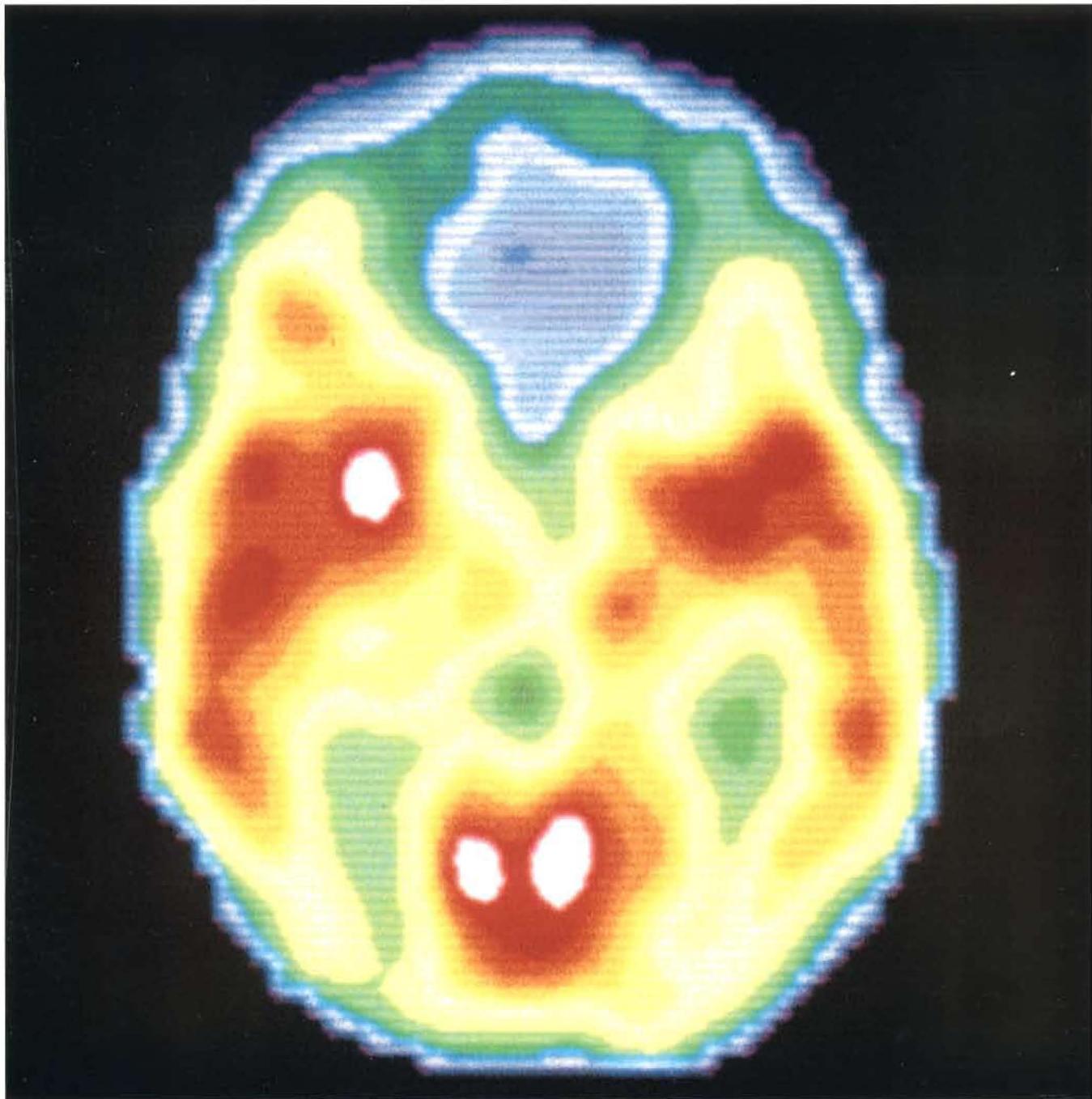


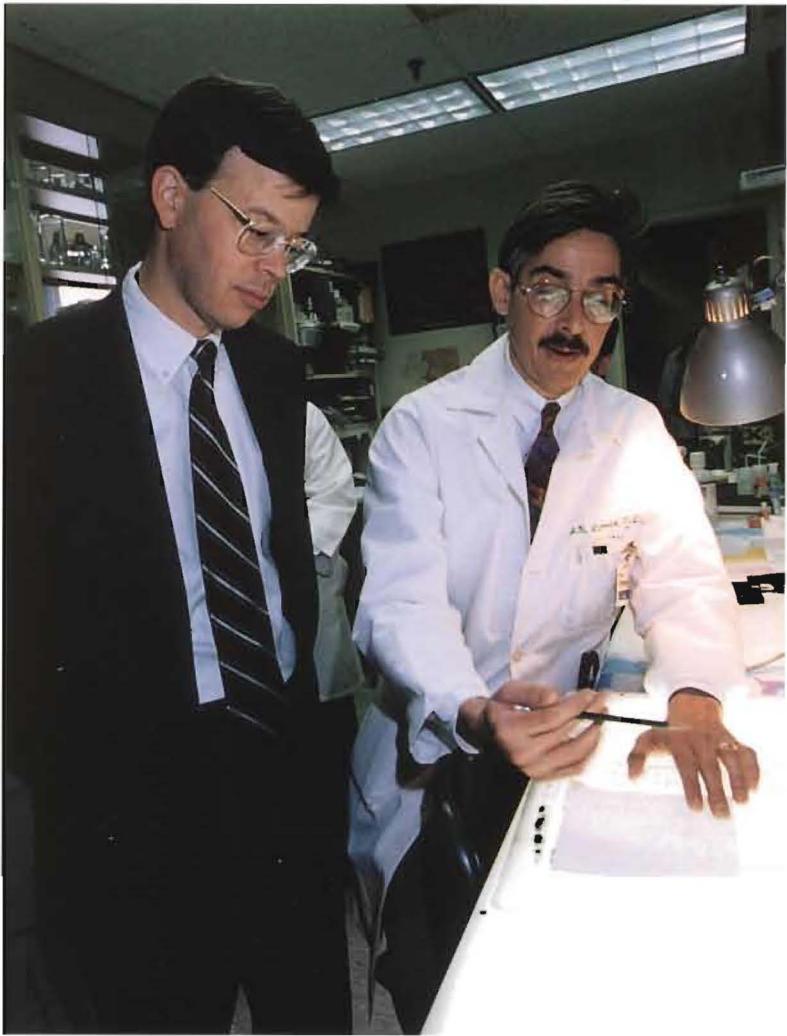
Outlook

Washington University School of Medicine

Summer 1995



Overcoming OCD Brain Injury HIV Trickery



U.S. Representative Jim Talent, left, learns about the underlying causes of autoimmune disorders such as lupus and arthritis from James Lefkowith, M.D., associate professor of medicine. Talent visited the School of Medicine campus in April at the invitation of the Eastern Missouri Chapter of the Arthritis Foundation. In addition to Lefkowith, he met with key administrators of the medical school and the arthritis foundation to discuss the importance of federal funding for basic research related to arthritis and other autoimmune diseases.

Outlook

Washington University School of Medicine



Page 16



Page 8

THE COVER

The image reveals the affected areas of the brain six days after the rupture of an aneurysm. The purple area denotes tissue that has died from lack of blood flow. A new PET study is enabling researchers to evaluate brain injury sooner — during the critical first hours after the event, when most of the damage occurs. As a result, they hope to intervene and prevent or minimize permanent damage before it happens. For more on the study, see the story beginning on page 12.



Page 24

FEATURES

To Speak and Understand..... 8

CID researchers find that cochlear implants help profoundly deaf children learn language skills.

Looking Into Brain Injury 12

A collaborative PET study will allow researchers to evaluate and intervene within hours of brain injury.

Over and Over and Over Again 16

Obsessive compulsive disorder can consume lives, but help is available.

The Nasty Bug 20

Researchers follow the evolution of the NEF gene, critical to HIV invasion of human cells.

DEPARTMENTS

People 2

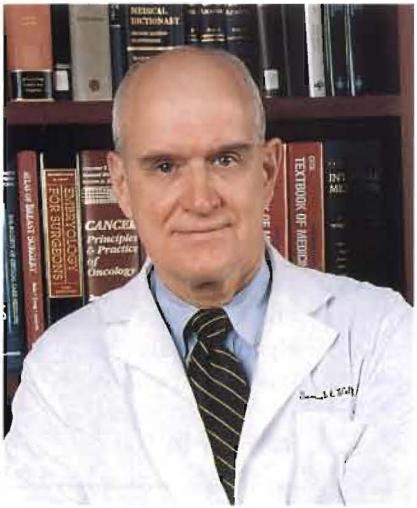
Events 4

Research 6

Student Stage 24

Reunion 1995 27

Wells To Preside Over Surgical Association



Samuel A. Wells, Jr., M.D.

SAMUEL A. Wells, Jr., M.D., Bixby Professor of Surgery and head of the Department of Surgery, has been elected president of the American Surgical Association.

Wells was elected to the post by a vote of the organization's members during the association's 115th annual meeting, held in April in Chicago. He will serve as the association's president and chief executive officer for one year and

also will preside over next year's annual meeting.

Two other Washington University surgeons have served as president of the association: Evarts A. Graham, M.D., former head of the Department of Surgery, and Eugene M. Bricker, M.D., professor emeritus of the division of general surgery. Wells is known for his research and clinical expertise in oncology and endocrinology. He has been particularly interested in cancer genetics, and last year he and his collaborators at the School of Medicine developed a genetic test that accurately identifies individuals who have inherited a certain type of thyroid cancer. Surgery to remove the thyroid gland in affected family members prevents the development of thyroid cancer.

Wells has been a member of the American Surgical Association since 1976. He also is a fellow of the American College of Surgeons and serves as vice-chairman of its Board of Regents. He is editor-in-chief of the *Journal of the American College of Surgeons*. ●

Klahr To Council

SAULO Klahr, M.D., John E. and Adaline Simon Professor and vice-chairman of the Department of Medicine, has been appointed to the National Diabetes and Digestive and Kidney Diseases Advisory Council (NIDDK).

Donna Shalala, U.S. Secretary of Health and Human Services (HHS), appointed Klahr, who also is chief of medicine at Jewish Hospital, to the council. The body makes recommendations about the study and treatment of kidney disease and diabetes to HHS, the National Institutes of Health and the NIDDK. ●

Robert L. Kroc Professorship

PAUL Allen, Ph.D., professor of pathology, has been named the Robert L. Kroc Professor of Pathology.

Allen, who joined the School of Medicine faculty in 1985, studies how the immune system distinguishes between "self" and "non-self," and how immune system disturbances can lead to autoimmune diseases such as diabetes, rheumatoid arthritis and multiple sclerosis.

The endowed professorship was established in 1985 to support biomedical research in diabetes and endocrine diseases. It is funded by the late Ray A. Kroc, founder of McDonald's Corp. The endowment is named for his brother, Robert L. Kroc, M.D., in recognition of his accomplishments as a university teacher and pharmaceutical researcher.

Allen is the second recipient of the Kroc professorship. Paul E. Lacy, M.D., Ph.D., former head of the Department of Pathology and now professor emeritus of pathology, was the first. ●

Wynder Prize For Preventive Medicine

FOUR fourth-year medical students received the first annual Wynder Prize for Preventive Medicine in April.

Krista Johnson and Jonathan Primack received the award for work pertaining to tuberculosis that was done between their first and second years of medical school. The two performed skin tests on psychiatric inpatients and outpatients and found a 10 percent rate of PPD positivity, which was much higher than expected. They also tested negative pressure isolation rooms in 10 St. Louis area hospitals and found that nearly half worked improperly or did not work at all.

Bobbi Hawk and Douglas Pogue received the award for their work in 1992 on the Reproductive Health Education Project. The two worked with teachers, community leaders and parents to develop a pilot curriculum for the Ferguson Middle School to address anatomy, physiology, sexually transmitted diseases, contraception and relationships and self-esteem. Their pilot project has grown significantly so that now some 350 Ferguson Middle School students receive reproductive health education instruction each year.

Ernst Wynder, M.D., a 1950 Washington University alumnus, established the prize. ●

Korsmeyer Elected

STANLEY J. Korsmeyer, M.D., professor of medicine and pathology, has been elected into the National Academy of Sciences, one of the highest honors that can be accorded a U.S. scientist.

Korsmeyer, who is chief of the division of molecular oncology in the departments of medicine and pathology and an investigator of the Howard Hughes Medical Institute, is known for his groundbreaking research on the genetic control of programmed cell death, a process in which cells are genetically predestined to die at a strategic time. Programmed cell death is known to occur as a normal part of human development. In recent years, Korsmeyer and other researchers around the world have discovered that programmed cell death plays an important role in many human diseases including cardiovascular conditions, Parkinson's disease and autoimmune disorders.

His laboratory has identified several genes that prevent and initiate programmed cell death. In 1985, he and his colleagues identified a new cancer-causing gene called *Bcl-2*, referred to as a "cell savior" for its ability to block programmed cell death. Korsmeyer has found that *Bcl-2* may be linked to lymphomas. The group later discovered another gene, called *HOX11*, which is involved in development of T cell leukemia. In recent years, he and his colleagues have uncovered several other genes, *Bax* and *Bad*, that promote cell death and regulate the balance between cell proliferation and cell demise.

Established in 1863, the National Academy of Sciences is a private organization of scientists and engineers dedicated to furthering science and its use to benefit the public. ●

Shile Receives Radiology Fellowship



Peter E. Shile, M.D.

PETER E. Shile, M.D., assistant professor of radiology at Washington University's Mallinckrodt Institute of Radiology, has received the GE-AUR Radiology Research Academic Fellowship.

Co-sponsored by General Electric Medical Systems and the

Association of University Radiologists, the two-year fellowships support approved research projects and encourage young investigators to pursue careers in radiology research.

Shile's research focuses on the evaluation of digital display technologies in mammography. He currently is collaborating with scientists in MIR's electronic radiology laboratory to improve diagnostic accuracy in mammography by developing new ways to process and display image information in mammograms.

Shile will receive a \$50,000 annual stipend for his project. ●

Honors To Goate For Alzheimer's Research



Alison M. Goate, D.Phil.

ALISON M. Goate, D.Phil., associate professor of psychiatry and genetics, is one of four scientists to receive a Metropolitan Life Foundation Award for Alzheimer's disease research.

Goate is internationally known for her discovery of the first genetic mutation linked to an inherited form of Alzheimer's disease. Working with John Hardy, Ph.D., of the University

of South Florida, Tampa, in 1991, she found a mutation in the amyloid precursor protein (APP) gene on chromosome 21. The gene produces beta-amyloid protein, the protein found in the senile plaques and neurofibrillary tangles that form in the brains of Alzheimer's victims.

The specific abnormality identified by Goate was connected to inherited cases of early-onset Alzheimer's disease which affects members of particular families before the age of 60.

Goate's discovery has led researchers to look for additional genetic abnormalities that could be linked to other subtypes of Alzheimer's disease. ●

Mark Wrighton Assumes Chancellor's Office

ON JULY 1, 1995, Mark S. Wrighton, Ph.D., officially became Washington University's 14th chancellor. Wrighton succeeds retiring Chancellor William H. Danforth whose tenure at the University's helm spanned 24 years.

Wrighton, 45, comes to Washington University from the position of provost and chief academic officer at the Massachusetts Institute of Technology (MIT). He was named to the post of chancellor on April 10 after a yearlong, nationwide search that began after Danforth announced his intention to retire.

"Washington University is most fortunate to find a person like Mark Wrighton to continue the tradition of strong leadership among its chancellors — leadership that has guided our emergence as one of the world's great teaching and research institutions," said William M. Van Cleve, chair of the search committee and of the Board of Trustees. "In our search, we sought a leader who could help us chart a course through the many challenges facing higher education in the next few years. Mark Wrighton is the person to accomplish that."

After reviewing hundreds of nominees, the search committee unanimously recommended Wrighton, and the board unanimously supported that recommendation. "We looked long and hard for a worthy successor to Bill Danforth," Van Cleve said.

"It is an honor to be selected the next chancellor of Washington University. I am mindful of the trust placed in me, and I pledge to do my

very best to demonstrate that the confidence in me is well-placed," said Wrighton on the occasion of being named chancellor. "Succeeding Bill Danforth as chancellor is a special privilege, and I look forward to his wise counsel in the years ahead."



Mark S. Wrighton, Ph.D.

Danforth congratulated the search committee "for finding and selecting someone of Mark Wrighton's excellent qualifications," saying that Wrighton "is a wonderful choice whose experience with faculty, students, staff, trustees, alumni and friends at MIT will serve Washington University well."

Wrighton has been provost at MIT since 1990, overseeing the institution's \$1.1 billion budget and coordinating the five-year planning process. He headed MIT's education

and research programs, and he has emphasized the value of teaching in a research university and the strengthening of undergraduate education. Wrighton led efforts to expand environmental education and research programs and worked to build diversity within the faculty.

He joined the MIT faculty in 1972 and became a full professor at the unusually young age of 28. Considered one of the nation's leading young scientists, Wrighton holds 14 patents. Within his field of chemistry, he explored ways to mimic the photosynthesis of plants and to tailor the optical, wetting and catalytic properties of surfaces. He earned a B.S. in chemistry from Florida State University, then went on to California Institute of Technology where he completed his doctorate in chemistry at the age of 22.

An outstanding teacher, he has received prizes for both graduate-level and undergraduate teaching at MIT. He also is recognized for his public service to government, serving the Air Force Office of Scientific Research, Sandia Laboratories, Department of Energy,

Oak Ridge National Laboratories, National Science Foundation, National Research Council and other bodies.

Wrighton, now divorced, has two children, James, 17, and Rebecca, 14, both of whom attend school in Boston. ■

Editor's note: A more complete article about Chancellor Wrighton will appear in an upcoming issue of Outlook.

Slowing Spread Of Disease

THE School of Medicine will play a leading role in establishing a regional center to train healthcare professionals to detect, treat and prevent sexually transmitted diseases.

The St. Louis STD/HIV Prevention Training Center is funded by a five-year \$2.1 million grant from the federal Centers for Disease Control and Prevention in Atlanta. The grant was awarded to the St. Louis County Department of Health, in partnership with the School of Medicine and the City of St. Louis Department of Health and Hospitals.

The School of Medicine will receive \$1.48 million of the grant to establish and maintain training center operations, says Bradley Stoner, M.D., Ph.D., assistant professor of medicine and anthropology, and the project's medical director.

Nine other U.S. sites were selected to offer regional training centers as part of a federal program to slow the rise in sexually transmitted diseases such as AIDS and syphilis. The St. Louis center will serve healthcare workers in Missouri, Iowa, Nebraska and Kansas.

"This is an outstanding opportunity for Washington University faculty to serve as experts in STD/HIV training," Stoner said. "It certainly raises the visibility of the School of Medicine and the St. Louis area as an important national site for STD training and research. We hope that the center serves to raise awareness of the importance of STDs as a major public health threat."

The local project also will involve the University of Missouri-St. Louis and St. Louis University. Training courses will begin in 1996. ●



Chris Garner, a student at Kirkwood High School, is interviewed by Channel 4 News as he leaves a workshop sponsored by the medical school's Students Teaching AIDS to Students (STATS) program. At the workshop, held in March, Garner and other student leaders from 70 area high schools discussed HIV biology, transmission, prevention and potential treatment strategies. The goal of the program is to encourage the students to implement AIDS awareness projects in their communities.

Any Innovative Ideas?

THE BJC Health System is offering grants for projects that investigate ways to improve healthcare within the BJC system through a new program called the BJC Innovations in Healthcare Program.

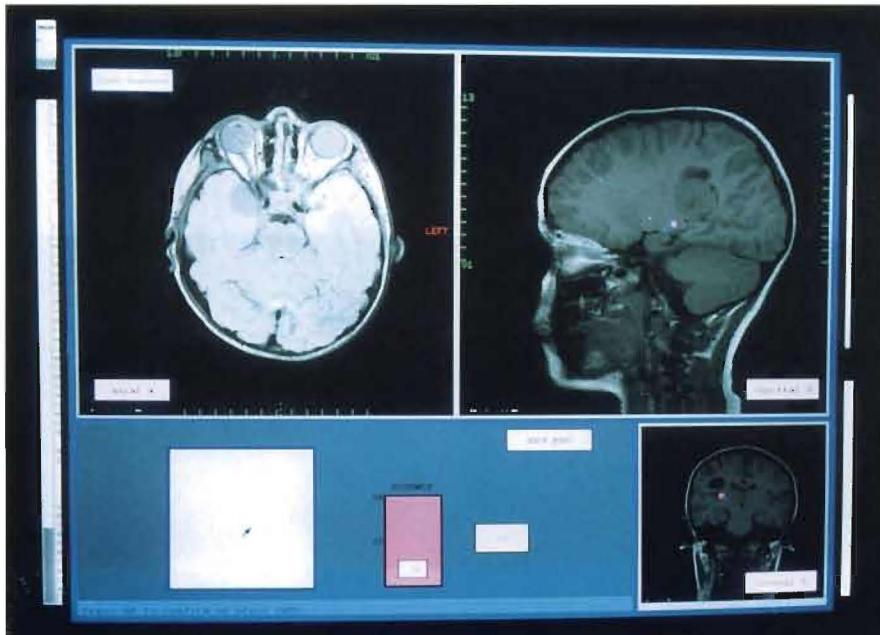
The program will consider projects designed to improve coordination of clinical services, to test innovative approaches to patient care (including new therapies or diagnostic procedures) or to increase the efficiency of system operations by improving quality or lowering costs. It is open to all BJC employees as well as School of Medicine faculty and staff involved with clinical operations at BJC.

Those interested in applying for grants must obtain an application packet and submit a proposal. A maximum of \$20,000 will be awarded for individual projects. Projects must be completed within 18 months.

Applications are reviewed based on the following standards:

- The proposed project should be consistent with the goal of the program, which is to improve the value of BJC's healthcare delivery.
- There should be scientific validity to the study (a clearly defined project with a measurable outcome).
- Innovative change should be the goal.
- The study should be feasible and have the likelihood of completion or implementation at BJC. ●

A New Concept In Brain Surgery



MRI images show the position of a rice grain-sized magnet (pink dot) which carries medications or sources of radiation through the brain. Surgeons use the images to plan brain surgery and navigate through the brain.

THE School of Medicine has entered into an agreement with Stereotaxis Inc. to test a computer-controlled magnetic system for delivering therapeutic agents to the brain.

"This technology will be a minimally invasive, more efficient and safer way of doing brain surgery," says Ralph G. Dacey Jr., M.D., professor and head of neurological surgery. Dacey will direct the research team, which will include collaborators from the University of Iowa, the Medical College of Virginia and the University of Washington.

The Magnetic Stereotaxis System (MSS) should improve treatments for brain tumors, Parkinson's disease and other neurologic disorders. The technology is being tested in gel models of the brain and should be ready for human trials in 12 to 18 months. Stereotaxis holds exclusive worldwide patent rights.

The major advantage of the magnetic system is that it will allow neurosurgeons to move precisely through the brain in any direction, avoiding sensitive areas that may lie between the surface and the area to be treated. Non-linear movement is possible because magnetic fields guide a rice grain-sized magnet that pulls a small implant containing drugs or sources of radiation.

The research will focus initially on improving treatments for malignant brain tumors.

Magnetic tumor surgery will allow a flexible radioactive catheter to be coiled into the tumor so that gamma rays can kill the tumor cells. The insertion will take one to two hours and potentially could be performed on an outpatient basis. The patient will return a few days later to have the implant magnetically removed.

BJC Health System will support the research and house the device in Barnes Hospital. ●

A New And Improved PSA

A NEW version of a common screening test for prostate cancer can more accurately predict which patients have cancer, according to a study by School of Medicine researchers. The updated test should enable many men with benign prostate conditions — for whom the traditional screening test often incorrectly indicates cancer — to avoid unnecessary follow-up biopsies.

The test can reduce up to 75 percent of unnecessary biopsies and still detect 90 percent of prostate cancers, says lead investigator William J. Catalona, M.D., urologic surgeon and head of the division of urologic surgery.

The new test, which is still experimental, may ultimately prove to be a major cost savings. A prostate biopsy costs about \$1,200.

The traditional prostate cancer screening test detects total blood levels of prostate-specific antigen (PSA), a protein produced by the prostate. Elevated levels are a possible indicator of cancer, which then must be confirmed by biopsy.

Critics of the PSA test point to its high rate of false positives. For every three men with elevated PSA levels who undergo a follow-up biopsy, only one patient is found to have cancer. A non-cancerous condition called benign prostatic hyperplasia (BPH), commonly found in older men, can also cause PSA levels to rise.

The new test better distinguishes between men with prostate cancer and those with BPH, the researchers found. The test measures blood levels of a free-floating form of PSA. For unknown reasons, men with prostate cancer have significantly lower levels of this "free" PSA compared to men with BPH, says Catalona, who pioneered PSA testing for prostate cancer. ●

FDA OKs Herpes Test

A NEW diagnostic test for the herpes simplex virus, developed at the School of Medicine, has been approved by the federal Food and Drug Administration. The new test is faster and easier to use than current diagnostic tests for the herpes virus.

Genital herpes is one of the most common sexually transmitted diseases in the world. Up to 500,000 Americans are newly infected with genital herpes every year. The test detects both herpes simplex virus Type 2, which typically causes genital herpes, and herpes simplex virus Type 1, which is most commonly associated with cold sores on the face and mouth.

The test was developed by Paul Olivo, M.D., Ph.D., an assistant professor of medicine and molecular microbiology. The test was licensed in 1994 to Diagnostic Hybrids Inc., a company in Athens OH. FDA approval gives Diagnostic Hybrids the go-ahead to commercially market the test.

The new test takes up to 18 hours to get conclusive results, compared with the gold-standard herpes test which can take up to a week. The test's speed helps ensure that patients infected with the virus will receive effective treatment quickly.

It also will enable physicians to confirm a herpes diagnosis faster and will be especially important in the quick diagnosis of neonatal herpes infection.

The new test theoretically could be modified to detect any type of virus and may be used to identify patients who have developed drug-resistant herpes infections. •

A Dark Side To Neurotrophins

NERVE growth factors promote the survival and differentiation of neurons, but certain growth factors, called neurotrophins, have a sinister side to their nature and can cause nerve cells to die.

The finding raises a cautionary note about the potential use of neurotrophins against brain disorders such as Alzheimer's disease, Parkinson's disease and stroke, says Dennis W. Choi, M.D., Ph.D., Jones Professor and head of neurology, who led the study.

Cultured mouse neurons die if they are briefly deprived of oxygen and glucose. These conditions mimic ischemic stroke, in which a clot stops blood flow to a region of the brain, cutting off the supply of these essential substances. But more

cultured cells died when a neurotrophin was present, the researchers found. A day after the deprivation, fewer than 20 percent of the control cells were dead, but about 50 percent of the cells exposed to a neurotrophin had disintegrated.

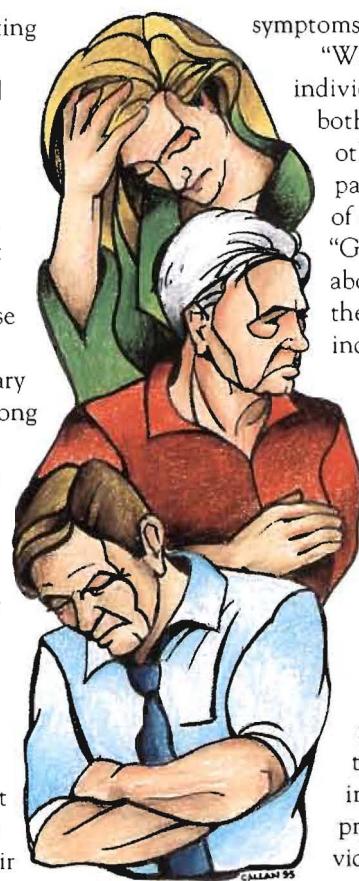
Discovering how the factors sabotage cells will be an essential first step toward explaining the results. Neurotrophins enhance necrosis via a glutamate receptor called the NMDA receptor. When an antagonist called MK-801 occupied these receptors, calcium ions did not invade the neurons, and the factors were no longer harmful. But antagonists of other types of glutamate receptors were not protective.

The researchers tried all four known neurotrophins in these experiments. •

No Two Chest Pains Are The Same

DOCTORS treating patients with chest pain need to pay more attention to how bothered patients are by their symptoms, says Robert Nease, Ph.D., assistant professor of medicine. Results of a study Nease conducted show that attitudes about pain vary substantially, even among patients with similar severities of angina, or chest pain, caused by heart disease.

Nease says standard guidelines for treating angina are primarily based on objective measurements of disease severity. However, those guidelines do not take into account how patients feel about their



symptoms of pain and discomfort.

"We found that some individuals are much more bothered by their pain than others — even among patients with similar levels of symptoms," Nease says. "Guidelines are often silent about the importance of the preferences of the individual patient."

One of the main benefits of treatment for angina is to reduce pain and discomfort. So, finding the best treatment should depend, in part, on how bothered each patient is by his or her symptoms, he says.

"Good decision-making should respect both the best available scientific information and the preferences of the individual patient," he says. •

To Speak and Understand

Study shows cochlear implants help the profoundly deaf learn language skills faster, better.

by Juli Leistner



Dorie Shapiro, age seven, reads aloud.

In classroom after classroom at Central Institute for the Deaf, small groups of children sit face to face with their teachers, being taught a skill that very few profoundly deaf children have the opportunity to learn: how to speak.

In most ways, this school is like any other elementary school; classrooms and hallways showcase colorful children's art, students expend boundless energy in the kid-sized gymnasium, and, outside of class, children laugh and talk with friends.

But there are a few differences. Central Institute for the Deaf (CID) is one of about two dozen schools in the country where deaf children are taught to speak. Because profoundly deaf children cannot hear what speech sounds like, they do not learn to talk the same way normal-hearing children learn — by mimicking the sounds of others. Instead, they need years of specialized, one-on-one training, which CID provides.

The Institute's 100 students, ages three to 15, are immersed in an environment focused on speech. Most classes have only two or three children who receive individualized instruction sitting at small tables with their teachers. The students learn the same subjects that other children their age learn, but, in addition, they spend about half their school day on language training.

"Learning to talk is very hard work for these children," says Jean Moog, M.S., principal of the nationally recognized school. "But even the youngest ones are eager to learn and are willing to work hard."

Recently, Moog and Ann Geers, Ph.D., both associate professors in the University's Department of Speech and Hearing, found a way that may help the most profoundly deaf children learn language skills faster and better. They conducted a study evaluating the benefits of cochlear implants, hearing devices designed for the profoundly deaf, and compared them to other sensory aids in 39 profoundly deaf children.

The researchers followed the progress of the children for three years as they learned language skills and found that those with cochlear

implants understood speech better, spoke more clearly and used speech more often to communicate than children who used other types of sensory aids.

"Cochlear implants seem to provide a dramatic advantage in helping these children learn to speak and understand spoken language," says Geers, director of CID's clinical services and principal investigator of the study. "These results are important to us because the ability to talk opens up options — social, vocational and intellectual — that these children do not have if they don't share a language with their culture."

Nationwide, only about 10 percent of profoundly deaf children learn to speak, largely because of lack of access to the specialized training required.



CID instructor Terri O'Donoghue works with four-year-olds David Browning and Danielle Hinton during speech class.



Alison Cohn and Ryan Slattery, both age four, listen as Jean Moog, M.S., principal of CID, explains an art project.

The researchers say they were interested in cochlear implants as a way to make the learning process easier for the school's most profoundly deaf students. These children get little or no benefit from conventional hearing aids — precisely the type of person cochlear implants are designed to help.

A cochlear implant has an internal unit that is surgically implanted into the inner ear. With the help of an external microphone and a sound processor, the device directly stimulates the auditory nerve to provide sound. "We reasoned that a device that could improve access to sound for our profoundly deaf children would provide an opportunity to get them talking earlier," Geers explains.

Children in the study represented the deafest segment of the population. Some had complete hearing loss, while

others needed the help of an aid to detect sounds of 100 decibels, a sound about as loud as a lawn mower at close range. The children's ages ranged from two to 10 years at the beginning of the study, with an average age of about five and one-half years.

All 39 children in the study previously had worn conventional hearing aids. For the study, 13 children received a cochlear implant; 13 continued to wear their conventional hearing aid, and 13 others wore their conventional aid plus a tactile aid, a device that transmits sound as vibration on the skin.

"After we got into the study, we saw that the children with cochlear implants were doing remarkably well and that comparing them to other children with similar hearing loss would not be stringent enough," Geers says. For an extra comparison, the

researchers collected data from 13 children with slightly less severe hearing loss. This "hearing aid plus" group wore hearing aids but gained substantially more benefit from them than children in the original study groups.

Dramatic Advantage

All of the children in the study progressed, but cochlear implants offered several advantages, including enhancing the ability to hear speech sounds.

Using a series of interactive tests designed at CID, the researchers rated each child's ability to hear speech. At the beginning of the study, most of the children could hear basic speech patterns — the difference between a one-syllable and a two-syllable word. But none could make more difficult distinctions, such as telling the



Jean Moog and Ann Geers, Ph.D., both associate professors in the University's Department of Speech and Hearing, found that cochlear implants help profoundly deaf children speak more clearly and understand speech better than other hearing devices.

difference between words with similar stress patterns (airplane and tooth-brush), or harder still, distinguishing between words that differ only in the vowel (boat and boot).

By the end of the study, most hearing aid and tactile aid wearers had not progressed much beyond their initial ability to hear speech patterns. By contrast, most cochlear implant wearers could distinguish between similar words, such as bear and pear, and were the only group that could identify spoken words without having a set of words to choose from.

Implants also helped children deal with the more true-to-life test of understanding conversational speech. All profoundly deaf children rely on a combination of lip reading and listening to understand speech, Geers explains; this study showed that implants helped children get more information from a speaker's voice. At the end of the study, most children could understand about 56 percent of a spoken message by observation alone. But with sound added, implant wearers understood an additional 12 percent of the message.

Implant wearers did far better than expected for their ages. According to standardized tests, the children started out with average abilities to understand spoken language compared to other deaf children their own age. "If they were to develop normally, we

would expect them all to hover around the same percentile over time," Geers says.

But by the end of the study, implant wearers had jumped to the 85th percentile in standardized tests, while tactile aid wearers scored in the 70th percentile and hearing aid wearers were still in the 55th percentile.

Implants not only helped children understand speech, but helped them produce better

speech as well. "Their voices have more intonation, and their vowel sounds and consonants are more on target," says Moog. "The implants allow them to hear as they learn, rather than learning to speak just from visual cues."

Children with implants also were more communicative. By studying the younger children during play sessions with their mothers, researchers saw that implant wearers initiated communication more frequently, and they communicated more often with speech as opposed to gesturing or touching their mothers.

Overall, cochlear implants seem to make the learning process easier. "The children with implants get less tired and seem to learn with less effort," Moog says.

An Edge In The Classroom

The researchers say cochlear implants could have a big impact in the classroom. One reason: Helping deaf children learn spoken language will help them learn to read. As Moog explains, normal-hearing children become familiar with the basics of English structure and grammar when they learn to speak. With that knowledge base in place, making the transition to reading is relatively easy. But deaf children who do not learn to speak may not acquire this knowledge base.

"Many people think that reading should not be a problem for deaf people because their eyes are not affected. But having a command of English syntax and vocabulary are critical factors in learning to read," Moog says. "Having a spoken English base greatly facilitates learning to read."

Deaf children who learn to speak generally end up able to read at a higher grade level than deaf people who do not learn this skill, Moog adds. Nationwide, deaf adults read at about the third to fifth grade level.

As soon as CID students catch up to their grade level in language, speech and academic skills, they leave the program to attend school in their communities with normal-hearing peers. One of CID's goals is to help this mainstreaming process happen as quickly as possible. CID students with moderate to severe hearing loss usually are mainstreamed during the early grade school years. Children with profound hearing loss require more training and typically are mainstreamed later, in the seventh or eighth grade.

Cochlear implants may enable students to catch up sooner by helping them learn to read faster and better, Geers says. CID already is seeing this trend among its students who wear implants. About 40 percent of CID's students currently wear the devices.

"We are already mainstreaming these children earlier than we would have without cochlear implants. So these devices are really accelerating the progress in our educational program," Geers says.

One of the most satisfying aspects of working at CID is watching graduating students give their required speech at the school's graduation ceremony, Moog says. "When these children are very young, they aren't aware of what they are achieving. It isn't until they get a little older that they realize how hard they have worked and what an extraordinary accomplishment they have made," she says. "And then they are very proud of it." ●

Looking into Brain Injury

*PET Allows
Researchers To
Assess The Brain's
Response To
Treatment*

by Linda Sage

Malcolm Strauss remembers his first wife, Lillian, as vivacious, fun-loving and "as beautiful inside as out." Petite with dark hair and dark eyes, she was a Girl Scout leader and volunteer with several organizations. She appeared to be in perfect health on February 8, 1973, when she met her younger daughter in a St. Louis store. But within her head, a time bomb was ticking. Before the shopping trip was over, a blood vessel had burst, spilling blood into her brain. Lillian Strauss died the next day at the age of 47.

Medical research has conquered smallpox and polio, saved millions of cancer patients and devised organ transplants and a host of new drugs. But patients with stroke and head injury still await a major breakthrough.

"If someone has a stroke right now, there is no medicine or surgery that has demonstrated value," says William J. Powers, M.D., associate professor of neurology and radiology.

Half a million Americans are hospitalized for head injuries each year, including many victims of assault or traffic accidents. Twenty percent of these patients die, and another 20 percent are left with long-term disabilities. Stroke affects 550,000 people each year, killing 150,000. Two-thirds of the survivors suffer long-term disabilities, and half of those have to rely on others for care.

When Powers first encountered stroke patients as a resident in San Francisco, he was not sure he could make a difference. "I realized I could go around for the rest of my life with this uncertainty," he says, "or I could try to figure out what was really going on."

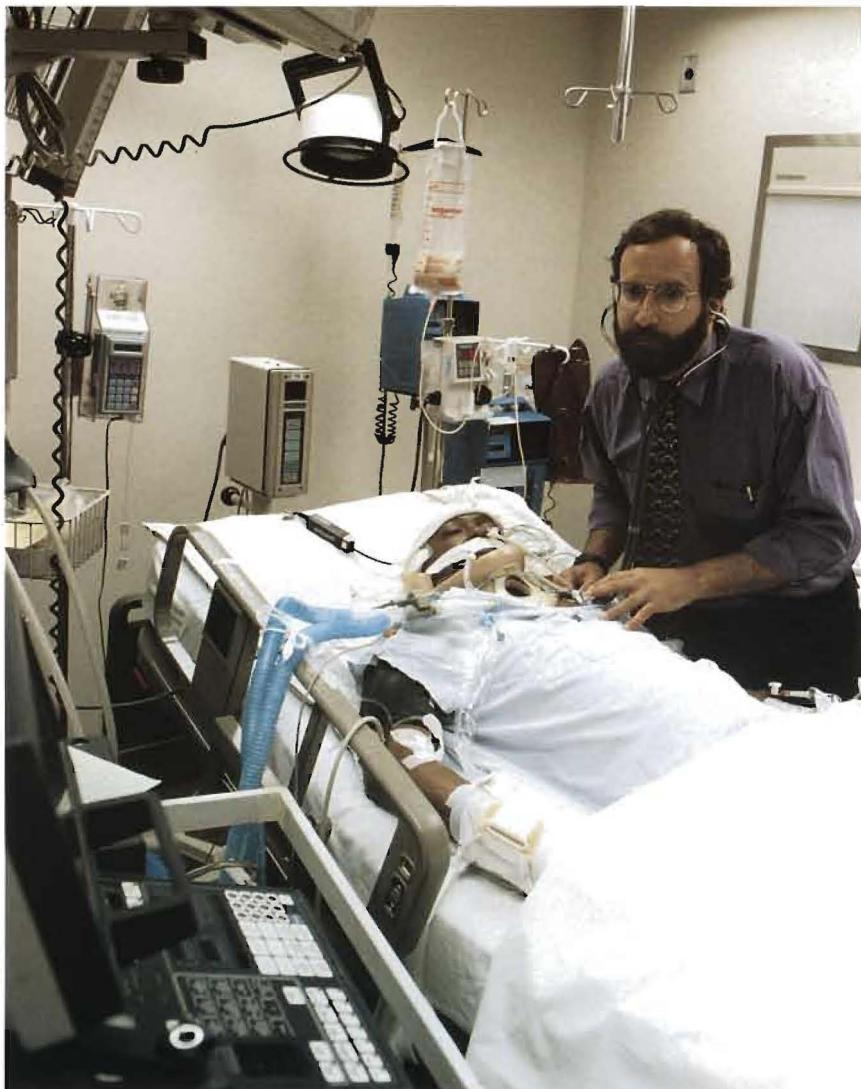
With this goal in mind, Powers heads a collaborative effort between the School of Medicine and Barnes Hospital. Last January, the hospital installed a PET (positron emission tomography) scanner in its neurointensive care unit. This arrangement — the first in the world — will permit researchers to look directly at the brain function of critically ill, brain-injured patients.

"At present, physicians don't have a good way of assessing the brain's response to treatments for neurological damage — we're working with a black box," says Michael N. Diringer, M.D., assistant professor of neurology, neurosurgery and anesthesiology. In 1992, Diringer became director of Barnes Hospital's neurointensive care unit. "I left Johns Hopkins because of this scanner," he says. "The opportunity to do this work seemed so unique."

The project is distinguished by the logistical challenges posed by PET and very ill patients. PET scanners cost about \$2 million and require facilities for generating radioactive isotopes. But Washington University has a long history of PET research — the first usable scanner was developed by Michel M. Ter-Pogossian and colleagues at the University's Mallinckrodt Institute of Radiology in the early 1970s. "Our ability to do this research reflects a happy coincidence of Washington University's previous history of PET research and its infrastructure," says Dennis W. Choi, M.D., Ph.D., Jones Professor of neurology.

Funds from the National Institutes of Health, Barnes Hospital, Washington University's McDonnell Center for Higher Brain Function and the departments of Neurology, Neurological Surgery and Radiology were used to purchase the scanner, which can image the entire brain. "The PET scanner will allow us to more fully understand situations in which acute brain injury occurs, either as a result of physical trauma, such as an auto accident, or after stroke involving ruptured blood vessels. Learning more about these conditions will, in turn, help us to take better care of our patients," says Ralph G. Dacey Jr., M.D., professor and head of neurological surgery.

"It was obvious to everyone concerned that there was a lot to be learned from PET," adds Choi, who also is head of neurology. "We now have reached the point where the goal of treating the acutely injured human brain is in sight. The scanner will provide a pipeline between molecular and cellular advances and improvements in clinical care."



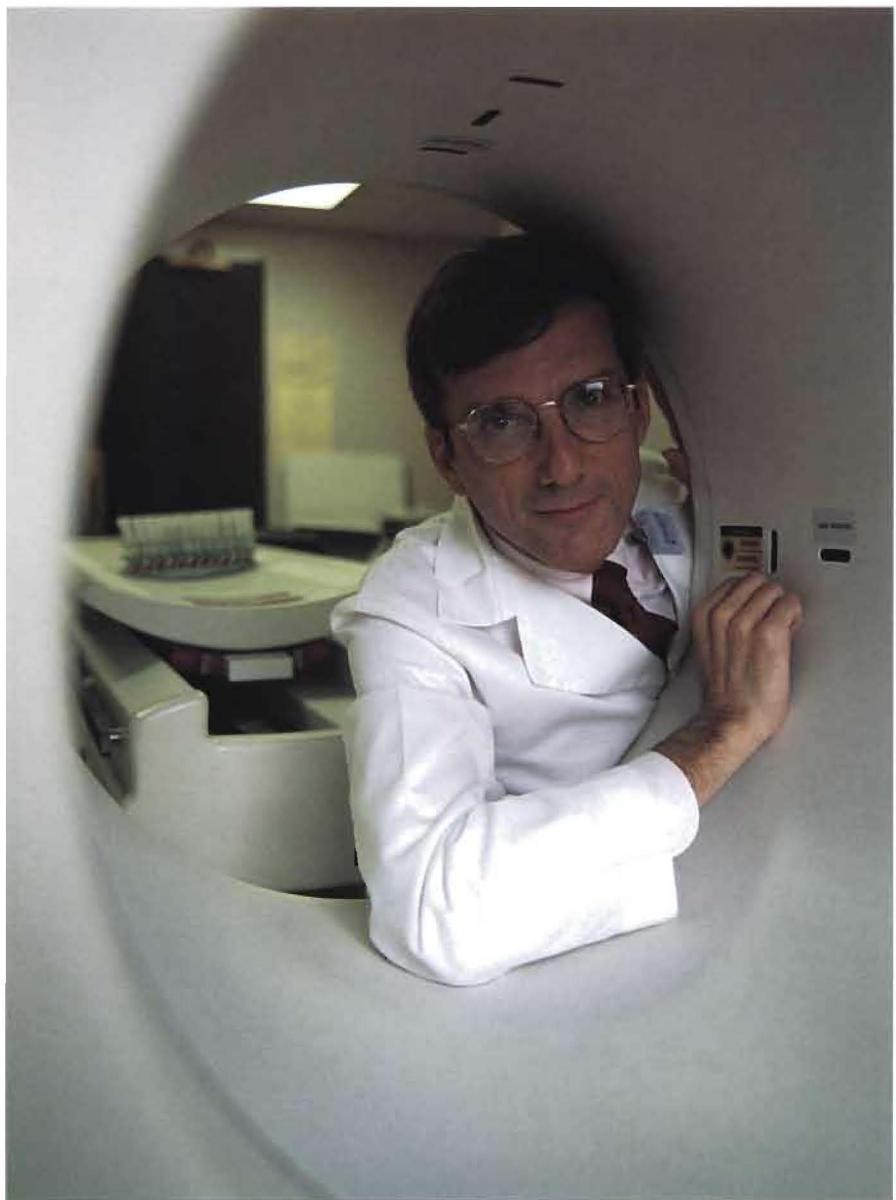
Michael N. Diringer, M.D., assistant professor of neurology and neurosurgery and director of Barnes Hospital's neurointensive care unit, checks on a patient who suffered a head injury.

Barnes Hospital is directing this pipeline to its patients. "This research will be instrumental in enhancing our ability to improve the outcome for patients with stroke or other acute brain injuries" says Jennifer Fallert, the hospital's neuroclinical service line director. "It will allow us to evaluate and improve our therapeutic options." One thousand patients enter the hospital's neurointensive care unit each year, and nearly half have these conditions.

The research requires a scanner in a neurointensive care unit because subjects must receive constant and specialized care. The neurointensive care unit provides the most sophisticated monitoring equipment available. When it was built in 1992, Barnes Hospital set aside space for the scanner. The arrangement allows

images to be obtained during the critical first hours after brain injury, when most of the damage occurs. "Other types of studies have looked at patients a few days after a stroke or head injury," Diringer says. "But we want to look within six hours, when there is a window of opportunity for intervention."

By generating images of blood flow and oxygen use in different parts of the brain, PET can reveal whether an injured region is receiving and consuming nutrients and oxygen. "It is the only way to measure how much oxygen a particular part of the brain is using," Powers says. "It can tell you which parts of the brain are getting as much as they need and which parts are barely hanging on. So it is absolutely the most direct way to figure out what is happening."



William J. Powers, M.D., associate professor of neurology and neurological surgery, peers through the PET scanner used to image the entire brains of persons who have suffered acute brain injury.

Current Treatments: Helpful Or Harmful?

The research, which began in June 1995, initially will focus on how to help the brain heal itself. Two studies will document the changes that occur in the brain after head injury or intracerebral hemorrhage, in which patients with high blood pressure have bleeding into the brain. Clinicians who treat such conditions lack a very basic piece of information — whether damaged regions of the brain run short of oxygen as they do in ischemic stroke, where a clot cuts off blood flow to the brain. "If we find that to be

true, we can apply drugs that are being tried for ischemic stroke to this patient population," Diringer explains. "Right now this is a big issue."

A third study will examine the controversial practice of treating hypertension in patients with intracerebral hemorrhage. "Blood pressure rises when people hemorrhage into the brain," Powers explains. "But if you called three neurologists, you would get three different opinions about how to respond. Some say you should leave blood pressure alone; others say you should bring it down a bit, and others say you should bring it down a lot."

The confusion arises because, while high blood pressure can damage the heart and kidneys, lowering blood pressure may reduce the supply of oxygen to the brain, "which is the last thing an injured brain wants," says Powers. But the PET study will monitor injured parts of the brain as blood pressure is gradually lowered. "This is a problem we face day in and day out, and we agonize over it," Diringer says. "So we would like some guidance."

Patients with subarachnoid hemorrhage — the type of stroke that killed Lillian Strauss — often are given drugs to raise their blood pressure. These patients bleed into the brain through a burst aneurysm, and their blood vessels often go into spasm. Drugs that force blood through those vessels by raising blood pressure can be damaging to the heart, so a PET study will determine whether less harmful drugs also can be effective. More aggressive treatments, such as angioplasty and intra-arterial papaverine, which are now being offered to these stroke patients, also will be examined.

Hyperventilation is a technique used on head injury patients to control pressure inside the head. "But there is a big controversy over whether hyperventilation is harmful or helpful," Diringer says, "because the blood flow to injured parts of the brain may be critically reduced." PET images before and during hyperventilation will show whether blood flow becomes so slow that it places the brain at risk for further damage.

Limiting Damage

These projects should narrow a major gap in our understanding of brain injury and the brain's response to current treatments. But plans to limit brain injury are also in progress. The Center for the Study of Nervous System Injury, headed by Choi, will test compounds that might protect the injured brain from damage by a neurotransmitter called glutamate, which normally is released in discrete amounts during cell to cell communication.

When a neuron runs short of oxygen, it releases its entire stock of glutamate, overexciting receptors on nearby cells. Because these receptors are ion channels, they let in deadly amounts of sodium and calcium ions. But if patients could receive a drug to block the receptors, damage might be curtailed. "Drs. Powers, Diringer and colleagues will use the scanner to guide the application of new neuroprotective strategies — for example, by identifying patients who have brain tissue in jeopardy and could benefit from a neuroprotective treatment," Choi says.

The PET studies will not replace clinical trials which test new therapies on thousands of patients. But they will help determine which new treatments or drugs may be worth evaluating. "We will be able to give therapy X and immediately get a much better understanding of whether that therapy is doing what we want it to do," Diringer says. "So this approach provides an intermediate step between basic research and clinical trials."

Testing these ideas will require funds to pay technicians, maintain a service contract, generate radioactive isotopes and support time-consuming data analysis. When the researchers have sufficient data, they will apply for grants to support ongoing research. Funds from the National Stroke Association, the McDonnell Center for Higher Brain Function and the Lillian Strauss Fund are supporting the preliminary studies.

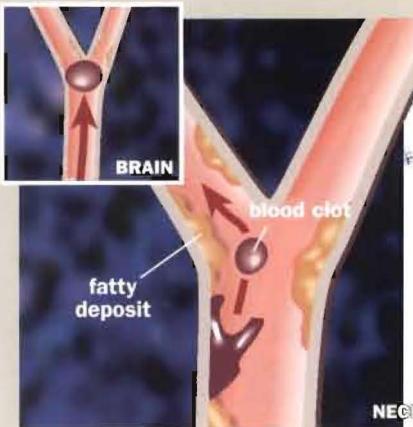
Malcolm Strauss and his two daughters, Stephanie Shuchart and Sandra Lynn Birenbaum, established the Lillian Strauss Fund in 1974. Then for several years, they organized Labor Day bowling contests at Strike 'N Spare Lanes in Creve Coeur to raise additional contributions. They hope doctors will one day be able to save stroke patients and know how to detect aneurysms before they burst. "An aneurysm took away my wife and my daughters' mother," Strauss says. "So we want to stop strokes in time to save lives." ■

A Stroke Primer

Ischemic Stroke: The most common type of stroke (80 percent of cases). Occurs when a blood clot plugs either an artery in the brain or an artery in the neck that carries blood to the brain. The clot may form in the brain itself or may travel to the brain from another part of the body.

Hemorrhagic Stroke:

Bleeding into the brain caused by either high blood pressure (intracerebral hemorrhage) or the rupture of a weak-walled blood vessel (subarachnoid hemorrhage).



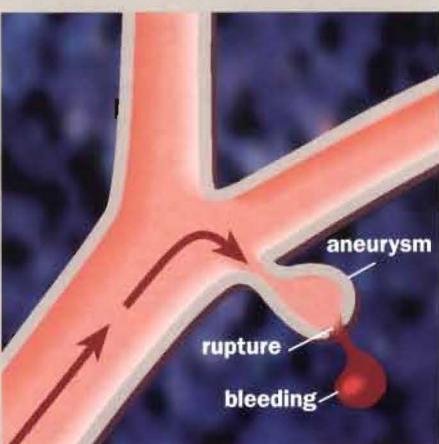
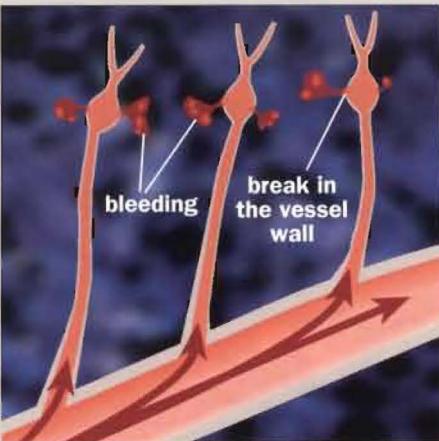
Symptoms Of Stroke:

- One-sided weakness, numbness or paralysis
- Blurred vision
- Problems speaking or understanding
- Dizziness or loss of balance
- Sudden, severe headache

Public Awareness:

A recent survey by the American Heart Association found that Americans are dangerously ignorant about stroke:

- Almost half of those surveyed did not know a single warning sign of a stroke
- Only 29 percent said they would go to an emergency room or call 911 if they experienced dizziness and loss of vision in one eye for more than 15 minutes



The Aftermath Of Stroke:

- Stroke is the leading cause of serious disability in the United States
- Stroke accounts for half of all patients hospitalized for acute neurological disease
- About one-third of stroke survivors die within the year following the event

Illustrations by Chris Callan

Source: American Heart Association

Over
And
Over
And
Over
Again





Obsessive Compulsive Disorder Takes On A Life Of Its Own

One summer day about three years ago, Carralee Mezo took a drive to Lake Carlyle to see her father, who was camping. Shortly after she got on the road, she met an ambulance headed in the opposite direction. 'Oh, my God. I've caused an accident,' she thought. She turned her car around and followed the emergency vehicle to witness the damage she had caused, but there was none; there was no accident.

Mezo met two more ambulances that day, and each time she felt compelled to turn her vehicle around to go to the scene of what she feared was a deadly automobile accident that she had caused. Both times she was wrong.

What should have been a 45-minute jaunt to see her father turned into an exhausting three-hour ordeal. "I always think that I'm going to cause catastrophe," says Mezo, a 54-year-old St. Louisan who has obsessive compulsive disorder, or OCD. "I would have to go over and over and over things in my mind — I was always checking."

Mezo's disturbing and difficult-to-dismiss thoughts, as well as the repetitive behaviors she performed in response to her thoughts, are typical of people with OCD, says Elliot Nelson, M.D., assistant professor of psychiatry who studies the disorder.

"People with anxiety disorders such as OCD have difficulty with some of the most basic aspects of life that we all take for granted," says Nelson. "They don't have voluntary control over their own thoughts. Thoughts pop into their head and persist to the point of becoming intrusive; their thoughts almost have a life of their own."

The most common types of obsessive thoughts are worries over dirt or germs and those which involve harm, either to the person with OCD or to others. Compulsions that occur in response to these thoughts include washing behaviors and checking rituals such as checking the door lock and making sure the iron or stove is turned off, Nelson says.

Other obsessions and compulsions that are fairly common but less talked about can be frightening when they occur, Nelson says, because they involve thoughts of causing harm to family members.

Mezo says the thought that most haunted her was that she either had killed or was about to kill someone. The first time such a thought came over her was when she was 23 and her eldest daughter was three.

by Kleila Carlson



At one point in her life, Carralee Mezo lived in constant fear she was going to poison someone if she offered them a cup of coffee.

"I love my daughter more than life, but one day she walked through the living room, and I saw her, and I saw a knife," Mezo recalls, the disbelief still apparent in her voice. "I became frozen with fear that I was going to kill her, but I couldn't understand why I would want to kill this child who was my life, that I loved so much."

After 12 months of therapy, Mezo still had no answers. She was advised by mental health experts to "keep busy," which she did for the next 28 years. She had another child (a daughter), went to beauty school and became a beauty school teacher, joined the Junior Women's Club, was a Brownie co-leader, coached a volleyball team, owned two successful beauty salons and was known for her lavish sit-down dinners.

"I had a really full life," says Mezo, who began receiving treatment three years ago. "I've always been a very determined person, so I convinced myself that whatever it was that I had,

I could get over. But I just masked it; it was always there, underlying."

Mezo began to live in constant fear that she was going to poison someone. At her first beauty salon, which she owned for about 15 years, coffee was always brewing, but Mezo hesitated to offer it for fear she would kill her customers. "I wouldn't let them drink a full cup of coffee," she says. "Once I saw that a customer had a few sips, I would say 'that's enough,' and take the cup. Then, I'd keep what they hadn't drunk for a day or two so it could be analyzed to prove that I hadn't poisoned them in case something happened."

She also agonized when left alone with small children and infants. Once, while at the drug store to purchase household supplies, she was certain that she had poisoned a toddler she came upon in a deserted aisle. The toddler, who was toting a bottle in her mouth, began following Mezo down the aisle. Mezo, who had a bottle of

liquid Wisk in her cart, broke out into a sweat, dashed to the checkout counter to pay for her items and ran to her car. All the way home, she tried to tell herself that she had not taken the child's bottle of milk, opened it and poured in liquid Wisk.

"When I got home, I opened the Wisk thinking that if the aluminum cover was over the opening I'd know I didn't get into the bottle," she recalls. "I opened the bottle and the cover was gone. 'Well, OK,' I thought, 'there are 32 ounces in the bottle, so I'm going to have to get a measuring cup and measure it. But I'll have to measure it exactly because it wouldn't have taken very much if I'd put some in that baby's bottle.'"

Although she was able to curb her erratic thoughts by exactly measuring the contents of the Wisk bottle, the first thing she did the next morning was look in the obituary section of the newspaper for the death of a child.

Unquestionably Common

Mezo's fears may seem unfathomable, but Nelson says millions of Americans with OCD have unusual thoughts that linger for hours or days, interfering with their way of life and livelihood.

Once believed to be a rare psychiatric disorder, OCD affects roughly 2 to 3 percent of the U.S. population, or 5 million people. The typical age of onset is late teens to early 20s — sometimes a little earlier in males than in females — and its cause is unknown.

Nelson says that often, people with OCD seek treatment for another illness such as depression or anxiety, not necessarily symptoms associated with OCD. Some 30 percent of individuals with OCD are depressed at the time they seek treatment.

"In general, people with OCD have good insight into their symptoms," Nelson says. "They know that their thoughts sound kind of odd. They don't make sense to the OCD sufferer, so why would they tell someone else about them? Many times they keep the problem to themselves for fear they will be embarrassed or made fun of."

Mezo told no one about her preoccupying thoughts, not even her closest friend of 30 years. "I couldn't tell her what I was thinking, that I thought I was going to kill somebody. You just don't do that," she says.

Although OCD is well described in the medical literature going back to the 17th century, Nelson says many people with the disorder do not realize their unusual thoughts are actually a symptom of an illness. "Unfortunately, when you have a mental illness, there is no direction book," he says. "So, until someone hears about OCD or until we really get the word out to the public, some people will continue to have unusual thoughts and not know why."

Psychiatry is doing its part to increase awareness by screening more for the illness than it has in the past. Using positron emission tomography (PET) to measure brain activity, researchers have homed in on two areas of the brain that appear to be involved in the illness: the frontal lobes, particularly the orbital frontal cortex around the eyes, and the basal ganglia, an area which is involved in selecting actions or putting actions together, Nelson says.

Research suggests the neurotransmitter serotonin plays a role in the illness. All of the medications that are effective in treating the disorder alter the level of this neurotransmitter in the brain, Nelson says.

Nelson, who studies potential drug therapies for OCD as well as various neuropsychological tests, also is interested in the genetic aspects of the disease. He plans to do a linkage study by looking at families who have multiple members with OCD. Currently, he is examining childhood-onset OCD patients who were initially treated at Children's Hospital.

"There's an increased rate of OCD among first-degree family members (parents and children) somewhere in the neighborhood of 10 to 15 percent," he says. "There's also an increased rate among monozygotic (identical) twins. If one twin has the illness, then approximately 60 percent of the co-twins have the illness."

When To Treat

Depending on the severity of the disease, Nelson says treatment may require behavior therapy, medication or a combination of the two. He says it is safest to begin with behavior therapy as opposed to medication, particularly when dealing with children. Behavior therapy involves basic relaxation techniques and gradually prepares patients to confront their thought/behavior problem by putting them in situations that spark the obsessive thoughts. Over time, and by regularly confronting situations that spur the thoughts, anxiety should lessen to the point that patients have no obsessions, he says.

When patients participate fully in behavior therapy, Nelson says there is significant improvement — up to 60 percent. He also encourages patients to participate in the OCD Foundation, a support group for people with obsessive compulsive disorder and their friends that he started five years ago. The group meets regularly at Barnes Hospital.

"It can be incredibly reassuring for them to know someone else has similar symptoms and to see that others who have the illness have done well with treatment," he says of the support group.

"People with OCD feel they are misunderstood by those around them who think they can 'just stop thinking about it,'" he continues. "They have to work very hard to challenge their thoughts and behaviors, and it requires a great deal of effort and tends to produce a great deal of anxiety."

Like Mezo, most OCD sufferers endure the seemingly bizarre symptoms for a long time — on average, seven years — before seeking professional help. Ironically, it was Mezo's friend of 30

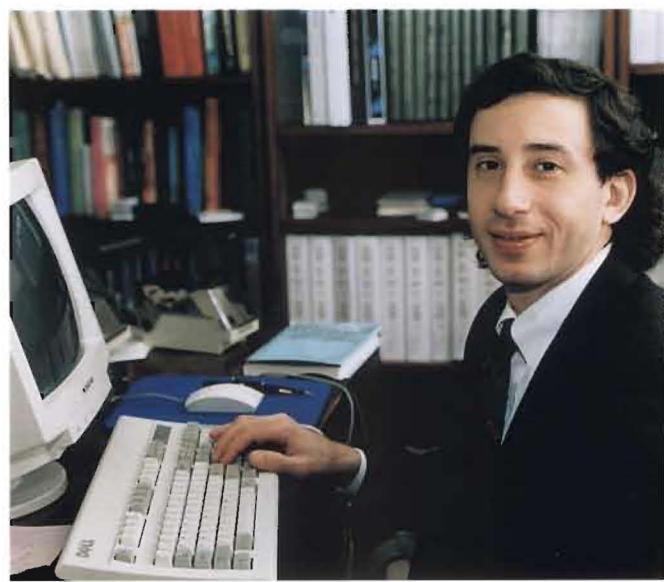
years — the one she was afraid to confide in — who told her she suspected Mezo was suffering from obsessive compulsive disorder and encouraged her to seek treatment.

Until that time, Mezo had never heard of OCD. Since then, her two daughters have been diagnosed with the disorder.

"My goal now is to do anything I can for this disorder because I've met people, especially older women, who are ridden with this illness," says Mezo. "Their whole lives were not fulfilled as they could have been because they were not diagnosed or properly treated. And treatment is so simple, but it's a lot of work."

Mezo, who works full time, also attends college and is studying psychology. A candid spokesperson who wants to demystify a crippling anxiety disorder, she regularly speaks to second-year medical students at the School of Medicine about OCD.

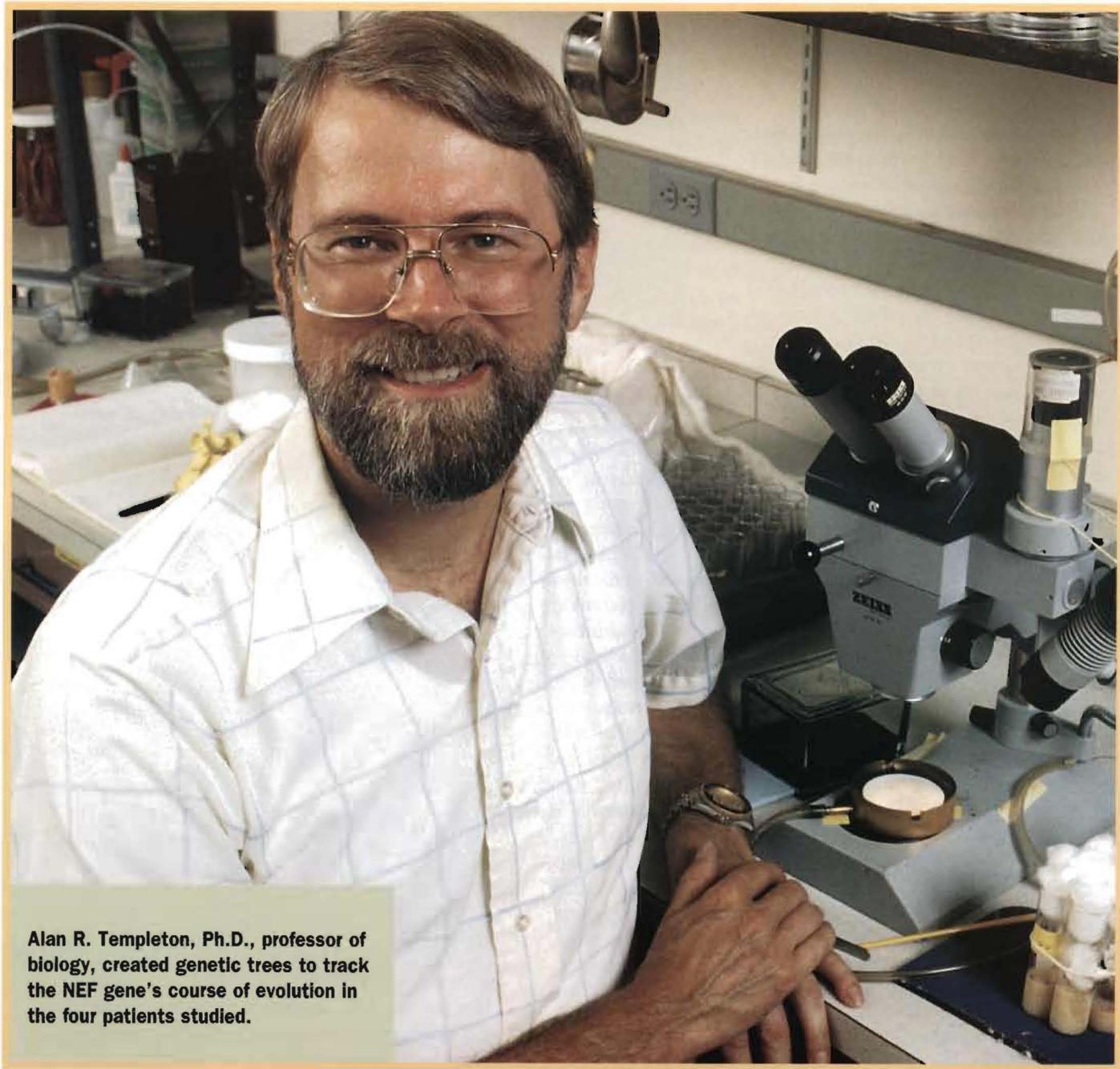
"I sometimes think of the things I could have done with my life had this disorder not manipulated me as it did," says Mezo, who now takes medication and can reason her harmful thoughts away. "Because I suffered so needlessly, and I know there are others out there suffering too, that's why every effort I have is given to this." ■



Elliot Nelson, M.D., assistant professor of psychiatry, says obsessive compulsive disorder can cause unusual thoughts that linger for hours or days, interfering with a person's way of life and livelihood.

**COLLABORATORS
DELETE A KEY GENE,
BUT HIV CONTINUES
TO EVOLVE**

THE NASA



Alan R. Templeton, Ph.D., professor of biology, created genetic trees to track the NEF gene's course of evolution in the four patients studied.

HIV BUG

by Tony Fitzpatrick

nef

The prospects for a safe, live vaccine in the near future to prevent HIV, the virus that causes AIDS, have diminished with the results of an innovative study by Washington University researchers.

Alan R. Templeton, Ph.D., professor of biology, and Lee Ratner, M.D., Ph.D., professor of medicine and molecular microbiology, have tracked the evolution of a key HIV gene in four patients over five years.

They found that, even in instances where the gene's molecular sequence had evolved and mutated so much as to be nearly non-functional and unrecognizable, all of the patients had some intact copies of the gene, and the virus kept replicating.

The gene, the negative factor gene (NEF), is one of the most important and variable genes in HIV which has a tiny genome (collection of genes) of less than a dozen genes. Molecular sequences are arrangements of four chemical units called base pairs. The various arrangements of base pairs constitute genes.

Researchers had been hopeful that a live, attenuated (weakened) vaccine based on deleted molecular sequences of the NEF gene could give immunity to HIV by causing an immune response in people infected with the weakened strain. There were encouraging results with a live vaccine in SIV (Simian immunodeficiency virus), the HIV counterpart in monkeys. The concept rests on the weakened strain

provoking an immune response while being unable to replicate inside the body. The Sabin polio vaccine works on this principle. But researchers here say results indicate that if a vaccine were to be made based on a deleted NEF gene, it would be unreliable because of HIV's ability to thrive with or without the NEF gene.

Study Is A First

The study, results of which were published in the April 1995 issue of *Virology*, is the first to analyze the evolution of the NEF gene in different patients over time. It combines the molecular biology expertise of one of the first researchers to sequence HIV, Ratner, and the population biology knowledge of a well-known evolutionary biologist, Templeton. It is representative of many different kinds of collaborations between scientists at the Hilltop and Medical campuses, who are often brought together because of their similar, complementary backgrounds. For more than a decade, Walter Lewis, Ph.D., professor of biology on the Hilltop Campus, and H. James Wedner, M.D., associate professor of medicine, have worked together in a number of allergy studies. Together, they discovered that feverfew, a relative of ragweed that is abundant in the Gulf states and grows as far north as southern Missouri, is both airborne and allergenic.

Andrew D. Dimarogonas, Ph.D., William Palm Professor of Mechanical Design, collaborates with Louis V. Avioli, M.D., Sydney M. and

Stella H. Shoenberg Professor of Medicine and director of the division of bone and mineral diseases, in osteoporosis studies and analyses of bone strength and density.

Dimarogonas is applying his patented method of vibration analysis, called the acoustic sweep method, to determine bone strength.

Ratner, who has made previous important discoveries on how HIV attacks the immune system and disables macrophages, coordinated the efforts to sequence HIV for the National Institutes of Health (NIH) in 1984. Templeton has done pioneering work in evolutionary biology and is perhaps best known for dispelling the notion of Eve, the hypothetical African genetic matriarch of all humans, with his genetic analysis. Templeton used the same algorithms in the HIV work that he used in the Eve analysis.

"HIV has such an enormous potential for evolution," says Templeton. "All of its genes are evolving at a tremendously rapid rate, making any strategy of treatment very difficult, because you're trying to get a handle on a constantly moving target. We wanted to monitor the evolution of one gene so we could speculate about the role it plays in the infection process. We wanted to see the evolutionary potential of the AIDS virus itself throughout the infection process. Our results clearly show that deletion of the NEF gene does not prevent the virus from replicating and evolving

within the patient. I wouldn't totally rule out the notion of a live, weakened vaccine, but for now, I wouldn't want one put into me."

Ratner, skeptical about a live vaccine from the start, considers the research illuminating from an evolutionary perspective, which is the reason he sought Templeton's expertise in the first place.

"We needed someone to produce gene trees for NEF and explain the significance of their evolution, and Alan does this as well as anybody in the world," says Ratner.

Ratner says one drawback with a potential live, attenuated HIV vaccine is the fact that HIV is a retrovirus — it replicates by using cell machinery the opposite way that human cells would use the same tools to replicate.

"I've never thought a live retrovirus vaccine is practical for humans, and these results support this belief all the more," Ratner says. "Retroviruses, whether attenuated or not, have the ability to insert their genetic information into our chromosomes forever and can express the virus at any time. To me, an entity that inserts itself into our genome forever does not appear to be something you'd want to give to a healthy individual."

Ratner is co-director of the Washington University AIDS Clinical Trials Unit, one of 50 nationwide established by the NIH to evaluate

new AIDS therapies. He collected data from four AIDS patients who take part in the Multicenter AIDS Cohort Study in Baltimore, a group of homosexual men that provides a natural history study of the disease. In previous work, he studied the molecular composition of a key protein, the envelope protein, in the same four patients. That work led to his conclusion that the envelope protein changes over time, and that the sequence early in infection is linked to infection of macrophages, which are the major cell infected in the brain and spinal cord. Infection of the macrophages is thought to be a key component in development of neurological problems in AIDS patients.

A Persistent Gene

In the NEF study, Ratner tracked the NEF gene over five years and looked at the molecular sequences of NEF during three points he labeled A, B and C. In all AIDS patients, the NEF gene is found intact during the early stages of the infection. But it is not always intact at later stages. One thing Ratner and Templeton wanted to determine was the importance of NEF during various stages of infection. They found that there were clones that develop deletions in the NEF gene over time, but there are also clones that do not have deletions over time.

"We see almost all of the deletions occur late in the disease stage," Ratner

notes. "I think the fact that we see NEF intact early in disease provides additional proof that NEF probably is very important early in infection and that later the virus will dispense with parts of the NEF gene like unneeded baggage. One of the key things Alan showed was that clones with deleted NEF genes are not dead viruses, but are instead continuing to grow and replicate within people."

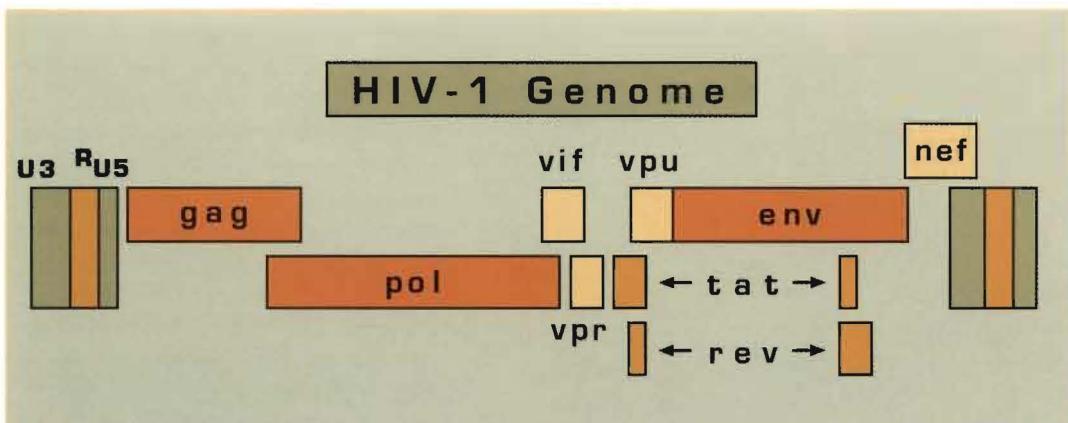
With the use of a sophisticated computer program that Templeton wrote and other algorithms, the population biologist created genetic trees to track the course of evolution in the four patients. What he found in all patients was a random distribution of potentially disruptive mutations of NEF gene function throughout the gene tree.

"Ideally, what we hoped to see was that every time the NEF gene got deleted, that would be the end of that lineage," Templeton explains. "When an important mutation occurs that disrupts gene function it means that lineage should rapidly go extinct. But what we saw is that in some cases the lineages don't go extinct. The viruses keep persisting and evolving, meaning they're replicating."

Ratner and Templeton speculate that deleted NEF genes may be able to persist by borrowing genetic material from other viruses and using that to replicate. The gene is located next to another important HIV gene, the LTR (long-terminal-repeat); together the genes are major factors in letting HIV enter human cells.

"One possibility is that the NEF-deleted viruses are coexisting with viruses that have intact NEF genes and are using these as helper viruses for their own replication," Templeton says.

"We've never found a patient where all the NEF genes are lost in a functional sense. That's why this helper



The HIV genome is composed of fewer than a dozen genes of different sizes, represented in this diagram by boxes and labeled with their abbreviated names, such as env., pol. and gag. Laid out here like cards on a table, they include the NEF gene (upper right), which is critical in the invasion of HIV into human cells and is the focus of a study by Lee Ratner, M.D., Ph.D., and Alan Templeton, Ph.D., who tracked its evolution in four patients.



Lee Ratner, M.D., Ph.D., professor of medicine and of molecular microbiology, says a vaccine based on a deleted NEF gene would be unreliable because HIV can thrive with or without the gene.

virus scheme is still quite feasible."

Templeton says the NEF-deleted viruses may exist in an almost parasitic way with the other ones that have the NEF gene. This makes him all the more uncertain about a live vaccine because there is proof that the NEF-deleted viruses can persist over time and evolve.

Ratner and Templeton will collaborate on another HIV evolutionary study of 10 patients from the Washington University AIDS Clinical Trials Unit. Ratner has gathered data on the patients to determine if there

are certain HIV genes expressed only at certain times in the disease. Templeton again will provide his genetic analysis.

"I think by understanding some of the aspects of how the virus operates, we'll eventually be able to develop better therapies and prevent some of the unfortunate complications of the disease," Ratner says. "One tremendous tool we have now is knowledge of the sequences of hundreds of HIV isolates. We can make any kind of sequence change to these isolates and make a virus out of it and then see how that one change can alter the

biological behavior in culture. A live attenuated vaccine for animal models still is a useful research tool because it might tell us something about what's important for protecting against infection. The current research might yield some clues about how to design a dead vaccine, for instance."

"I think the current study shows that by coupling the evolutionary analysis with the molecular genetic data, you get a really powerful inference that you couldn't get from one type of analysis alone," says Templeton. ■

Match Day 1995

THE annual Match Day took place on March 15 with 111 of the 129 graduating medical students participating in the national residency matching program.

Of the participants, 64 percent received residency positions at their first choice of institution and 80 percent matched one of their top three choices. The other 18 students who did not take part found positions independent of the matching program or chose not to take residencies immediately.

Primary care specialties of internal medicine, pediatrics and family practice captured the interest of 61 students. Family practice attracted 10 students this year, up from three last year. Otolaryngology, diagnostic radiology and ophthalmology were fourth in popularity, with each attracting seven students.

Forty-two of the new physicians will remain in St. Louis, with 41 at Washington University Medical Center institutions. Other popular destinations were California (12), Illinois (9), and Massachusetts and Texas (each with 8).

Arizona

Tucson

University of Arizona Affil. Hosp.
Pediatrics
Jeffrey M. Couchman

California

Irvine

University of California-Irvine
Internal Medicine
Jamie T. Nguyen

Ophthalmology
Mike Kim

Los Angeles

Kaiser Perm Med.-LA
Pediatrics
Dina K. Faulkner

Merced

Merced Community Med.
Family Practice
Patrick H. Zimmerman



Fourth-year students Gregory Bauer, Ann Starr and Carl Kraus (L to R) celebrate at Match Day after learning where their medical training will continue.

San Francisco

California Pacific Med. Ctr.

Internal Medicine
Robert Striker

University of California-SF

Internal Med.

Kenneth R. Hirsch
William Lee Lyons

Stanford

Stanford University
Otolaryngology
Lance E. Jackson
Ophthalmology
Timothy J. McCulley
Psychiatry
Po Wei Wang

Torrance

Harbor-UCLA Med. Ctr.
General Surgery
David A. Oliak

Ventura

Ventura County Med. Ctr.
Family Practice
David B. Richardson

Connecticut

New Haven

Yale University
Neurology
Jocelyn F. Bautista
Yale-New Haven Hospital
Pathology
Mark Velleca

Florida

Miami
University of Miami
Otolaryngology
Soham Roy

Georgia

Rome
Floyd Med. Ctr.
Family Practice
Andrew A. Smith

Iowa

Iowa City
 University of Iowa Hospital
 Internal Medicine
 Mark M. Belz
 Radiology
 S. Leon Burrows

Illinois

Chicago
 Children's Memorial Hospital
 Pediatrics
 Ajay Ahuja
 University of Chicago
 Ob-Gyn
 Carol F. Ellman
 Internal Medicine
 Brian K. Gehlbach
 Krista M. Johnson
 Carl N. Kraus
 Radiology
 Gregory S. Stacy
 McGaw Med. Ctr.-NW Univ.
 Internal Medicine
 Matthew D. Sirinek
 Ob-Gyn
 Ann Elizabeth Starr
Urbana
 University of Illinois
 Family Practice
 James Hampton, Jr.

Kansas

Kansas City
 University of Kansas Sch. of Med.
 General Surgery
 Matthew T. Janzow

Kentucky

Lexington
 Univ. of Kentucky Med. Ctr.
 Pathology
 Nancy C. Muller

Louisiana

New Orleans
 Alton Oschner Fdn.
 Orthopaedic Surgery
 John M. Reynolds

Maryland

Baltimore
 University of Maryland
 Pediatrics
 Alice J. Ho
 Internal Medicine
 Douglas H. Pogue
 Johns Hopkins
 Pathology
 Renae S. Lattiboudere
 Internal Medicine
 Steve Dudek
Bethesda
 Bethesda Naval Hospital
 Pediatrics
 Nichol M. Trump

Massachusetts

Belmont
 McLean Hospital
 Psychiatry
 Christopher M. Palmer
Boston
 Boston Univ. Med. Ctr.
 Ophthalmology
 Vahid Feiz
 Brigham & Women's
 Pathology
 Jonathan Glickman
 Massachusetts Gen. Hospital
 Anesthesiology
 Francisco Delacruz-Newlan
 Brian W. Dubois
 Children's Hospital-Boston
 Pediatrics
 Sandip Godambe
 Patrick Jay
 Charles Roberts

Michigan

Grand Rapids
 Blodgett Mem. Med. Ctr.
 Orthopaedic Surgery
 David M. Huebner
Ann Arbor
 University of Michigan
 Neurology
 Brett M. Kissela
 Otolaryngology
 Thomas C. Robey
Detroit
 WSU/Detroit Med. Ctr.
 Emergency Medicine
 Richard Mickevicius
 Pediatrics
 Suzanne E. Rastorfer

Minnesota

Minneapolis
 Univ. of Minn. Hosp. & Clin.
 Radiology
 Joel C. Schein
 Univ. of Minn.
 Ophthalmology
 Jennine Cabanellas
Rochester
 Mayo Clinic
 Otolaryngology
 Douglas L. Schulte
St. Paul
 St. Paul-Ramsey
 Family Practice
 David J. Caccamo

Missouri

Columbia
 University Hosp. & Clinic
 Family Practice
 Martha Sue Terry
 Natawadee Young
St. Louis
 Barnes Hospital
 General Surgery
 Scott I. Reznik
 General Surgery-Prelim.
 Theresa Zogakis
 Internal Medicine
 David J. Brown
 Michael G. Jakoby
 Yoon Kang
 Michael J. Kraujalis
 Mark Lastarza
 John J. Lehman
 Internal Medicine-Prelim.
 D. Russell Johnson
 Laboratory Medicine
 Thomas Daly
 Jonathan Heusel
 Orthopaedic Surgery
 Gregory S. Bauer
 Ob-Gyn
 Mary Ruth Board
 Jamesina M. Dickson
 Pathology
 Brian Strauss
 Deborah J. Novack
 Psychiatry
 John D. Rogakos
 Radiology

Lawrence S. Kaskowitz
 Kraig R. Kirkpatrick
 Michael J. Naylor

Jewish Hospital
Internal Medicine
Scott Wasserstrom
Internal Medicine-Prelim.
Benjamin Hsu
St. Johns Mercy
Family Practice
Caroline Rudnick
St. Louis Children's
Pediatrics
David A. Hunstad
Lori Kutka
Kenneth An-Kai Liu
Nancy E. MacDonald
Cali C. Matheny
John Zempel
Janet Kao
Kim Aiken
Howard Goodkin
Brenda Porter
St. Louis University
Ob-Gyn
Kari A. Schmidt Oliver
Washington University
Ophthalmology
Jonathan Silbert
Ivan Tarle
Otolaryngology
Brian Lawner
John Park
John C. Sun
Research
Avinash Amin
Urology
Howard E. Jarvis
Jason Krumholtz

New York

New York
Mt. Sinai Hospital
Internal Medicine
Michael E. Blam
Mt. Sinai School of Medicine
Ophthalmology
Jonathan D. Primack
North Shore Univ. Hosp.
Radiology
David H. Miller
Rochester
Univ. Rochester/Strong Mem.
Internal Medicine
Debbie C. Wu

North Carolina

Durham
Duke University
Neurosurgery
Amy B. Heimberger
Duke University Med. Ctr.
Psychiatry
Eric L. Kirchmann

Ohio

Columbus
Ohio State University
Orthopaedic Surgery
Abdolreza Raissi
Dayton
Wright Patterson AFB
Pediatrics
David P. Miller

Pennsylvania

Philadelphia
Hahnemann Univ. Hospitals
Orthopaedic Surgery
Timothy E. Schendel
Hosp. of University of Pennsylvania
Psychiatry
Ian C. Parker
Sheryl Salaris
Internal Medicine
Steven L. St. Peter
University of Pennsylvania
Internal Medicine
Phil Horwitz

Rhode Island

Providence
Rhode Island Hosp.
Internal Medicine-Prelim.
Michael Kolodney
Emergency Medicine
Nona M. Perez

Tennessee

Memphis
Univ. of TN College of Medicine
Pediatrics
Kristin D. Strawhecker

Texas

Dallas
Univ. of Texas SW Med. Ctr.
Internal Medicine
Todd K. Horiuchi
Orthopaedic Surgery
James C. Walter II

Houston
Baylor College of Med.
Plastic Surgery
Douglas J. Ball
Internal Medicine
Wai Leong Lee

San Antonio
Brooke Army Med. Ctr.
Pediatrics

Joel Ruff
Wilford Hall
Bobbi Joy Chambers-Hawk
General Surgery
Mark A. Koler
Internal Medicine
Brent A. Porter

Utah

Salt Lake City
University of Utah Affil. Hosp.
Pediatrics
Justin C. Alvey

Washington

Seattle
Providence Family Med.
Family Practice
Lisa Erlanger
University of Washington
Neurosurgery
Gregory D. Foltz
Univ. of Washington Affil.
Internal Medicine-Primary
John D. Thornton
Internal Medicine
Robert Young

Wisconsin

Madison
Univ. of Wisconsin-St. Marys
Family Practice
Caroline E. Day

Seven Honored With Awards



The 1995 Reunion Award recipients (front, L to R): Llewellyn Sale, Jr., M.D. '40; Margaret C. Telfer, M.D. '65; Dennis P. Cantwell, M.D. '65; (back, L to R) Phillip E. Korenblat, M.D.; Philip O. Alderson, M.D. '70; Arnold Strauss, M.D. '70; and Gustav Schonfeld, M.D. '60.

Alumni Achievement Awards

Philip O. Alderson, M.D. '70, is James Picker Professor of Radiology and chairman of the Department of Radiology at Columbia-Presbyterian Medical Center in New York City. He has made major contributions in pulmonary and cardiovascular nuclear medicine and is acknowledged as a superb teacher and clinical nuclear radiologist. He has made more than 200 presentations at meetings and is a prolific author.

Dennis P. Cantwell, M.D. '65, is Joseph Campbell Professor of Child Psychiatry at the University of California at Los Angeles School of Medicine.

His work in child psychiatry sets the pace for much of the research in the field. He led the way in establishing a clinical depression diagnosis in children and is an expert on attention deficit hyperactivity disorder. Highly respected as a clinician and teacher, he is frequently sought for consultation on difficult cases.

Margaret C. Telfer, M.D. '65, is director of the Hemophilia Center at Michael Reese Hospital in Chicago, Illinois, where she is also interim director of the division of hematology/oncology. She dedicates her career to the care and treatment of hemophiliac patients and has pioneered home infusion as a treatment alternative. As co-director of the Michael Reese HIV Clinic, she has assisted patients through hemorrhagic crises and the problems of AIDS.

Alumni/Faculty Awards

Llewellyn Sale, Jr., M.D. '40, is professor of clinical medicine and president of Central Medical Group, Inc. For 20 years he was associate director of the Department of Internal Medicine at Jewish Hospital, and he directed the Student Health Service on the Hilltop Campus for 18 years. He is described as a "fine teacher and role model," and "a forthright and honest person

for whom his profession and his patients are paramount."

Gustav Schonfeld, M.D. '60, is William B. Kountz Professor of Medicine and director of the atherosclerosis, nutrition and lipid research division. He has been conducting lipid research for more than 23 years. His expertise in the areas of lipoproteins and atherosclerosis has made him sought after as a speaker and consultant around the world. The National Heart, Lung, and Blood Institute recently honored him with MERIT status, given only to investigators whose work is consistently outstanding.

Arnold Strauss, M.D. '70, is director of the David Goldring Division of Pediatric Cardiology at St. Louis Children's Hospital and professor of pediatrics and of molecular biology and pharmacology. He is internationally known for investigation into the evaluation and treatment of heart disease in children. Most recently, he has directed a study that identified a genetic defect which causes Sudden Infant Death Syndrome in some infants.

Distinguished Service Award

Phillip E. Korenblat, M.D., is medical director of The Asthma Center and the Clinical Research Center at Barnes West County Hospital and professor of clinical medicine. He is the force behind the success of an approach that empowers patients and their families in the treatment of asthma. His research focuses on medications for asthma and allergies. He is listed in *The Best Doctors in America, 1994-95*, and the Department of Medicine at Jewish Hospital named him Teacher of the Year in 1986. ●



Alumni listen to a presentation during a tour of the new Mallinckrodt Institute of Radiology Imaging Center.



The Class of 1935 shares memories during the Friday night dinner. From left: reunion social chair Dr. Richard A. Sutter, Jarry Maughs, Dr. Sydney Maughs, Dr. Richard McIlroy, Mercy McIlroy, Dr. Mark Gregory and (across the table) Dr. Patricia Gregory (director of corporate and foundation relations in the medical alumni office), Dr. C. Rush McAdam, reunion gift chair Dr. Jerry Flance, Rosemary Flance and Betty Henby Sutter.



Drs. Helmuth "Hap" Hoff, Jay Gibson, and reunion gift co-chair Sam Guze at the 50th reunion of the Class of 1945.



Paula Clayton, M.D. '60, brings her classmates up to date on her activities, while Boyd Terry, M.D. '60, and Carolyn Terry, M.D. '60, listen.



Reunion social chair Dr. Llewellyn Sale (arms crossed) enjoys a light moment with his Class of 1940 classmates: Drs. Bill Curtis, reunion gift chair Robert Anschuetz and John Skinner, and spouses Frances Curtis, Ella Anschuetz, Betty Skinner and Kathleen Sale.

R E U N I O N 1 9 9 5



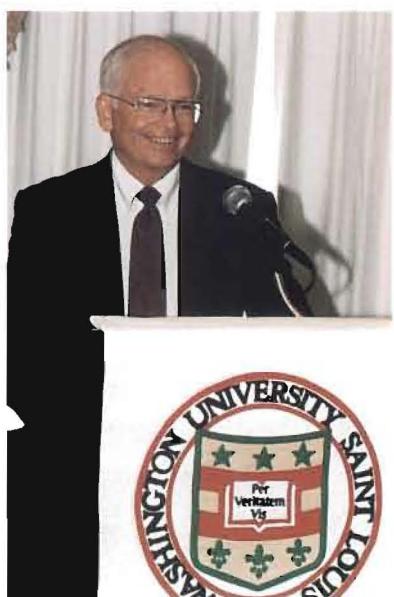
James Davis, M.D. '45, and Florrilla Davis sample the fare at the welcoming party.



Miles Whitener, M.D. '55 and social chair for his class, reads letters from classmates unable to attend the reunion. Around the table from left: reunion gift co-chair Robert C. Drews, M.D. '55, Lorene Drews, William Paris, M.D. '55, Ann Paris, Glen King, M.D. '55, and Scotty King.



Reunion gift committee member Joann Data, M.D. '70, WUMCAA president and class gift chair David Ortballs, M.D. '70, Jane Brassel, Doris Miller, Alec Miller, M.D. '70, and Marilyn Escobedo, M.D. '70.



Winston Tustison, M.D. '60 and a certified financial planner, advises fellow alumni about retirement strategies during the Saturday luncheon.



Reunion social chair Meredith Payne, M.D. '50, emcees the class dinner.



Devoree Clifton-Crist, M.D. '80, and Michele Bloch, M.D. '80, reminisce.



Gustav Schonfeld, M.D. '60 and reunion social chair, is surrounded by family members who admire his Alumni/Faculty Award.



Members of the Class of 1970 at the Dean's Lunch in Olin Residence Hall. From left: reunion gift committee member Ronald Gaskin, Tom McMahan, Lyle Pahnke, David Ortbals, Donald Anderson, Gene Crews, Marilyn Escobedo, reunion social chair Francisco "Paco" Garriga, Ron Marshall, Eric Zurbrugg and Jo Beamer Zurbrugg.

Dr. Gene Rubin,
Judy Clifford,
Douglas Tollefson,
Dr. Sherida
Tollefson, and
reunion class
social chair Dr.
David Clifford
arrive at the Ritz-
Carlton for the
Class of '75
dinner.



Class of 1975 members, from left: Drs. Doug Mayers, Jo-Ellyn Ryall, Bruce Schainker, Ed Hume and his spouse, Susan Ferrara, at the cocktail party.



Bradley A. Evanoff,
M.D., M.P.H., the
Richard A. and
Elizabeth Henby
Sutter Professor of
Occupational,
Industrial and
Environmental
Medicine, makes a
presentation at the
reunion scientific
program.

R E U N I O N 1 9 9 5



Reunion class social chair Marshall Conrad, M.D. '45, responds to a tribute to the 50th reunion celebrants and welcomes the Class of 1995 into WUMCAA.



1985 classmates Howard Yerman, Vera Bennett and Karen Mathews.



Al Baudendistel, M.D. '85, Peter Weiss, M.D. '85, Sharon Weiss and reunion class social chair Herluf Lund, M.D. '85.



Kathy Pohl and Tim Frost, M.D. '85, enjoy the class photo display.



William A. Peck, M.D., executive vice chancellor for medical affairs and dean of the School of Medicine, and David Ortvals, M.D. '70 and 1994-95 president of WUMCAA, share a light moment.



Retiring Chancellor William H. Danforth, M.D., welcomes alumni and friends to the reunion banquet. The guests greeted him with a standing ovation in appreciation of his 24 years as chancellor.

R E U N I O N 1 9 9 5



Reunion social chair Tom Ott, M.D. '65, and Mary Ott enjoy the class dinner.



Bill Tisdale, M.D. '55, and his wife, Pat, dance to the music of the Hot Docs.



Members of the Class of 1995 pose with Dean Peck after the banquet.



William A. Peck, M.D., executive vice chancellor and dean, presents the 1995 Distinguished Service Award to Phillip E. Korenblat, M.D.



WUMCAA president-elect, Richard A. Blath, M.D. '71, and 1994-'95 WUMCAA President, David Ortvals, M.D. '70.

Abdolreza Raissi,
president of
the Class of
1995, responds
to Dr. Marshall
Conrad's remarks.





Colorful Hawaiian leis complemented Todd Horiuchi's mortarboard at commencement exercises held on the Hilltop Campus on May 19. The School of Medicine conferred 97 M.D. degrees, 19 M.D./Ph.D. degrees and eight M.D./M.A. degrees.



WASHINGTON UNIVERSITY IN ST. LOUIS

School of Medicine

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At a reception following the dedication of the Bernard Becker Medical Library, Bernard Becker, M.D., professor and emeritus head of the Department of Ophthalmology and Visual Sciences, shows a keepsake program to his granddaughter, Amariah Becker, and his son, Robert Becker. Dr. Becker chaired the committee that oversaw design and construction of the eight-level, 113,000-square-foot library, which was completed in 1989. The Becker Collection of rare books on ophthalmology and the visual sciences is a major component of the library's internationally recognized rare book collection. Becker served as head of ophthalmology from 1953 through 1988.