plan, including focus groups and an online survey. It plans to relaunch the campaign in the fall and hopes to develop a program for other universities across the country.

Students across campus talked about the high visibility of the campaign. "It was everywhere," said one. A student mental health advocate and organizer of the campaign recalled: "My friend saw me putting up the table tents...and said that already he's had all these conversations with people and thinks it's cool that there's something about men's issues."

RMRD was launched in April 2003 to respond to a growing awareness that depression in men is overlooked and undiagnosed. The NIMH campaign features real people, not actors, telling their personal stories of how depression affected them. One was a college student, who happened to be enrolled at Michigan. Today, Rodolfo Palma-Lulión still lives in Ann Arbor and now works for the university. His face and story were prominently featured in the U-M campaign, and he was interviewed for a documentary put together by the Division of Student Affairs and the Depression Center.

For more information on U-M's implementation of the campaign, visit <a href="http://www.med.umich.edu/depression/college\_2005\_general.htm">http://www.med.umich.edu/depression/college\_2005\_general.htm</a>.

## NIMH Conducts Outreach Meeting in Nebraska

With the help of its outreach partner in Nebraska, NIMH held its 6th annual meeting of the Outreach Partnership Program in Omaha. The program enlists national and state organizations in partnerships to help bridge the gap between research and clinical practice by disseminating the latest scientific findings, informing the public about mental disorders, alcoholism, and drug addiction, and reducing the stigma and discrimination associated with these illnesses.

State Sen. Jim Jensen, an NIH Council of Public Representatives member, opened the recent meeting by welcoming the 51 outreach partners. His assertion that "we must remove the stigma of mental illness and empower mental health consumers" resonated with the audience of representatives of national mental health organizations and state and local partners. Two years ago, Jensen began to address this prob-

lem by introducing a bill to increase community-based services that would allow people with mental illnesses to more easily live in their communities where they have support systems.

Dr. Richard Nakamura, NIMH deputy director, began the formal program by providing an update on NIMH research advances. Throughout the meeting, attendees learned about the latest advances and treatments for

mental illnesses and substance abuse from NIMH and NIDA staff, grantees and other experts.

Some of the topics covered in the meeting included media outreach, evidence-based treatments and practice, and reaching out to minority and underserved populations. The plenary sessions can be viewed at http://videocast.nih.gov. ©





Тор:

Nebraska State Sen. Jim Jensen, a member of the NIH Council of Public Representatives, opened the recent NIMH outreach meeting.

Bottom.

NIMH deputy director Dr. Richard Nakamura meets with an attendee.

#### Top:

Marie Conrad (1) of the Clinical Center's department of laboratory medicine gives demonstration to a gowned cadre of children.

Children are intent on a demonstration of phlebotomy.

#### Relow.

Master Fire Fighter Charles Weaver welcomes a youngster to an engine at the NIH Fire Department.

#### Bottom:

Valeria Maduro of the Genome Technology Branch, NHGRI, engages a roomful of youngsters.



#### KIDS AT WORK

CONTINUED FROM PAGE 1



ics appear to be very popular topics among NIH'ers because parents from many institutes jumped at the chance to sign their children up for "Fun with DNA." Like tickets to a U2 or Rolling Stones concert, the 45 allocated spots were snapped up within 12 minutes after the web registration site opened. In the end, a total of 48 students, ranging in age from 8 to 15, attended the three hour-long sessions.

Taking on the role of teacher for a day, Jackie Idol, a biologist in NHGRI's Genome Technology Branch, explained to her young audience what the Human Genome Project was all about and why scientists study DNA. She also shared



many interesting facts about DNA, such as that a human has 23 pairs of chromosomes while a chicken has 39.

Using a conference room in Bldg. 50 as a makeshift laboratory, Idol led the children through hands-on activities that taught them the basic genetic concepts that scientists employ every day in NIH laboratories. The activities included purifying DNA from a strawberry, building a model of DNA out of gumdrops and licorice twists and decoding gene sequences to spell out the hidden phrase "genes are in all cells."

Although other NHGRI researchers and some parents were there to lend a hand, the children quickly took to the activities without much assistance. "I was impressed with the ability of the kids to 'get it'," says Idol. "They may not understand the whole picture, but at least we introduced them to the fun of science and the 'wow' feeling that you get when something cool happens unexpectedly."

NHGRI scientific director Dr. Eric Green said he was very pleased with the results of his staff's efforts. "They were terrific. It was also wonderful to see young, inquiring minds get excited about DNA, about genetics and about science in general. The energy from the students was electrifying, thanks to the efforts of Jackie Idol and her able assistants."





Indeed, the children did seem to be thrilled to be part of the NIH lab experience. Smashing a cold strawberry in a bag, extracting a slime of DNA with a coffee stirrer and eating a DNA model made of candy proved to be just the ticket for arousing curiosity about science.

Lara Haft, an elementary school student and daughter of Carol Haft of NIDDK, cruised through the experiments. "If I become a scientist," she said, "then I want to be a genome scientist. It's more fun." And one proud parent could be overheard saying, "One of these kids could cure a disease one day just because they got interested in DNA from this program."

If you and your child missed out on the fun with DNA, there's always next year. According to Green, NHGRI is planning similar activities for Take Your Daughters and Sons to Work Day in 2006. •

#### Right:

Employees interested in Native American outreach wore tribal regalia and engaged kids in dancing, story-telling and gift-giving; they include (from l) Rebecca Tudisco, Sophia Delgado, Debbie Sweitzer, and Cynthia Delgado of the Office of Science Education, who is Sophia's mom. Below:

Kids and parents alike were delighted with the presentations during Take Your Daughters and Sons to Work Day 2005.



#### Left:

Dr. Matthew Starost (r) of ORS demonstrates lung function in both health and disease.

#### Below:

Kids wobble through an obstacle course, hindered by goggles that induce the visual impairments of drunkenness.

PHOTOS: ERNIE BRANSON AND MAGGIE BARTLETT







Above:
"Fun with DNA" participant proudly displays her extraction of strawberry DNA.

#### PEDIATRIC CANCER

CONTINUED FROM PAGE 1

well as altruism, voices in the media and grassroots efforts—basically it takes everybody working together with common goals."

#### Where We've Been

Many can remember the days when a diagnosis of childhood acute lymphoblastic leukemia (ALL) was "a death sentence and survivals were poor." Wayne recalled. "In the 1960s to 70s. less than 5 percent survived long term. Because of systematic improvements in therapy—and particularly pediatric cooperative group trials here in North America—there have been steady improvements such that now when children are diagnosed with ALL they have an 80—potentially 90—percent chance of cure."

Nonetheless, cancer is the number one cause of death from disease in pediatrics, he said.

Approximately 1,600 cancer-related deaths occur each year in children under age 21. Of the deaths from cancer, one third are the result of leukemia, mainly ALL, which is the most common pediatric cancer diagnosis.

"Up until a few decades ago, leukemia was defined as a fatal disorder of the blood-forming organs," stressed Dr. Donald Small of Johns Hopkins University School of Medicine. "That is something that has very much changed over time, thanks to improvements in therapy."

Small, the Kyle Haydock professor of oncology at JHU's Sidney Kimmel Comprehensive Cancer Center, described several factors that have boosted cure rates:

- Pediatric clinical trials—"Most of the drugs used to fight childhood cancers have been around a long time," but the progression of clinical studies in kids allowed doctors to discover how best to combine the drugs.
- Combinations of chemotherapy—Doctors

Pioneers in Pediatric Cancer Drug Therapy

#### Owen Family Made Memories, History

Ten days before Christmas and just a couple of weeks before the predicted Y2K D-day, a Georgia family of six experienced a devastating event of its own: 5-year-old Killian Owen was diagnosed with leukemia. In the 30 months ahead, Killian would wage a fierce battle with the disease that accounts for about 30 to 40 percent of childhood cancers.

By early 2003, after exhaustive treatments with several rounds of chemotherapy and a bone marrow transplant procedure (using marrow donated by fraternal twin brother Garrett), Killian suffered yet another relapse.



One legacy of Killian Owen is the fundraiser his parents started to help other kids with cancer.

"At that time we were told pretty much 'we could do nothing [more]," recalled dad Clay recently at the Children's Inn at NIH. "We were told to go make some memories, so we did."

The Owens whisked their four sons off to Disney World to shore up the good times. However, when they returned home, mom Grainne refused to sit and wait for what they thought was inevitable. She went to work searching the Internet for answers. There had to be something, some experimental drug or some final treatment option

available to Killian. Sure enough, she found a glimmer of hope in an online article about a doctor at Emory University investigating what he described as a targeted therapy.

"Traditional chemotherapy had failed," she explained. "Bone marrow transplantation had failed. But, a drug called BL22 was designed for children with chemo-resistant leukemia, which Killian had."

Within a week or so, her research led her and the entire family to NIH and the inn.

"At that point, we really were hoping for the Hollywood ending," Clay said.

Killian became the first child to receive BL22, a new drug targeted to kill cells specific to his cancer.

"We were made very aware of all the risks," Grainne stressed, choking with emotion. "But you see at that point he was dying anyway. What did it matter if there were risks, because there was no hope otherwise. The fact that Killian was given a chance has led to so much hope for so many other children."

For several reasons, drug companies often hesitate to offer new drugs for pediatric clinical trials, pointed out Dr. Lee Helman, chief of the Pediatric Oncology Branch at NCI's Center for Cancer Research.

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have learned to use different drugs together to attack tumors.

• Treating spinal fluid, "which serves as a sanctuary where cancer cells grow."

In addition, he explained, doctors can now better estimate patient risk factors in order to change therapy, depending on how high the child's relapse risk is. That was not possible even a decade ago.

Wayne said bone marrow transplantation also has contributed to better cancer-free survival. "Donor lymphocytes can eradicate cancer cells without chemotherapy in an immunologic reaction referred to as the 'allogeneic graft-versustumor effect," he explained.

#### Where We're Going

Researchers are now studying the biology of immune effectors and targets of the immune reaction in order to develop therapies using immune system cells as primary cancer treatments. Wayne said his team is working on the first pediatric cancer clinical trial of an allogeneic tumor vaccine.

Another new approach uses information derived from genomic studies, he continued. "What is clear not just in leukemia but in all cancers is that the story lies in the biology of the disease," he explained. "Chromosome and gene abnormalities inside leukemia cells influence the outlook for a given individual. Genetic analysis now allows us to identify children at greater risk of relapse who need more intensive therapy. In addition, this technology can be used to point out potential targets for therapeutics."

To illustrate the promise of targeted drugs and the importance of pediatric clinical trials, Wayne told the story of Killian Owen, a 9½ -year-old boy with ALL who became the first child to receive BL22. [see sidebar, p. 10]

"Kids and families who work with us on these early developmental trials absolutely know that CONTINUED ON PAGE 12



Dr. Donald Small of Johns Hopkins describes several factors that have boosted cure rates.

PHOTOS: JULIE HYKES

"A lot of the drug companies are reluctant to move any of these drugs into pediatric clinical trials," he said. "Pediatrics is not a really big market and companies are worried that adverse events that may occur in pediatric trials will ruin chances for approval of the drug in adults."

That's why Killian's participation in the BL22 trial was an important milestone in the fight against pediatric cancer.

"The Owen family played a pivotal role in releasing a logjam," explained Dr. Alan Wayne, clinical director of Helman's branch. "Those logjams are opening daily. The old paradigm—where drugs have to go from mice to monkeys to adults to children—is changing. The lessons [learned from treating Killian] are clearly important. Those of us involved in the scientific work feel more and more optimistic every day, based on translating advances at the bench to movement forward in the clinic."

The Hollywood ending did not happen for the Owen family, though. BL22 was not able to save Killian, who died at age  $9\frac{1}{2}$  in July 2003. However, hope for other children is what brought mom and dad Owen back to the inn.

"There is a desperate lack of money in funding childhood cancer research,"

Grainne explained. "You shouldn't have to jump through the hoops that we had to jump through to get your child to try a new drug. Two classrooms full of children are being diagnosed [with cancer] every single day; one in four of those children is going to die. That is an amazing thought, that we're allowing that to happen. And a lot of it is due to lack of funding."

The Owen family launched Coaches Curing Kids' Cancer, a nationwide fundraiser that benefits Cure-Search and the National Childhood Cancer Foundation. Instead of buying little league coaches a trinket or trophy at the end of a season, team families pool their donations and send the amount to the fundraiser to help further cancer research and its related expenses.

"We're going to get families in America behind this initiative," Grainne declared. "We're going to raise awareness of childhood cancer. We believe that it is possible to find cures to childhood cancers in our lifetime. The technology, the science is there. Killian's dream was to be a normal healthy child—a very simple dream. Combine the power of science with the power of the normal happy emotions that go with having normal healthy children and help us find a cure for childhood cancer."

For more information on Killian's legacy and the charitable foundation, visit Curingkidscancer.org.





Killian's parents, Clay and Grainne Owen, discuss the tribute they began in his memory.

CONTINUED FROM PAGE 11

the decks are stacked against them," Wayne said. "However, they come to NIH with hope and a huge dose of altruism. Yes, they are looking for magic bullets and we are trying to design magic bullets. Ultimately when we come together here, most everybody realizes that a miracle would be great for the individual child, but the likely outcome will be a step forward in the very steady, systematic progress in the war on pediatric cancer."

Steady progress, he pointed out, is based on rigorous scientific work, which requires huge effort and resources. It also takes years of intense teamwork. As examples, Wayne discussed several drugs that target leukemia and

• BL22, which Killian Owen was the first child to receive, was developed at NCI and now with pharmaceutical partner Genencor. Doctors have given the agent to more than a dozen children in a phase I study at NCI.

are in the clinical trial pipeline for kids:

- LMB2, a similar agent also designed by NCI to target a different protein than BL22 found on the surface of certain cancer cells, is also now under study in children.
- HA22, a newer generation agent related to BL22, is under development jointly by NCI and Genencor.

Small predicted that similar tailored therapies are the near future of cancer treatment. "Ultimately what will happen," he said, "is people will come in with a tumor. We'll determine each individual's mutations. [Then] we'll pull off the shelf a specific inhibitor for a designer therapy."

However, such progress cannot occur without the help of brave pioneers like the Owen family, who become partners with the research community, said Wayne.

"Though the ultimate cure wasn't achieved for Killian," he remarked, "I don't consider his case a failure. From a purely scientific standpoint, we continue to use Killian's cancer cells and data to help us develop a treatment that we hope will someday have a place in the curative outcome for children like him in the future.

"Killian really does live on and continues to help us in many ways, he concluded. "Families like the Owens highlight the highs and



lows of pediatric cancer therapy. Their experiences show us where we've come from and where we need to go, which is critical. We hope to get to the point where folks like the Owens only have happily-ever-afters."

#### **Detours Along the Way**

Small also discussed another common childhood cancer, acute myeloblastic leukemia (AML). The AML cure rate is only 40 percent. AML cells are much more resistant to chemotherapy. He said researchers have spent the last few decades defining changes that turn normally growing cells into abnormally growing cells, or cancer. His group cloned the human gene FLT3, which was later discovered by a team in Japan to have a mutation that is instrumental in turning good cells bad in some patients.

"[Expression of the FLT3 gene] takes a disease that is really, really bad and makes it worse," Small explained. "These patients have very little chance of cure."

Because of the FLT3 data, he continued, a number of research teams have launched aggressive searches for FLT3 inhibitors. Several agents already have been identified, including a drug called CEP-701 that Small's team is now ushering through various clinical trial design and approval stages.

"Unfortunately chemotherapy is the best we have to deal with these tumors, and we have gotten some really good cure rates with chemo for certain types of tumors," Small said. "But really all they are is poisons that kill rapidly proliferating cells, but also kill normal cells that proliferate as well. In addition, because these chemotherapies are non-specific, they can damage non-proliferating cells as well, so you can get side effects that damage the brain, heart and liver—just about any organ. [Scientists are now focusing on] molecular targeted therapy, where you have small molecules that kill only the cells that have the targeted protein in them and will leave normal proliferating cells unaffected and should have no effect on non-proliferating cells."

NCI Pediatric Oncology Branch chief Dr. Lee Helman, who studies solid tumors in children, offered a sobering summary of the battle against cancer that has spread.

NCI Pediatric Oncology Branch chief Dr. Lee Helman addresses moral and ethical concerns raised by a burgeoning era of designer therapy.

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"While progress has been good for non-metastatic disease," he said, "little progress has been made for patients diagnosed with widely spread cancer...For children who walk in our doors with disseminated disease, we really haven't changed things in 25 years. We're very unhappy about that and we're not going to stand for it."

His group is researching how to identify tumors that demonstrate aggressive behavior. Already they have found a protein that regulates metastasis. Soon, they will publish results of their successful attempts to use proteomics—the study of proteins in a cell or tissue—to predict cancer recurrence probability.

"We don't view pediatric deaths as statistics," he said. "Every single child who dies of pediatric cancer is a real catastrophe, a real tragedy."

Helman also talked frankly about the economics of cancer research and treatment. For example, he said that in the United States, about 10,000 cases of adult leukemia occur each year, with about 40 percent (4,000 cases) expressing the FLT3 gene. In contrast, there are 3,000 pediatric leukemia cases per year, with 15 percent (450) of those diagnosed with AML. A quarter of those express the FLT3 mutation, he said, "so you're looking at just about 100 cases—not much of a monetary incentive" for companies to develop the drug.

Finally, Helman addressed moral and ethical concerns raised by a burgeoning era of designer therapy. It's fortunate, he said, that so far, so many aspects of cancer biology have been universal, their lessons transferable from patient to patient, whether adults or children. "But," he concluded, "there will be unique features that are totally specific to a cancer and that's where the industry—and we as a society—deal with individualized therapy. What if we find a drug that totally cures just 300 cancers? Who's going to pay for developing that drug? There are huge ramifications."

## A 'Family Reunion' at Rocky Mountain Labs

The detective work that faced parasitologist Tom Schwan of Rocky Mountain Laboratories

had nothing to do with fleas, ticks or even science. Yet, resolving the mystery is among the most satisfying feats of his career: The family of Dr. Ralph Parker now possesses his 1910-era college scrapbook.

Parker is recognized as the first director of RML, a branch of the National Institute of Allergy and Infectious Diseases located in Hamilton, Mont. Parker held the post from 1928 until his death in 1949; during his career he co-developed the first vaccine against Rocky Mountain spotted fever.

After Parker's death, colleague William Jellison of RML acquired some of Parker's personal belongings. When Jellison died in 1995, Schwan found himself inheriting Parker's scrapbook.

"I've been trying to locate family members ever since," said Schwan, who is an amateur historian with a fascination for early-day RML research.

He was thrilled in early April when he heard that Parker's granddaughter had contacted RML unexpectedly to arrange a visit from Kansas with her father Robert, 80, who grew up on the RML campus in the 1920s and '30s. Robert hadn't visited Hamilton in 42 years and wanted to see his childhood home, which is now an RML administrative building on the National Register of Historic Places.

Schwan immediately telephoned the family to tell them about the scrapbook, which he presented to them during their visit on Apr. 20.

"Did you used to live in Colorado?" Schwan asked Robert Parker during the visit, still trying to piece together his sleuthing. "That's where I was last able to locate you."

"I'm thrilled they're here to accept this," Schwan said. "Dr. Parker collected everything in this scrapbook from his days in Massachusetts and it should be with his family." •



Robert Parker, son of eminent RML scientist Dr. Ralph Parker, visits Hamilton for the first time in 42 years and reclaims some family history.

PHOTO: JEREMY LURGIO, RAVALLI
REPUBLIC

#### **CIT Computer Classes**

All courses are given without charge. For more information call (301) 594-6248 or consult the training program's home page at http://training.cit.nih.gov.

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#### **NIH Training Center Classes**

The Training Center supports the development of NIH human resources through consultation and provides training, career development programs and other services designed to enhance organizational performance. For more information call (301) 496-6211 or visit http://LearningSource.od.nih.gov.

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Delegated Acquisition Training Program	5/24-27	
Introduction to NIH Property Management	6/2-3	
Advanced Time and Attendance Using ITAS	6/6	
Consolidated Purchasing Through Contracts	6/6	
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Buying From Businesses in the Open Market	6/7	
NBS Travel System for Approving Officials	6/8	
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Purchase Card Processing System	6/9	

#### **New Patient Entrance to Campus**

A special entrance to the NIH campus for patients and their visitors has just opened. It is located at the intersection of West Cedar Lane and West Drive (near the Children's Inn and just north of the main entrance to the Clinical Research Center).

The new entrance, which will be open 6 a.m. -7 p.m. weekdays (except holidays), is designed to provide patient-friendly access with one-stop security screening.

Clinical Center hospitality staff will be on site at the facility to assist patients. For more information visit http://www.cc.nih.gov/about/visitor.shtml.

#### **Wednesday Afternoon Lectures**

The Wednesday Afternoon Lecture series—held on its namesake day at 3 p.m. in Masur Auditorium, Bldg. 10-features Dr. Stuart Schreiber on June 1, speaking on "Dissecting Disease Biology and Advancing Medicine with Small Molecules." He is HHMI investigator and Loeb professor and chair, department of chemistry and chemical biology, Harvard University.

For more information or for reasonable accommodation, call Hilda Madine, (301) 594-5595.

#### Two NIH'ers Use MC to Boost Careers

Carol Hayden, contract specialist, and Wendy Rivera, purchasing agent with the Division of Station Support Acquisitions, OLAO, OD, are completing Cooperative Education I this spring through Montgomery College. This 3-credit course targets new learning in work situations.

Both Hayden and Rivera were recently promoted to their respective positions and are focusing on new learning in their jobs. The two students, their supervisors, and the Montgomery College instructor collaborated to create learning



Carol Hayden

contracts that link new learning and new job responsibilities. The course and discussions were a factor in at least one of the promotions.

Along with meeting the requirements of their jobs, students attend three seminars at Montgomery College, create a critique of their job performance and develop a resumé at the completion of the course. Both Hayden and Rivera are pursuing business degrees at Montgomery College.

## volunteers

#### **Volunteers Needed for Vaccine Research**

The Vaccine Research Center is looking for healthy volunteers 10 to 50 years old to participate in studies of experimental vaccines for infectious diseases. We are currently seeking volunteers for a study of an investigational SARS vaccine. Volunteers will have medical examinations and blood test to see if they are eligible for the studies. Financial compensation is provided. To volunteer, or for more information, call 1-866-833-LIFE (toll-free) or TTY 1-866-411-1010.

#### **ADHD Genetics Study**

Take part in an NIH study seeking to identify the genes that contribute to attention deficit hyperactivity disorder (ADHD). For more information call 1-800-411-1222 (TTY 1-866-411-1010). Refer to study # 00-HG-0058.

#### **NEI Seeks Volunteers**

The National Eye Institute seeks volunteers to participate in a study evaluating the effects of oral supplementation of the antioxidant vitamins lutein and zeaxanthin, with or without omega 3 fatty acids (fish oil), on the levels of these vitamins in the blood. The effects of these supplements in the eye will also be measured. Participants should be 60 or older, and may or may not have age-related macular degeneration (AMD). Volunteers should not have regularly taken lutein, zeaxanthin or fish oil supplements in the past 3 months or have any severe vision-impairing eye disease other than AMD. Participants will take the study medication daily for 6 months. The study will consist of 5 visits to the Clinical Center over 9 months. Interested participants should send an email to neiluteintrial@nei.nih.gov for more information.

#### **Healthy Volunteers Needed**

Doctors at NIH are conducting a study that examines the tongue. Call 1-800-411-1222, TTY 1-866-411-1010. Refer to study 01-CC-0044. Compensation is provided.

#### Lyme Disease Study

Do you think you have Lyme disease? People with active Lyme disease are invited to participate in a study at NIH. Evaluation and treatment provided. For information call (301) 496-8412.

#### **Gray Platelet Syndrome Study**

Join an NIH study of gray platelet syndrome. Call (301) 496-9101 (TTY 1-866-411-1010). Refer to study # 03-HG-0131.

#### **Study of Uterine Fibroids**

Call NIH at 1-800-411-1222 (TTY 1-866-411-1010) for information on a treatment study of uterine fibroids. Refer to study # 02-CH-0287.

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nih record

#### NIH Grant to 'Rocket Boys' Pays Dividends

In 1957, a 9-year-old named Terence Boylan sent a letter to the National Institutes of Health asking for a grant of \$10 to build a rocket ship. The unusual request made its way to the outside experts who served on the NIH national health advisory council. Though they could not recommend government funding, they decided to make personal investments in the future, passing the hat to send Terence the money he needed for his research.

Many years later, after finding and interviewing Boylan, the Center for Scientific Review has brought his story to life: "Shining Lady in the Sky: How the Rocket Boys of Buffalo Were Launched by a Government Administrator and Committee at the National Institutes of Health" is viewable online at http://www.csr.nih.gov/history.

"The story says a lot about the drive and dedication of researchers—both young and old," says Don Luckett, CSR communications director and author of the story. "Research rarely advances without the dogged passion and imagination of individuals who want to do something no one has done before."

The story also says a lot about the unsung heroes who have helped NIH advance medical research through the years, including reviewers and staff who have served with little fanfare. Among these individuals is the late Dr. Ernest Allen, one of the forefathers of the NIH grants program, who took the time to help the Rocket Boys of Buffalo. Though it was a small gesture, the little "grant" to Boylan continues to pay off in unexpected ways like many of the official grants NIH has awarded over the years.

#### **NIEHS Teams Wins 'Best Paper'**



Researchers in the Laboratory of Computational Biology and Risk Analysis, within the National Toxicology Program at NIEHS, have something to smile about these days. Their paper, "Gene Interaction Network Suggests Dioxin Induces a Significant Linkage between Aryl Hydrocarbon Receptor and Retinoic Acid Receptor Beta," was selected best paper by the Society of Toxicology. The paper was published in the NIEHS journal Environmental Health Perspectives in August 2004. Paper authors include (from 1) Hideko Sone; Nigel Walker; Fred Parham; on the computer screen is Hiro Toyoshiba, lead author, who has now returned to Japan; Chris Portier, senior author and director of the Environmental Toxicology Program at NIEHS; and Janelle Martinez. Not shown is Takeharu Yamanaka, who has also returned to Japan.

#### **Kerr Named NINR Deputy Director**

Dr. Mary E. Kerr recently joined the National Institute of Nursing Research as deputy director.

"Dr. Kerr brings to NINR an outstanding record of scientific achievement and leadership in studies of nursing science," said NINR director Dr. Patricia Grady. "We're excited that she has joined us."

Kerr comes to NINR from the University of Pittsburgh, where she has served most recently as UPMC Health System chair in nursing science in the School of Nursing. Her primary appointment is professor in the department of acute and tertiary care nursing in the School of Nursing and she has a secondary appointment as professor in the department of neurological surgery in the School of Medicine. Kerr is also associate director, clinical core, Brain Trauma Research Center at UPMC.

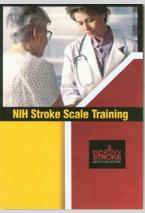
Kerr's research has focused on preventing cerebral ischemia and maximizing cerebral perfusion in the critically ill patient with a neurologic condition. She is particularly interested in identifying early biomarkers or parameters that help identify individuals at risk for cerebral ischemia. This includes genetic-specific variation in an individual's response to and recovery from an acute neurologic condition such as traumatic brain injury or a ruptured cerebral aneurysm.

A faculty member at Pitt since 1991, Kerr served as director of the Center for Nursing Research, where she mentored junior investigators, sponsored research activities and advised, taught and supervised research of undergraduate and graduate students. In recognition of her teaching skills, she was honored with a Distinguished Teaching Award in 1996. Kerr served as a member and chair of multiple university committees, primarily focused on issues related to research and technology.

She has received numerous honors and awards throughout her career. In 2004, she received the University of Pittsburgh School of Nursing Outstanding Alumni Award. She received the Excellence in Nursing, Nightingale Award of Pennsylvania for Nursing Research in 2002, and in 2001 the Distinguished Research Lectureship Award from the Eastern Nursing Research Society. She is also a fellow in both the American Academy of Nursing and in the American College of Critical Care Medicine.

In addition to authoring and coauthoring over 100 research papers and publications, Kerr has served as manuscript reviewer for medical and nursing publications. She has partici-





pated in a number of review activities for NIH, such as a permanent reviewer for the adults and older adults study section of CSR, and an ad hoc reviewer for several other divisions in CSR. Recently, she participated in the research themes meeting on public access chaired by NIH director Dr. Elias Zerhouni. 3

#### **NINDS DVD Wins CINE Golden Eagle**

The NIH Stroke Scale Training DVD, produced by the NINDS Office of Communications and Public Liaison, recently won a CINE Golden Eagle Award. The training DVD is an interactive tool that teaches medical professionals how to administer and score the scale, a measure of stroke severity, in a clinical setting.

The studio-produced footage provides views of doctors performing the scale and illustrates every score on each item of the scale. The DVD includes two demonstration cases that let viewers practice the test and grade themselves, and three sets of six patients each for scoring and submission to an accrediting organization for certification in the use of the scale. The two-disc set also includes commentary and tips from national stroke experts.

Since the DVD's release, thousands of physicians, nurses and other health care professionals have learned how to administer the scale. In addition, NINDS partnered with the American Stroke Association to put the footage online, so medical professionals now have web site access to the training. NINDS recruited a faculty of experts to help design the training tool to take advantage of the latest technology and ensure a user-friendly product.

Founded in 1957, CINE is dedicated to discovering, educating and supporting talent in film and video. The Golden Eagle award distinguishes excellence in professional and amateur works and is an internationally recognized symbol of the highest production standards in filmmaking and videography. Among former winners of the award are Steven Spielberg, George Lucas and such documentarians as Ken Burns and Charles Guggenheim. @