Bush’s Science Adviser

NIH Leads Revolution in Biology, Says Bromley

By Rich McManus

NIH is a model of scientific excellence that has begotten a worldwide revolution in biomedicine and should be emulated far more widely, said President Bush’s science adviser Dr. D. Allan Bromley at an NIH Lecture Jan. 7 in Masur Auditorium.

“The benefits that have flowed from science and technology have been almost miraculous in the past 50 years,” said the Yale nuclear physicist, “and the promise of future benefits is certainly as rich.”

Describing his role as science adviser as one chiefly of translating for politicians the advantages of investment in certain areas of scientific research, Bromley looked back on what brought the United States to its current “precarious pre-eminence” in biomedical science and looked forward to a future marked by more coordination between government and industry in setting research agendas that will strengthen the U.S. economy.

As his legacy of 4 years directing the White House’s Office of Science and Technology Policy, Bromley leaves “an unprecedented level of interagency cooperation in the federal government. We have agreements and memoranda of understanding now between agencies that, in the past, never used to talk to each other.”

Bromley chaired two groups charged with surveying the entirety of federal research and development, with the goal of coordinating scattered efforts into a unified whole in such areas as biotechnology, semiconductor technology, materials science, and supercomputing. The two groups—PCAST and FCCSET—linked the more than 20 federal agencies that do R&D with their counterparts in American industry.

Bromley found that 12 of these agencies do significant biotech research, spread out among some 250 programs, most of which are health-related.

“What was most striking about our inventory is that the most exciting developments in biotechnology were not in health but in such areas as agriculture, aquaculture, manufacturing and environmental research,” he reported.

Bromley’s office then crafted a 5-year plan based on this overview, designed to keep the U.S. lead in science. Budget increases of from 10 to 40 percent were proposed by Bush to support this advantage, and were accepted by Congress in all except the current year.

Gender Bender

Menopause for Men?

By Carla Garnett

The Clinical Center’s first grand rounds of 1993 recently shed light on a topic that has been speculated upon, joked about and generally debated for decades. With the so-called baby boomer generation now reaching middle age and beyond, perhaps only the topic’s female counterpart has received more attention in recent years. “Male Menopause: Menace or Myth?” was presented by Dr. S. Mitchell Harman, chief of the endocrinology section of NIA’s Laboratory of Clinical Physiology.

“I want to suggest a third possibility [to the title],” he began, “and that is misnomer.” Harman defined menopause in a woman as a decrease in the production of sex hormones to a level that would represent hypogonadism, or reduced sexual development, in a younger woman.

“This does not seem to be the case in men,” he said. “Nonetheless, there are changes of note, some with possible physiologic significance.”

Harman addressed three main questions in his presentation: Does male sex steroid activity change with age? What components of the (See MENOPAUSE, Page 6)

NIH’s Judith Rapoport To Give Mider Lecture, Jan. 26

Just as the human species has evolved over millions of years, so, too, has the human brain developed. Research conducted by NIMH reveals an intriguing connection between brain evolution and two neurological disorders—dyslexia and obsessive-compulsive disorder—that affect millions of Americans, many of them children.

NIMH researcher Dr. Judith L. Rapoport has (See RAPOPORT, Page 2)

NHLBI Hosts Major Cytokines Symposium

By Louise Williams

The recent NHLBI symposium on cytokines proved a resounding success, exceeding its organizers’ expectations: Not only did it explore new scientific ground, but it also mapped out a whole new discipline.

At the close of the symposium, organizers told the 600 experts gathered from around the world that the past 2 days had demonstrated that cytokine research fits into no single field, but “crosses many disciplines, uses various techniques, and observes broad-ranging effects, both basic and clinical.”

Consequently, the organizers said, a new society to promote cytokine research would be established. They also announced that the next major cytokines symposium will be held Oct. 17-21, 1993, in Osaka, Japan.

The symposium, “Cytokines and Cytokine Receptors in Health and Disease” was held in early December in the Clinical Center’s Masur Auditorium. It marked the 19th in the NHLBI’s popular Frontiers in Basic Sciences series. The series, started in 1983 at NHLBI director Dr. Claude Lenfant’s recommendation, seeks to inform clinical investigators about the latest advances in basic science. The goal is (See CYTOKINES, Page 4)
RAPPORT
(Continued from Page 1)

studied mental disorders common in children and adolescents for nearly two decades. On Jan. 26, Rapoport, chief of the Child Psychiatry Branch at NIMH, will share what she has learned as part of the G. Burroughs Mider Lecture titled "Child Psychiatry and the Brain." The lecture is at 3 p.m. in Masur Auditorium, Bldg. 10.

Rapoport will discuss how studies of people with dyslexia and OCD can shed light on some very basic questions about brain organization and development.

Dyslexia—a major disorder affecting children that causes difficulty in learning to read—is closely tied to brain development and the evolution of language, according to Rapoport. Using PET scans, her NIMH colleague Dr. Judith Rumsey has demonstrated that in dyslexia, the parts of the brain associated with language and visual discrimination are not activated. These areas are critical in processing written language into the sounds we associate with words.

"These are recently evolved, highly specialized regions of the brain," said Rapoport. "Given their relatively recent development, it's very possible that these parts of the brain are more vulnerable to genetic disorders like dyslexia, and that the genes for processing language are not completely established."

Another area of the brain that may be highly vulnerable to disorders is the basal ganglia, a series of structures at the base of the brain where the memory associated with habits is stored. This area of the brain also coordinates what the senses detect and how the body responds. According to Rapoport, studies of people with severe obsessive-compulsive disorder suggest the involvement of the basal ganglia.

OCD is a mental illness that affects nearly 6 million Americans, at least one-third of them children. It causes recurring, distressing thoughts that lead the person to perform repetitive, senseless behaviors like cleaning, checking, and counting.

"The basal ganglia are involved in very complex behavioral routines that are controlled through biological mechanisms," said Rapoport. "We believe that in people with OCD, some circuits in this area of the brain 'fire' too quickly, leading them to doubt what their senses are telling them—so they perform the same grooming or counting behaviors over and over."

Recent studies by Rapoport and NIMH colleagues Dr. Susan Swedo and Dr. Henrietta Leonard also show a close correlation between OCD in children and Tourette's syndrome, a disease of the basal ganglia. Tourette's syndrome, another mental disorder that strikes during childhood, features multiple motor and vocal tics.

NIAID Gives Push to Inner-City Asthma Studies

Although deaths still are infrequent among the 10 million to 15 million asthma sufferers in the United States, the asthma mortality rate has increased 46 percent since 1980. Today, 5,000 people a year die from asthma. With proper medical treatment and management, these deaths could have been prevented. Minorities, particularly African-Americans living in the inner-cities, account for a disproportionate number of those who have and die from the disease.

Because of the urgency of this problem, in 1991 NIAID funded the National Cooperative Inner-City Asthma Study, a network of eight sites established to design and evaluate a comprehensive intervention program to reduce the number of asthmatic episodes and asthma-related deaths among inner-city children, predominantly African-American and Hispanic.

"In addition to supporting collaborative basic and clinical research, we strongly urge all of our center grantees to sponsor and participate in education and community outreach programs," says Dr. Robert A. Goldstein, director of NIAID's Division of Allergy, Immunology and Transplantation.

In June, Albert Einstein College of Medicine, Mount Sinai School of Medicine, and NIAID cosponsored a 1-day seminar in New York City titled "Future Directions in the Management of Asthma and Allergic Diseases." More than 300 health care workers attended.

Dr. Lawrence J. Prograis, deputy director of DAIT, says, "Through such programs, NIAID transmits results of basic and clinical research to physicians and other health care professionals responsible for the care of those with asthma and allergies."

A similar workshop for health care professionals, "New Directions in the Treatment of Asthma and Allergic Diseases," took place Nov. 14 at Case Western Reserve University's Rainbow Babies and Children's Hospital in Cleveland. The following day, Case Western sponsored a program to acquaint children, parents, teachers, and friends with the latest information about asthma treatment.

The city-wide event was similar to "Asthma Awareness Day for Family and Friends" held at Howard University, a year before it became a network site. This event, cosponsored by NIAID, brought together 500 children with asthma and allergies and their parents and teachers for a day of learning and fun. Participants were entertained by a puppet show about asthma, Captain America (a superhero who fights asthma), clowns, and dance groups. Participants also learned breathing and relaxation techniques, experimented with using a peak flow meter to monitor their breathing, and received literature on asthma and allergies.

"NIAID views Asthma Awareness Day for Family and Friends at Howard University as a model educational component for asthma and allergy management," says Prograis. "I can personally attest to the enthusiasm and enjoyment on the part of the children who had fun learning about how to manage their own asthma."

A similar community outreach series is planned soon for the Asthma and Allergy Center at Johns Hopkins University.—James Hadley

Trout Quintet Performances Set

The NIH Chamber Players will present two performances of a concert including Trio No. 25 in G of Haydn, and the "Trout" Quintet, Op. 114, of Schubert. The concerts will be held in the 14th floor assembly hall, Bldg. 10, on Friday, Jan. 22 at 12 noon, and on Sunday, Jan. 24 at 3 p.m. Scientific staff and retirees Morton Raff (violin), John Wolff (viola), Suzanne Epstein (cello), and Carl Banner (piano) will be joined by guest double bass players Newton Pacht (Jan. 22) and John Nazdian (Jan. 24). The concerts are sponsored by the Foundation for Advanced Education in the Sciences and the Clinical Center's patient activities department. All are welcome.
Gene for Hereditary Deafness, Blindness Identified
By Jo Bagley

The first crucial step in identifying the cause of one type of hereditary deafness and blindness has recently been reported by scientists who have mapped a gene responsible for the disorder Usher syndrome (US) type I.

US type I, a hereditary disorder characterized by severe hearing loss, late-onset blindness and complete loss of balance, affects approximately one of every 18,000 people. It is an autosomal recessive disorder, meaning that the responsible gene from both parents needs to be transmitted for a child to inherit the syndrome. Parents who carry the gene have a 25 percent chance of passing the disorder on to their child.

“The mapping of this gene brings scientists closer to finding an effective method for the prevention and treatment of this syndrome,” said Dr. James B. Snow, Jr., director of NIDCD.

The mapping of the US type I gene was led by Dr. William J. Kimberling from the Center for Hereditary Communication Disorders at the Boys Town National Research Hospital, Omaha, Neb. His research was partially funded by NIDCD. Other team members include scientists from around the world, including Dr. Richard J. H. Smith from the molecular otolaryngology research laboratories at the University of Iowa, a member of an NIDCD-supported international consortium of scientists committed to locating and characterizing the genes responsible for US. Their report appears in the December issue of the medical journal Genomics.

To map the gene, Kimberling's team analyzed the hereditary material extracted from blood samples of 48 affected individuals from 27 families. Unaffected family members, including all children, both parents and available grandparents, also were tested. The families in this study were from the United States, Sweden, Ireland and South Africa.

Gene mapping is a process where scientists determine the relative location of a specific gene on one of the 23 pairs of chromosomes found in each cell of the body. Scientists then attempt to copy or clone the gene in the laboratory to decode the gene or identify a gene defect. Once a gene defect is identified, treatment such as gene substitution therapy may be attempted.

A factor complicating the study of US is that there are several subtypes of the disorder. According to Kimberling, scientists agree on the existence of two US subtypes referred to as US type I and US type II. He added that there are possibly two other subtypes of US, however, there is no universal agreement on the number and definition of additional US subtypes.

Scientists differentiate US types I and II by the degree of hearing impairment and the presence or absence of balance problems. US type I patients have severe hearing loss, complete loss of balance and blindness, whereas US type II individuals are affected by moderate hearing loss and blindness. Together they account for approximately 10 percent of all hereditary deafness.

Kimberling reports that currently there is evidence suggesting at least five possible genes responsible for the two types of US. While his group mapped a gene for US type I to the long arm of chromosome 11, a team led by Smith from the Usher consortium reports mapping a gene for US type I to the short arm of chromosome 11. The location of another gene for US type I has been mapped to the long arm of chromosome 14. Although a US type II gene has been mapped to the long arm of chromosome 1, the gene for 5 percent of US type II families cannot be mapped to that location, suggesting the existence of another gene.

The diverse clinical and genetic picture of Usher syndrome adds to the importance of this recent discovery. Kimberling, who has been studying Usher syndrome since 1984, will continue his investigations of both Usher types I and II with the ultimate goal of finding an effective method for treating and/or preventing this syndrome.

Patients’ Own Immune Cells Used in Experimental HIV Therapy
By Greg Folkers

A first-of-its-kind pilot study sponsored by the National Institute of Allergy and Infectious Diseases has begun to evaluate the treatment of HIV-infected persons with large numbers of their own HIV-fighting immune cells grown in the laboratory. HIV is the virus that causes AIDS.

The study will assess the safety and feasibility of infusing HIV-infected persons with cytotoxic “killer” T cells that have been taken from their blood, selected for their ability to kill HIV-infected cells and cultured in the laboratory.

A similar approach has been used for patients with cancer, but the NIAID trial is the first to administer HIV-specific, laboratory-selected cytotoxic T cells to patients with HIV infection.

“Cytotoxic T cells, sometimes called killer T cells, are important weapons in the body’s immune defense against viruses, including HIV, that have infected cells,” explains Dr. Anthony S. Fauci, NIAID director. “Previous studies suggest that patients who progress to the late stages of HIV infection may lack functional cytotoxic T cells.”

Between 15 and 24 patients will take part in the study at the New England Medical Center in Boston, a site of the Division of AIDS Treatment Research Initiative (DATRI), one of NIAID’s three AIDS clinical trials networks. Study physicians will enroll patients with CD4+ T cell counts in the range of 100 to 400 per cubic millimeter of blood. CD4+ T cells are the crucial immune system cells depleted during HIV infection. Patients in the study will continue to take any prescribed anti-HIV medications and preventive drugs for Pneumocystis carinii pneumonia, a common HIV-related lung infection.

After study doctors evaluate participants’ health with physical examinations and laboratory tests, the investigators will test blood samples from eligible patients to determine whether their cytotoxic T cells can kill HIV-infected cells. Selected cells will then be grown in the quantities required for infusion. At a subsequent visit to the hospital, patients will be admitted for the night and receive intravenous transfusions of 1 billion, 5 billion or 25 billion cytotoxic T cells derived from their own blood. Study investigators will follow the patients for 24 weeks to determine the effects of the treatment on their infections and to monitor any side effects.

“This is a highly complex and labor-intensive study,” said Dr. Daniel F. Hoth, director of NIAID’s Division of AIDS. “As a result, it likely will not be possible to enroll more than one patient per month. Two years may be required to complete the study, but this study design should provide us with the most definitive data to use to assess this therapy.”

In previous laboratory studies, the blood from approximately two-thirds of HIV-infected patients has shown the ability to kill HIV-infected cells. The investigators anticipate screening 40 to 64 patients to attain the desired number of eligible patients.

“Innovative approaches to treatment, such as that being evaluated in this latest DATRI study, are crucial to our goal of making HIV a manageable disease,” said Hoth. “Currently only AZT, ddl and ddC in combination with AZT have been approved for treating HIV infection. These therapies can slow the progression of HIV disease but have not been shown to control it.”
First HIV Vaccines Move Into Phase II Testing, Says NIAID

The expanded, phase II clinical trial of experimental vaccines to prevent HIV disease has begun in Seattle, Baltimore, St. Louis, Nashville and Rochester through the network of AIDS Vaccine Evaluation Units sponsored by NIAID.

The vaccine trial will employ two genetically engineered products based on gp120, one of HIV’s envelope proteins. The goal is to gather extensive information about the safety and immune-stimulating ability of each preparation by testing both in a large and diverse population of uninfected people. An important aspect of the investigation will be to determine if host factors specific to different populations influence how the volunteers respond to each experimental vaccine.

NIAID will continue to work with the manufacturers of these and other products to identify the best candidate vaccines for such large-scale efficacy trials as modified formulations and other vaccine preparations become available.

"Ideally, a preventive vaccine will stimulate binding antibodies, neutralizing antibodies and/or cellular immune responses of sufficient intensity, duration and breadth to prevent the virus from causing disease," explains Dr. Daniel Hoth, director of NIAID’s Division of AIDS (DAIDS).

"The breadth of the immune response is believed to be particularly important to ensure that the vaccine will effectively counter a variety of HIV strains," comments Hoth. Many HIV strains exist, individuals can become infected by more than one strain and any strain that infects an individual usually mutates over time. Both candidate vaccines have caused no adverse effects in small phase I clinical trials in humans and have shown promising evidence that they induce antibodies that can neutralize several different HIV strains.

The gp120 proteins in the trial vaccines were genetically engineered from two of the most common HIV strains circulating in the United States today. Recombinant gp120 (rgp120), made by Genentech of San Francisco, uses the HIV-1 MN strain; rgp120 made by Biocine of Emeryville, Calif., uses the closely related HIV-1 SF-2 strain. Biocine is a joint venture of Chiron and CIBA-GEIGY.

Both candidate vaccines are made in mammalian cells, ensuring that their three-dimensional structures closely resemble that of native gp120, an attribute thought to be important for stimulating better immunity.

Because they are made from a subunit of the virus and are not produced from live HIV or an infected human cell line, neither preparation can cause HIV infection in any trial volunteer.—Laurie Doepel

Cytokines (Continued from Page 1)

...effects on normal and disease processes.

The 24 scientific talks, given by scientists from Australia, Canada, Japan, and the United States, covered six general topics: the biological effects of cytokines; cytokines in the lung; cytokines in hematopoiesis; regulation of cytokine gene expression; cytokines related to the cardiovascular system; and cytokine receptors.

Several themes emerged during the symposium. For instance, many speakers noted the influence of the molecular microenvironment in determining cytokine behavior. Dr. William Paul, chief of the Laboratory of Immunology at NIAID, said that studies of transgenic mice had shown that the presence of interleukin 4 determined whether a cell produced interleukin 4 or interferon gamma.

"Naive T cells," he said, "can be stimulated into one of two pathways—helper cells 1, believed to produce cellular immunity, or helper cells 2, which have antibody production as their major function—depending on the presence of interleukin 4."

Dr. Alan Bernstein, of the Samuel Lunenfeld Research Institute at Mount Sinai Hospital in Toronto, described the effects of microenvironments on cell growth and proliferation in bone marrow and other cells.

He also noted that "the c-kit receptor pathway is an ancient mechanism of signaling between cells. It's a family of receptors that we can study, learn from, and manipulate."

A second major theme was the potential clinical application of cytokines. For instance, Dr. Maureen C. Howard, director of immunology at the DNAX Research Institute in Palo Alto, Calif., suggested possible applications for interleukin 10, produced by various cells.

"Interleukin 10 was discovered because of the heterogeneity of helper T cells," she said. "We now know that there are several subsets of helper T (TH) cells, TH1 and TH2 produce different patterns of cytokines," each regulating different processes, although some crossregulation also exists.

She described the regulatory effects of interleukin 10 on different cell types. Mouse studies indicate, she continued, that this cytokine has the potential to become an anti-inflammatory agent, protecting against such conditions as septic shock.

Dr. Michael Sporn, chief of NCI’s Laboratory of Chemoprevention, discussed the role of TGF-8 related to the cardiovascular system. He suggested that TGF-8 is a "switch" cytokine, which can oppose the effects of interleukin 1 and can influence both heart rate and the production of nitric oxide synthase.

Dr. Malcolm Moore, Enid A. Haupt professor of cell biology at the Memorial Sloan Kettering Cancer Center in New York City, also spoke of cytokines’ clinical potential, specifically with hematopoietic stem cells.

"The biologic features of early stem cells include a subset that is highly proliferating and another that does not proliferate if exposed to certain factors, such as interleukin 2," he noted. His research indicates that cytokines could be used to prime stem cells to produce certain responses. For instance, the time required for the cells to mature into blood cells might be shortened, aiding the treatment of people with bone marrow failure.

Moore also has been manipulating cytokine factors to make peripheral blood a source of progenitor stem cells.

Dr. Mathew Vadas was one of many speakers who discussed how a cytokine’s structure influences its function. A professor and the chairman of the Department of Medicine at Indiana University School of Medicine, he outlined the structures of two cytokines, interleukin 3 (expressed in T cells) and GM-CSF (expressed in monocytes, fibroblasts, and endothelial cells). He has deciphered the composition of a mutant interleukin 3 and, by changing its structure, intensified the molecule’s potency.

Dr. Thomas Waldmann, chief of NCI’s Metabolism Branch, spoke about the use of anti-interleukin 2 receptor antibodies as therapeutic agents for adult T-cell leukemia. He also described ongoing studies using the same agents in monkeys.

Dr. Tadamitsu Kishimoto, professor and chairman of the department of medicine at Osaka University Medical School in Japan, also discussed the link between structure and function, showing how interleukin 6 produces a signal by combining with its receptor and transducer GP 130.

Various speakers described cytokines’ varied effects in different cell types. "Different cytokines have redundant functions," said Dr. Steven Ziegler, a staff scientist at Immunex Research and Development Corp. in Seattle. He discussed the ILIF and G-CSF receptors, specifically how their signaling ability can be influenced by varying the receptor’s cytoplasmic domain.

Finally, several investigators spoke about the importance of understanding transcription factors as modulators of cytokines and cytokine receptor gene expression. Dr. Anjana Rao, assistant professor of pathology at Harvard Medical School, explained the critical role of nuclear factor NF-AT in the activation of interleukin 2.

And NHLBI’s Leonard discussed the NF-kB family of transcription factors, which regulate suppression of numerous cytokines. He believes that oxidation-reduction may play a critical role in regulating NF-kB DNA binding and transcriptional activation.

The next NHLBI Frontiers in Basic Sciences Symposium is already planned: It will be held Nov. 29 and 30, 1993, on inflammation. — Harold Kinney
**Novel Vaccine Protects Monkeys Against AIDS-Like Disease**

By Laurie K. Doepel

Researchers have developed an experimental vaccine that provides the strongest and most durable protection to date against an AIDS-like disease in monkeys, according to a report in the Dec. 18 issue of *Science*.

The research team, led by Dr. Ronald C. Desrosiers of the New England Regional Primate Research Center, developed and tested the vaccine—a modified version of the HIV-like monkey virus, simian immunodeficiency virus (SIV)—with funding provided largely by NIAID and the National Center for Research Resources.

Said NIAID director Dr. Anthony S. Fauci, "This is a significant advance in our search for an HIV vaccine. Their model can teach us a great deal about what constitutes protective immunity, information that will help us design more effective HIV vaccines."

Added Dr. Judith L. Vairukaitis, acting NCRR director, "This development underscores the importance of primate research centers, which are a little-known but vital part of the federal government's attack on AIDS."

More than 3 years after being given the experimental vaccine and more than 8 months after being challenged with 10 infective doses of SIV, all four test rhesus monkeys show no signs of disease, very little SIV and normal levels of SIV's main target, CD4+ T immune cells. More striking, two of these monkeys that were rechallenged with 1,000 infective doses of live SIV about 3 years after their vaccinations have shown the same evidence of protection for more than 18 weeks as of this date.

In contrast, 11 of 12 healthy, unvaccinated monkeys experimentally infected with SIV during the study have died.

"This SIV vaccine has given the first indication of truly strong protection against an immunodeficiency virus challenge," says Dr. Margaret Johnston, associate director of NIAID's Division of AIDS Basic Research and Development Program.

Desrosiers' team created the vaccine by deleting one SIV gene, nef, whose function is not known. Deleting this one gene allows the resultant mutant SIV to thrive in monkey cells in the laboratory but, surprisingly, not in the monkeys. The vaccine is live but attenuated, a common type of vaccine in human use today for other diseases. Such vaccines contain a weakened form of the disease-causing organism that stimulates the immune system without causing disease.

The major challenge in constructing live-attenuated vaccines for HIV, which like SIV is a retrovirus, is assuring its safety. Retroviruses are RNA viruses that transcribe their genetic material into DNA using an enzyme called reverse transcriptase. One concern is whether a mutant retrovirus vaccine could revert to a disease-causing state by recombining with fragments of retroviruses that naturally exist in the vaccine recipient. A second concern is whether cancer-causing genes could be turned on when the genetic material of a mutant retrovirus integrates into that of a cell. Some integrated retroviruses have such cancer-causing potential.

Well aware of these concerns, Desrosiers' group has begun building SIV vaccines with four or five genetic elements deleted. If these additional changes do not alter the effectiveness of the SIV vaccine, such vaccines should be even safer than the nef-deleted vaccine, says Desrosiers. The situation can be likened to taking just one part out of a gun, in which case the gun might still fire, taking four or five parts out of a gun, which significantly reduces the chance of having the gun fire.

The cancer-causing potential of modified retroviruses, Desrosiers explains, has been seen with some retroviruses but not to his knowledge, not with lentiviruses, the class of retrovirus to which SIV and HIV belong.

How these mutant SIV vaccines perform in further testing will help determine the potential for developing a live-attenuated HIV vaccine based on this animal model. SIV and HIV have most genes in common, including nef.

"We're going to push our system to see how good it really is," says Desrosiers. They have already begun experiments to determine if their SIV vaccine protects against infected cells, against vaginal challenge and against challenge with different strains of the virus, for example.

"Much depends on how bad the epidemic gets, and what HIV vaccine candidates become available," says Dr. Alan Schultz, chief of NIAID's Division of AIDS Vaccine Research and Development Branch. "We must prepare for alternatives."

Additional support for the study came from Deutsches Krebsforschungszentrum.

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**New Gallstone Treatment Found Safe, Effective**

Laparoscopic cholecystectomy is a relatively new surgical treatment for gallbladder removal that is as safe and effective as traditional open cholecystectomy, according to a consensus panel recently convened by NIDDK and the Office of Medical Applications of Research.

The advantage of the new procedure over conventional cholecystectomy is that it causes less postoperative pain, which leads to shorter convalescence. Currently, 80 percent of gallbladder surgeries are performed laparoscopically.

The panel emphasized that laparoscopic cholecystectomy, like open cholecystectomy, should only be used for gallstone patients who have symptoms. The usual symptom of gallstones is pain in the upper abdomen lasting 1 to 5 hours, which often wakes the patient at night. In complicated cases, jaundice and fever arise.

First performed in the United States in 1988, laparoscopic cholecystectomy requires the insertion, through tiny incisions into the patient's abdomen, of a fiber optic instrument attached to a small video camera. Viewing the gallbladder through this instrument on an external television monitor, the surgeon can dissect, clamp, and remove the gallbladder using specially designed equipment inserted through two small incisions in the abdomen.

Although there is no increase in overall mortality or morbidity with laparoscopic cholecystectomy, the rate of common bile duct injury appears to be increased over open cholecystectomy. However, the rate is still sufficiently small to justify the use of laparoscopic cholecystectomy in the treatment of symptomatic gallstones.

The procedure is not usually recommended for persons with certain serious complications of gallstones, including abdominal inflammation (peritonitis), severe acute pancreatitis, end-stage cirrhosis of the liver, and gallbladder cancer. The panel also cautioned that women who are in the third trimester of pregnancy should not undergo laparoscopic cholecystectomy because of increased risk of damage to the fetus. In addition, the panel said that if the surgeon's view of the patient's anatomy is obscured, excessive bleeding occurs, or other problems arise during a laparoscopic cholecystectomy, the surgeon should convert to traditional open surgery.

Nonsurgical methods for treatment of gallstone disease such as oral bile acid therapy, with or without the use of shock wave therapy (extracorporeal shock wave lithotripsy), and endoscopic removal or dissolution of gallstones are useful alternatives for patients who are not candidates for surgery. However, the panel said that these medical treatments are ultimately less effective than surgery because stones tend to recur.

The panel endorsed strict guidelines for training and credentialing in laparoscopic surgery, for determining surgical competence, and for monitoring the quality of the surgery.

Finally, the experts recommended that future research focus on developing noninvasive approaches to gallstone treatment that will eliminate existing stones and also prevent their formation or recurrence. More than 20 million people in the U.S. have gallstones and approximately 600,000 individuals are operated on annually at an estimated cost of more than $5 billion.—Leslie Curtis
BROMLEY (Continued from Page 1)

In a budget climate that features more opportunities than funds to pursue them, Bromley suggests NIH ers get more involved in setting national priorities by talking directly to Congress, and by helping educate the public about the advantages of scientific research.

"There are 5 million scientists and engineers in the United States, which is three times the number of lawyers and doctors. The public outreach potential is enormous."

Bromley is appalled, however, at how badly informed Americans are about science in general.

"The level of scientific literacy and numeracy is scandalous in the United States," he declared.

Bromley leaves office with pride that he helped coordinate far-flung research enterprises, and supported a national initiative to create a new children's vaccine effective against some 30-40 illnesses.

"It has been a rare privilege to serve with President Bush," he concluded. "He has received nothing like the recognition he deserves. I am sure that history will remember him fondly."

He said that, had Bush won a second term, his highest priority would have been a careful look at R&D utilization in the U.S. "It is not at all obvious that our existing structures are appropriate to today," Bromley observed.

Two great surprises occurred to Bromley during his tenure, he related. "The first is that the quality of the people has been vastly higher than I expected. Second, I learned that it takes infinitely longer to make things happen in government than anyone could possibly believe."

Bromley left the real credit for U.S. science supremacy with people like NIH employees, not the White House: "Your ingenuity, your creativity and perseverance have led the way, despite the obstacles people such as myself have put in your way."

A former English major, Bromley ended by quoting poet W.H. Auden, who called scientists "the only true men of action."

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MENOPAUSE (Continued from Page 1)

system are involved and what, if any, are the clinical consequences?

In 1970, much of what was known about testosterone—the major male sex hormone—and age was represented by a bell curve configuration, Harman said, showing that hormone levels in boys rise in puberty, remain in a wide, normal range through youth to middle age, and begin to fall in late middle age. Showing a slide from a 23-year-old study by Dr. Alex Vermeulen, Harman pointed out that about half of the male subjects were found to have pathologically low testosterone levels—"a highly significant and problematic change," had it been true.

However, the bell-curve research was found to be somewhat misleading.

"Vermeulen took [data for] the young men from his colleagues, students and perhaps from the children of his colleagues and students," Harman said. "He took the data for the old men from clinics, nursing homes and hospitals," which introduces a variable other than aging—illness.

More recent research—the Baltimore Longitudinal Study on Aging (BLSA)—looked at a similar population of males, but eliminated several groups from its prescreened, basically healthy subjects: obese men, those with chronic health problems or those taking medication regularly. The testosterone levels in BLSA's group barely changed at all with age.

A third study, done by Dr. William Bremner in 1983, further complicated the issue, finding diurnal differences in testosterone production by young and older men. Older men showed little change in levels throughout the day, but young men showed peak production times in the early morning hours.

"Clearly there is an impact of chronic illness," Harman continued, citing additional research conducted with his colleague Dr. Marc Blackman contrasting healthy men and men with lung cancer. "The more severe the illness the lower the testosterone is likely to be."

The last word Harman offered on the subject was his own. "If one looks at a large population," he said, "one is going to see a significant and steady decrease in testosterone with age, and some men will have levels that are quite low."

Reasons for the decreased production ranged from failure of the hypothalamic-pituitary axis—the channel system for, among other body processes, proper gonadal function—to failure of the testis and its cells to changes in the sex hormone transport system or peripheral target tissues, which could possibly trigger faulty responses by end organs to testosterone.

A 1980 study of younger and older men by Harman's group included injecting subjects with human chorionic gonadotropin (hCG).

Bromley leaves office with pride that he received nothing like the recognition he deserves. He is sure that history will remember him fondly."

He said that, had Bush won a second term, his highest priority would have been a careful look at R&D utilization in the U.S. "It is not at all obvious that our existing structures are appropriate to today," Bromley observed.

Two great surprises occurred to Bromley during his tenure, he related. "The first is that the quality of the people has been vastly higher than I expected. Second, I learned that it takes infinitely longer to make things happen in government than anyone could possibly believe."

Bromley left the real credit for U.S. science supremacy with people like NIH employees, not the White House: "Your ingenuity, your creativity and perseverance have led the way, despite the obstacles people such as myself have put in your way."

A former English major, Bromley ended by quoting poet W.H. Auden, who called scientists "the only true men of action."

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Breast Cancer Meeting Set

The National Cancer Institute is hosting a meeting Jan. 28-29 in Masur Auditorium, Bldg. 10, focusing on "Breast Cancer in Younger Women."

It will concentrate on breast cancer occurring in women ages 20-40. Speakers will address a number of topics for which no clear answers are available, including:

- Is the incidence of breast cancer in younger women rising? What are risk factors for breast cancer in younger women? Do young women have the same response to treatment as older women?
- Is pregnancy safe after breast cancer?
- To register, call TASCON, Inc., (301) 907-3844 or fax (301) 907-9655. For information about scientific matters, contact Dr. Edward L. Trimble, 496-2522, fax 402-0557.

HCG is a placental product similar to pituitary luteinizing hormone, which stimulates testosterone production. The hCG study confirmed a Leydig cell component in the reduction of testosterone. The Leydig, or interstitial, cells are found in between the tubules of the testis.

"Young men had very nice response to the CG," Harman noted, "and while the older men responded, they had a significantly lower response." A study of the pituitary response was also found to be consistent with an additional element of pituitary failure, he added.

Finally, Harman discussed the clinical consequences of decreased sex hormone activity. Well documented already, he said, is the effect of decreased testosterone on muscle and bone as well as on secondary sex characteristics and potency, in addition to such psychological factors as libido, energy, focus and mood. "The really good studies are only now being conducted," Harman noted.

"There's little question that hypogonadal men lose muscle mass and lose bone mass," Harman continued. "Both can be reversed using testosterone." Less clear but possible, however, is testosterone's effect on lipids and cardiac function as well as its effect on bone marrow and the secretion of other hormones, for example, growth hormone.

Harman cautioned against drawing simple conclusions from the data presented. "Changes in testosterone level are not the major determinant in decreased sexual activity," he said, comparing the BLSA study of testosterone level with a study of reported sexual activity of the study population. Although BLSA found no discernible decrease in testosterone, the number of sexual events by the men fell with age anyway. In another study, however, old men with more active sex lives had higher testosterone levels.

"Maybe the men who are staying active for other reasons are also stimulating their secretory system to produce more testosterone," Harman suggested. "And the men who have quit are making less testosterone. The effect of sexual activity on testosterone levels in humans is another area of controversy."

In other research, findings suggested that estrogen in men may be protective against cardiac disease, as has been shown in women. Testosterone was not found to be a risk factor for heart disease.

"Testosterone treatment of older and late middle age men may have a beneficial impact on cardiac risk," Harman concluded. "I think there's a lot left to learn. There are a number of clinical trials going on now looking at the effects of testosterone intervention. I think there's going to be a lot more exciting information of potential clinical value in the next few years."
Maclmdad: Computer-Assisted Window on Chemical Structures

Many NIH researchers are aware that the three-dimensional structures of proteins and nucleic acids are becoming available in growing numbers through a central online repository of crystallographic information called the Brookhaven Protein Data Bank. This databank's computer files are now conveniently accessible through a Macintosh program called Maclmdad, written by Michael Levitt of Stanford University. Maclmdad makes it easy to browse through the databank to find macromolecules of interest to you. Search for molecules by name, author, or other keywords, and then view the located structure in color, using the program's various kinds of molecular graphics techniques (molecules can even be rotated in space with a mouse). In addition to graphics and databank searching, Maclmdad provides limited capabilities to create compute models of small organic molecules and nucleic acid sequences.

Maclmdad offers several specialized functions:

• Create any organic molecule by specifying a simple chemical formula; the structure is built with standard geometry unless otherwise specified (any rings are closed automatically). Modify the structure by editing the chemical formula and nonstandard geometry, and output the coordinates for use in molecular mechanics, ligand fitting, drug design, etc.

• Construct standard DNA double helices of arbitrary sequence in either A or B form, facilitating visualization of possible protein recognition sites. Peptides of any sequence and conformation can also be modeled and manipulated as desired.

• Use dual-colored stick bonds, van der Walls dot surfaces, and space-filling (CPK) representations together in any combination. Smooth, anti-aliased, depth-cued bonds combine with space-filling spheres to give very attractive ball-and-stick illustrations.

• Read in up to three different molecules that are displayed together but manipulated independently. Fit an arbitrary organic molecule (defined by its chemical formula) into a receptor binding site and then output the coordinates of the hypothetical complex.

• Superimpose all or parts of different molecules to compare different structures, and change amino acid side chains by such manipulation and superposition.

• Save stick and space-filling drawings to files for subsequent editing by standard drawing programs or direct output as PostScript files on a laser printer. This makes it easy to prepare complicated but clear color or black-and-white illustrations for publication.

DCRT has purchased an NIH site license for Maclmdad, and copies are available upon request. However, your Macintosh must be capable of running this program, which requires:

• At least a Macintosh II (e.g., IIfx, Iici, Quadra, etc.)

• 8-bit color video card

• System 6.07 or greater (and at least 2 Mb of hard disk space)

• At least 3.2 Mb RAM over and above the RAM used by your operating system (i.e., more than 5 Mb RAM for System 6.07+, and more than 6 Mb RAM for System 7)

• An additional 15 Mb hard disk space to install the Protein Data Bank files if your Macintosh is not on the NIH AppleTalk network.

The program is also available on Macintosh in the Scientific Computing Resource Center (SCRC) located in Bldg. 12A, Rm. 1050. (Make a reservation, 402-3488, and request Maclmdad so that the appropriate machine is reserved.) You can use Maclmdad in the SCRC if you do not have access to an adequately equipped Macintosh in your lab, or want to test-run the software.

Copies of Maclmdad with documentation are available from DCRT. Materials will be mailed to you. Send your name, ICD, NIH mailing address, electronic mail address (if applicable) and telephone number, all clearly printed, to the computational molecular biology section, DCRT, Bldg. 12A/Rm. 2051 or by electronic mail to rpearl@helix.nih.gov.

Assistance with Maclmdad can be obtained by electronic mail (to rpearl@helix.nih.gov) or through the SCRC.

NIH Communicators Honored By NAGC

The National Association of Government Communicators recently announced the 1992 winners of its annual Blue Pencil-Gold Screen awards. The Blue Pencil awards are given for outstanding publications, and the Gold Screen awards honor excellence in audiovisual materials. The following are the Blue Pencil awards and the categories for which they were entered:

Public Service Announcement (ad slick)
Second place: NCI’s International Cancer Information Center (ICIC)-“Get the Fax on Cancer”
Honorable mention: NCI’s Office of Cancer Communications (OCC) “Breast Cancer Size of Tumors Detected by Mammography”

Feature/Release/Article
Honorable mention: Dr. Gene Cohen, NIA-“The Famous Case from London, December 1843—The Rest of the Story”

Visual Design (posters, maps)
Second place: NEI-Poster “Get Your Eyes Examined—Don’t Lose Sight of Glaucoma”

Visual Design (miscellaneous)
First place: NIA-NIA Logo
Honorable mention: NEI-Pocket Folder “National Eye Health Education Program”

Press Kit
First place: NEI-“National Eye Health Education Program Press Kit”
Honorable mention: NIA’s Public Affairs Cluster-“STOP/IT”

Publication for General Brochure
Third place: NCI/OCC-“Pubettes: Series of Question and Answer Publications”

Publication for General Brochure (two or three colors)
Honorable mention: NEI-“Don’t Lose Sight of Diabetic Eye Disease-Information for People with Diabetes”

National Institute on Aging


Publication for General Audience
Second place: NCI/OCC-“Managing Your Child’s Eating Problems During Cancer Treatment”
Third place: NIA-“Bound for Good Health”

Publication for Technical Audience
First place: NCI/IICIC-“Scientific Information Services of the National Cancer Institute”

Cover art from NEI’s award-winning press kit

Publication for Technical or Professional Audience (one color)
First place: NHLBI-“NCEP Report on the Expert Panel on Blood Cholesterol Levels in Children and Adolescents”

Publication for Technical or Professional Audience (two or three colors)

Periodical for Technical or Professional Audience
Honorable mention: NCI/IICIC-“JNCI”

Book for Technical or Professional Audience
Third place: NCI/IICIC-Final Report-An Integrated Oncology Workstation

Newsletter (seven or more pages)
Honorable mention: NCI Pediatric Branch-“Clinical Research”

NCI also received two Gold Screen awards: First place for a television news story/report was OCC for the “Patti LaBelle Video News Release.” Honorable mention went to the Pediatric Branch for “Finding Strength: A Look at the Pediatric Branch.”
Management Intern Program Announces 1993 Recruitment

The NIH administrative training committee has announced that applications for the 1993 Management Intern (MI) Program will be accepted from Feb. 1 until Mar. 2. The program is designed to prepare individuals demonstrating high potential for careers in administrative management at NIH.

To be eligible to apply for the program, you must be a U.S. citizen; be willing to work full-time; be eligible for an Outstanding Scholar appointment or be a current federal employee eligible for a GS-5 level or above or the wage grade equivalent and currently employed in either a career or career conditional appointment (DHHS employees must currently be a GS-5 or above—you cannot be promoted into the program) or be eligible for reinstatement at the GS-5, GS-7, or GS-9 level.

If currently a nonstatus employee you must be eligible for an Outstanding Scholar appointment or some other type of noncompetitive appointment such as 30 percent disabled veteran, Schedule A appointment, VRA appointment, etc.

To qualify for consideration under the “Outstanding Scholar” provisions, you must be a college graduate and have a grade-point average of 3.5 or above on a 4.0 scale, for all undergraduate course work, or have graduated in the upper 10 percent of your college or university or major university subdivision (e.g., College of Business Administration or School of Engineering). At time of application a transcript indicating GPA must be provided.

Positions are offered at the GS-5, 7 and 9 levels. Some applicants, especially those above the GS-9 level, may be required to accept a voluntary downgrade but retain their salary.

Additional information on minimum qualifications for DHHS and non-DHHS employees is available in the application package available beginning Jan. 25 at the NIH Training Center, Executive Plaza South, Suite 100 and selected NIH personnel offices and offsite work locations such as the Parklawn Training Center, Frederick (FCRDC) and the NIEHS personnel office in North Carolina.

Management Intern Program information sessions have been scheduled for the following dates and times:

Jan. 26, 12 noon, Parklawn 3B55
Jan. 27, 11 a.m., Bldg. 10/Masur Auditorium
Jan. 28, 11 a.m., EPN/Conf. Rm. G
Jan. 29, 11 a.m., HHH/OASH/729 G
Feb. 3, 11 a.m., Bldg. 31/Conf. Rm. 10
Feb. 4, 12 noon, WW/Conf. Rm 3

All potential applicants are encouraged to attend these sessions. For more information, contact Cynthia Miller, 496-6211.

John Fletcher Closes Door on DCRT Career

Dr. John Fletcher, acting head of DCRT's Laboratory of Applied Studies (LAS) and a widely recognized expert on the application of mathematics to biomedical research, closed out a DCRT career of 26 years on Jan. 3.

Fletcher, whose early work years included a stint in the Air Force, rose from LAS research mathematician to acting chief of the laboratory, finding time to obtain his doctorate in mathematics from the University of Maryland along the way. His work at NIH has centered on applying mathematical methods and models to problems in the biological, physical, engineering, and computing sciences. Models described by ordinary and partial differential equations (PDEs) have been the focus of his attention, and he has been responsible for developing nationally and internationally recognized research projects that applied these equations to complex biological problems. Particularly notable have been his contributions to the areas of: interactive protein binding by blood constituents; modeling the physiological activities of the microcirculation system; the kinetics of T-cell lymphocytes in HIV infection; computer and mathematical algorithms for data and model fitting; and general-purpose algorithms for the solution of time-dependent partial differential equations.

In addition, his algorithms for data and model fitting influenced the development of the successful computer program MLAB, which continues to be widely used by scientists at NIH.

The long-time chairman of the FAES mathematics department, Fletcher is also highly regarded for his skills as a teacher. He has taught at several other institutions, including Montgomery College, and has been closely involved in the career development of many graduate students and professional mathematicians. In his leisure hours, his teaching skills have extended to the sporting fields of Montgomery County, where he has coached baseball, soccer, and basketball.

Fletcher has more than 50 published journal articles, and additional manuals, reports, and book sections and chapters to his credit. He also holds membership in such professional organizations as SIAM (the Society of Industrial and Applied Mathematics), and ISOTT (the International Society on Oxygen Transport to Tissue), of which he is a charter member. He has garnered numerous honors, including the Director's Merit, Leadership, and Outstanding Service Awards.

His retirement, he insists, will be a happy mixture of leisure and the pursuit of his chosen profession. Says Fletcher: "I'm looking forward to having some free time to spend with my family, to doing some fishing, and to devoting more time to teaching mathematics."—Ray Fleming

Donor Center Says, 'Be Mine'

This Valentine's Day, bring a date to donate at the NIH Blood Donor Center. The center is currently in need of new blood donors, so why not take someone special and together share a gift of love?

This February, the Blood Donor Center will have a suggestion box available for ideas on its future annual awards ceremony and reception. The center is eager to please its donors and wants everyone to have the opportunity to plan a special honors day. The center also wishes everyone a happy Valentine's Day and thanks donors for their support.

The NIH Blood Donor Center is located in Bldg. 10, Rm. 1N416. Its hours are Monday-Friday, from 7:30 a.m. to 3:30 p.m., and Tuesday from 7:30 a.m. to 12:30 p.m. For an appointment, call 496-1048.

NUPUD Sponsors Seminar

Feb. 10 at Executive Plaza

The NIH Users of Public Use Data (NUPUD) is sponsoring a seminar, "Geographic Information Systems: New Possibilities for Epidemiologic and Public Health Analysis," on Wednesday, Feb. 10 from 3 to 5 p.m. at EPN, Conf. Rm. H. The speaker will be Dr. Charles Croner from the National Center for Health Statistics. NUPUD is an informal NIH-wide collaborative group that shares access to public use data such as vital statistics and national survey data collected by the National Center for Health Statistics and Census data collected by the Department of Commerce. For access to these and other datasets, consult the NUPUD bulletin board at DCRT. For more information contact Dr. Mary Frances Cotch, 496-7065, or Dr. Jay Everhart, 496-8933.
Scientists have successfully treated arthritic rats by blocking the action of a molecule that regulates the body’s response to infection or tissue injury. The molecule is called transforming growth factor-beta (TGF-β). When an antibody that inhibits TGF-β (anti-TGF-β) was injected directly into the animals’ joints, arthritis symptoms were greatly reduced.

This finding could have applications for treating arthritis, periodontal diseases, and other chronic inflammatory disorders, said Dr. Sharon Wahl of NIDR, who led the study. She cautioned, however, that the use of antibodies for therapy has inherent problems, but added that these studies serve as a prototype for local administration of other TGF-β antagonists currently under development.

TGF-β is a multifunctional molecule that plays a pivotal role in switching the immune system on and off. In the early stages of an infection, TGF-β is secreted by white blood cells and acts as a signal that attracts other white cells and stimulates them to fight the infection. As the infection subsides, TGF-β reverses its role and suppresses the activity and recruitment of white cells.

However, in chronic disease situations such as arthritis, the normal cycle of events does not occur and TGF-β continues to attract white cells. It is the excessive accumulation of white cells that produces red, swollen joints and eventually leads to tissue and bone destruction.

Scientists examined rats with experimentally induced arthritis to determine the therapeutic effect of anti-TGF-β, which specifically binds to TGF-β and blocks its activity. Rats were first injected with a bacterial cell preparation that produces symptoms that mimic human rheumatoid arthritis. Without additional treatment, the rats experience an acute form of arthritis that appears within 24 hours and is characterized by swelling of the joints and feet and redness of the overlying skin.

The acute phase subsides within several days, and after a period of 2 to 3 weeks, the disease enters the chronic stage. This phase is identified by joint deformity brought on by the gradual destruction of cartilage and bone and replacement with connective tissue containing large numbers of white blood cells.

Rats receiving a single injection of anti-TGF-β into a hind ankle just prior to injection with the bacterial cell preparation experienced a significant reduction in both acute and chronic forms of arthritis. Acute symptoms were reduced by more than 75 percent and chronic symptoms by more than 60 percent. Moreover, when anti-TGF-β was administered only after the chronic disease phase had begun, arthritis symptoms were still reduced by almost 70 percent.

According to Wahl and her associates, anti-TGF-β works by interrupting the cycle of white cell migration into the joints. The researchers feel this antibody and other TGF-β inhibitors may provide a mechanism for treating arthritis and other chronic inflammatory diseases.—Wayne Little

Healthy Males Needed

USUHS and NIMH seek healthy male volunteers ages 21-40 to participate in a collaborative study; volunteers may earn up to $500. Procedures may require up to 7 sessions, totaling approximately 24 hours. For more information call (301) 295-3672.

AHA Honors NHLBI’s Hoak With Achievement Award

Dr. John C. Hoak, director of the National Heart, Lung, and Blood Institute’s Division of Blood Diseases and Resources (DBDR), has received the American Heart Association’s (AHA) prestigious Scientific Councils Distinguished Achievement Award.

The award was presented at AHA’s annual meeting, held recently in New Orleans. It recognizes Hoak’s significant contributions to scientific knowledge about cardiovascular medicine and to the association’s Council on Thrombosis, which he chaired from 1986 to 1988.

Hoak became DBDR director in 1989, after a 30-year career in academic medicine, which included serving as professor of medicine and director of the division of hematology-oncology at the University of Iowa and as professor and chairman of the department of medicine at the University of Vermont.

Besides heading DBDR, Hoak is a clinical professor of medicine at the Uniformed Services University of the Health Sciences. He also is a consultant to the Walter Reed Army Hospital. His research interests center on blood coagulation, thrombosis, blood platelets, and the vascular endothelium. He has published more than 125 articles, covering basic and clinical research in vascular medicine. He also has developed innovative training and research programs.

Dr. Kenneth Gruber recently joined the NIDCD staff as a program administrator in the Division of Communication Sciences and Disorders. He shares responsibility for research grants in the extramural hearing program. He received his Ph.D. from the department of basic medical sciences at New York University and subsequently was a postdoctoral fellow at the Roche Institute of Molecular Biology. He has held faculty positions at Long Island University, Middlesex College and Wake Forest University School of Medicine. Prior to coming to NIDCD, Gruber was professor of physiology at the University of Puerto Rico School of Medicine. In addition, he is currently a captain in the Medical Service Corps of the U.S. Army Reserve. His area of research expertise is in neuropharmacology and neurochemistry.

DCRT Computer Training Classes

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Classes are offered by the DCRT Training Program without charge. Call 496-2339 for more information.
NIGMS' Rossie Fitzgerald Retires

Rossie Fitzgerald, a supervisory grants management assistant in the National Institute of General Medical Sciences, retired recently after 29 years of government service. She spent 24 of those years with NIGMS, and the remainder in the Veterans Administration. She joined NIGMS in 1968 as a file clerk, and over the years advanced to grants clerk and grants technical assistant positions before her promotion to a supervisory job. Among her many honors are an NIH Merit Award, two Quality Step Increases, and four Special Act Awards.

A native of Virginia, she plans to spend her retirement in the Washington metropolitan area, where she can be near her family and visit with them more often. Fitzgerald has nine children (eight sons and one daughter) and 26 grandchildren. Her husband passed away 17 years ago. She notes that, at one point, the family had grown so large that it became necessary to rent a place twice a year for their family reunions.

When asked what special plans she has for retirement, she said, "My goal is to sleep past 6 o'clock in the morning."

Her hobby is books. She plans to continue as the librarian at the Southern Baptist Church of Washington, D.C.

In mid-December, NIGMS held a luncheon to honor Fitzgerald and pay tribute to her many contributions to the institute's grants management activities.—Wanda Wardell

NHLBI Needs Volunteers

The Cardiology Branch, NHLBI, needs normal volunteers between ages 50 and 70 to participate in a study assessing the mechanisms of certain cardiovascular conditions. Volunteers must not be taking any medication. The study includes transthoracic echocardiography (a procedure similar to an endoscopy) and takes approximately 2 hours. Participants will be paid. For more information, call Joy Laurienzo, 496-3015.

NCI's Shambaugh Ends Career After 31 Years in Government

Evelyn Shambaugh is retiring after 31 years at NCI, first with the end results group and then with the Surveillance, Epidemiology and End Results (SEER) Program. her work entailed quality control of the tumor registries participating in these NIH programs.

Her career in the tumor registry field began in the early 1950's when she worked nights at the University Hospital while she was a student at the University of Michigan. She abstracted and coded cancer patient records, put the information on punch cards, and prepared reports for the medical staff using EAM (precomputer) equipment.

Upon graduation, she worked for the Commission on Professional and Hospital Activities in Ann Arbor, establishing computerized systems for disease indices used by hospitals across the country. The hospitals completed the abstracts for each patient and the computerized reports were generated in Ann Arbor.

In 1961 she was recruited by the end results group, a combination of hospital, state, and regional registries, to ensure the quality of the data submitted by each of its 12 registries in the United States. In 1973, a population-based registry system, the SEER Program, was established, made up of 6 state registries and 4 metropolitan registries.

Shambaugh became head of the quality control unit developing the methodology commonly used in all cancer registries today. She planned and implemented all quality control activities from case-finding studies to ensure completeness of data, to recoding and reabstracting studies to ensure accuracy. She identified issues to be addressed by training programs and conducted workshops.

She is editor-in-chief of the SEER self-instructional manuals for tumor registrars. These manuals cover functions of a tumor registry, medical terminology, how to abstract, anatomy related to tumor formation, classification of extent of disease, statistics for tumor registrars, and antineoplastic drugs. Her manuals have been translated into Spanish, Japanese and German.

She has also played a key role in the development of the SEER extent of disease code, the SEER summary staging guide, and the comparative staging guide for cancer, all dealing with cancer staging.

Shambaugh is a founding member of the National Tumor Registrars Association and acted as its president from 1980 to 1981. She has also served on its certification, education, nominating, liaison, government liaison, and various advisory committees. She was the first recipient of their Distinguished Member Award.

As an expert on tumor registry operations, she has been a consultant to both hospital and population-based registries. In 1991, Shambaugh received the NIH Director's Award for "exemplary and sustained leadership in promotion of quality control standards and excellence in the profession of tumor registration."

Meeting on Women's Health Research

Dr. Joan McGowan, director of the Bone Biology and Bone Diseases Branch, NIAMS, will discuss the NIH Office of Research on Women's Health and the Women's Health Initiative at the arthritis and musculoskeletal diseases interagency coordinating committee meeting on Thursday, Jan. 28. A group discussion will follow her presentations. For more information, call Geraldine Pollen, 496-0801.

Social Drinkers Wanted

USUHS is recruiting female moderate social drinkers ages 21 to 45 for a study on alcohol, behavior and psychophysiological reactivity at USUHS. Volunteers will be paid. Leave a message at (301) 295-3278 or call 295-3265 Monday, Wednesday or Friday between 1 and 5 p.m.

Martial Arts Classes Offered

The NIH Taekwondo Club is offering a beginner's class for adults, women and men, starting Mar. 1. The class will meet in the Malone Center (Bldg. 31C, B4 level near NIH Fitness Center) for 1 hour on Mondays and Wednesdays: 5:45-6:45 p.m., and continue for 1 or 2 months until participants can be integrated into the regular club training. Fees are $80—$40 dues (3 months), $20 American Athletic Union (an annual fee), $20 uniform. The NIH Aikido Club is also accepting new members. The club meets Tuesdays and Thursdays, 5:45-8 p.m. at the Visitor Information Center, Bldg. 10, and Saturdays from 11:30 a.m. to 1 p.m. in the Malone Center in Bldg. 31C. Fees are $95—$40 dues (3 months), $40 American Athletic Union (an annual fee), $20 uniform, $15 American Aikido Association (annual fee). Those interested are welcome to watch regular club training sessions. For information call Don Murphy, 496-1736.

Evelyn Shambaugh
The NIH Training Center of the Division of Personnel Management offers the following:

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**Personnel Management**

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**Clinical Center Garage Faces Repair**

The Clinical Center parking garage will undergo a 6-week testing phase as part of a multimillion dollar repair project to counteract deterioration caused by years of road salts. Road salts have penetrated the concrete and corroded reinforcing bars in parts of the facility. A total of 66 parking spaces will be displaced during the trial period scheduled to last from mid-February through the end of March. Concrete in the test areas will be removed by hydrodemolition, a state-of-the-art method using high pressure water jets. This method generates noise and water, but less vibration and dust than traditional chipping hammers. The areas directly beneath the concrete removal sites will be blocked off, and dust barriers erected. This work is scheduled to be done between 7 a.m. and 3:30 p.m. Appropriate safeguards will be placed to minimize disturbance to CC operations, patients and employees, as well as to protect automobiles and utilities from damage.

Construction for the full-scale repair project should begin approximately in mid-1994. Additional information and more details will be provided as available.

**NIDR Mourns Barbara DeGraff; Worked in Same Lab 17 Years**

Barbara Anne DeGraff, a secretary at NIDR, died after a long battle with breast cancer last Nov. 4, at her home in Rockville. The Washington, D.C., native had worked at NIDR for 17 years.

She joined NIDR's Laboratory of Biological Structure (now called the Laboratory of Cellular Development and Oncology—LCDO) in 1975. In 1981, she became the laboratory's senior secretary, and served four chiefs through its many reorganizations.

Dr. Marie Nylen, the laboratory chief who hired DeGraff, said, "From the very first day, Barbara demonstrated the qualities that made her such a valuable employee. She was a hard worker, a quick learner, and always helpful and pleasant even under the most difficult circumstances."

A former chief of the laboratory, Dr. Arthur Hand, commented, "Barbara was a unique person. She was quiet, but strong and intelligent. She always had a kind word, and made life a little nicer for everyone. We will all miss her."

NIDR recognized DeGraff's exceptional skills, high quality work, and administrative abilities by honoring her with a special achievement award, cash award, and many quality increase awards.

"Barbara's willingness to serve beyond the required standards, her attention to details, and her kind consideration for all were invaluable to me when I served as acting chief of the lab. I count it a blessing to have had this good fortune and to have had Barbara as a friend," said Dr. John Folk, chief of the enzyme chemistry section in LCDO.

Dr. Keith Robbins, the current chief of the laboratory, recommended DeGraff for a cash award for helping the office staff during her illness. She continued to work at home and in the hospital, communicating by telephone to provide guidance and training to a clerk-typist who had assumed her duties. Robbins remarked in his recommendation, "The dedication she has shown toward the laboratory while ill continues to be an inspiration to all of us."

For the last year, Carol Walker, a clerk-typist in the laboratory, worked closely with DeGraff. "Her lovely personality and her sharp sense of humor were an inspiration to me and to all who knew her," said Walker. "She will live in our memories."

DeGraff is survived by four daughters, Kelly Lynn, who works at NIDR, Leslie Alfreda, Stacey Anne, and Cori Michelle DeGraff; two grandsons, Kevin Heath and Trevor Foster; three sisters, Alfreda Simmons, Shirley Ellis, and Lillian Hadley; and a brother, Junius Johnson.

Services were held at the Lee Memorial A.M.E. Church in Kensington and burial was at Ash Memorial Cemetery in Sandy Spring. The family asks that expressions of sympathy be made to the American Cancer Society.

**Medical Arts, Photography Branch Holds Open House**

Do you need professional-looking slides for a presentation you are planning? Do you need an attractive announcement to advertise a meeting you are organizing? Do you need photographic work or a medical illustration prepared for your research project?

If you answered yes, but do not know where to turn, check out the Medical Arts and Photography Branch's (MAPB) open house on Tuesday, Jan. 26. The branch, part of the National Center for Research Resources, can meet almost any need you might have for photography, medical illustration, brochure design, video work and exhibit design, to name a few. The open house will run from 1 to 4 p.m. and feature five concurrent demonstrations throughout the afternoon. They include computer-aided graphic design; converting data to charts, graphs, and slides; exhibits on the go; the latest in video and medical illustration; and multi-media slide shows.

The MAPB is located on the B2 level of Bldg. 10. For more information, contact Bill Hall, 496-1144. The program is sponsored by the NIH public affairs forum committee.
Cable TV Series Approaches NCNR for Premiere

The National Center for Nursing Research will be featured on the first show of Nursing Approach, CNBC Cable TV’s new nationally distributed program about the issues and activities of nursing. NIH director Dr. Bernadine Healy appears on the show with Dr. Ada Sue Hinshaw, NCNR’s director, and Dr. Mary Lucas, acting chief of NCNR’s Extramural Division, who discuss areas of research funded by the center. Healy talks about NCNR’s contribution to the NIH community and the importance of nursing research to people’s health nationwide. The interviewer is NIH’s Dr. Marianne Chulay, clinical nurse specialist with the critical care nursing service at the Clinical Center.

Nursing Approach is a half-hour show produced by Sigma Theta Tau International, the honor society of nursing leaders, and Samuel Merritt College’s Studio Three Productions of Oakland, Calif. The premiere program airs in January 1993 each Saturday and Sunday at 1 p.m. Afterward, each show will air on Sundays only throughout the year. The program is divided into 15 minutes of news, which changes biweekly, and a 15-minute feature, changing monthly.

According to Hinshaw, “This program provides nursing with visibility and a new way to communicate, as well as an audiovisual historical record. And nursing research funded by the NCNR is certain to be an important part of that record.”

The NCNR looks forward to a continuing association with Nursing Approach, one that will help keep the nation’s 2.1 million nurses and the public informed about nursing research findings, she added.—Linda Cook

MIT Genome Center Uses New Technology to Map Entire Genome

The human genome center at the Whitehead Institute for Biomedical Research and the Massachusetts Institute of Technology (MIT) is gearing up to construct low-resolution physical maps of the entire human genome. Physical maps are made by matching up overlapping segments of cloned DNA in order to generate progressively longer sets of DNA pieces, which can represent an entire chromosome. Since the beginning of the human genome project, researchers have only been able to construct physical maps one chromosome at a time. But the recent development of improved and more automated technologies for generating physical maps has now led the Whitehead-MIT researchers to attempt the procedure on all of the 24 different human chromosomes at once.

The National Center for Human Genome Research is awarding a grant to renew and expand the work of Dr. Eric Lander and his colleagues. These researchers have already developed and tested techniques for genome-wide mapping when they constructed another type of map, known as a genetic linkage map, covering the entire mouse genome. The new grant, which will total $8.3 million in the first year, will apply these techniques to completing genetic linkage and physical maps of the mouse genome. It will also take advantage of newly developed DNA clones called “mega-YACs” to construct a low-resolution physical map of the entire human genome.

“Progress in physical mapping has been greater than we expected in our planning for the human genome project,” says NCHGR deputy director Dr. Elke Jordan. “It is prudent for us at this time to take full advantage of newly developed mapping technologies to speed the project along so the tools can be delivered to the scientific community as quickly as possible.”

Work on both the mouse and human genomes will allow scientists to compare information about the functions of genes in the two species. The mouse genome, for example, is more than 90 percent similar to that of the human, and many regions are essentially identical. Also, most mouse genes carry out functions identical to their counterparts in humans. Relating knowledge from mouse studies to human depends on the ability to identify and isolate a gene associated with a disease in mice and then looking for that gene’s counterpart in humans.

The genome center will have components at Whitehead, MIT, France’s Centre d’Etude du Polymorphisme Humain, Princeton University, and the Jackson Laboratory.

Maps of the Mouse Genome

Lander and his coworkers will continue to refine the genetic linkage map of the mouse genome by generating 6,000 DNA sequence-based markers, called simple sequence length polymorphisms (SSLPs), which will be spaced an average of 300,000 base pairs apart. Such a set of markers will allow scientists to quickly locate individual genes and provide them with better tools to tease apart the contributions of several genes may make to a single trait or disease.

SSLPs from the genetic linkage map will also provide continuity with the physical map of the mouse genome. The Whitehead-MIT center group will develop a YAC, or yeast artificial chromosome, library of cloned DNA from the mouse genome and order those clones using 10,000 sequence-tagged sites (STSs). STSs are short, unique stretches of DNA that can be detected by polymerase chain reaction. Because an SSLP can also serve as an STS, they will be used to tie information from the genetic map with that of the physical map. And because physical maps represent actual pieces of cloned DNA, the maps can provide genetic hunters with the exact piece that contains their gene, once its location has been flanked by markers on the genetic linkage map.

The recent successes using YAC technology to construct large-scale physical maps have led the Whitehead genome center to expand and apply its whole-genome methods to the human.