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Record

Oct. 14, 1999

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Washington University in St. Louis



Confronting racism The Rev. Gary Braun (right foreground), director of the Catholic Student Center, leads a dialogue titled "Racism: Is It a Mental Disease or Is It Human?" Oct. 6 in Friedman Lounge, Wohl Center, as part of a week-long Student Union initiative on race relations. The week's events, similar to programs at colleges and universities across the country, also included small group conversations, panel discussions, a town hall forum and graffiti boards where students could express their views. The U.S. Department of Education sponsored the nationwide effort as part of President Clinton's Initiative for One America.

George Bush headlines Founders Day

Former President George Bush will address this year's Founders Day dinner Oct. 30 at the America's Center, St. Louis. The annual event is sponsored by the Washington University Alumni Board of Governors to commemorate the University's founding in 1853.

The event will begin with cocktails at 6:30 p.m., followed by dinner at 7:15 p.m. The program will begin at 8:30 p.m.

The Founders Day ceremony includes the presentation of the Distinguished Faculty awards, the Distinguished Alumni awards and the Board of Trustees' Robert S. Brookings awards.

Bush began his career in government in 1966, when he was elected to the U.S. House of Representatives from Texas' 7th District. In 1971, he was named U.S. Ambassador to the United

Nations. Two years later he became chairman of the Republican National Committee. In October 1974, Bush traveled to Peking, where he served as chief of the U.S. Liaison Office during the critical period when the United States renewed ties with the People's Republic of China. In 1976, he was appointed director of the Central Intelligence Agency.

Bush was selected to be Ronald Reagan's running mate in 1980. He served as vice president for two terms. Bush was elected the 41st president of the United States in 1988 and served through 1992.

Since leaving office, Bush has written three books, including "A World Transformed," co-authored with Gen. Brent Scowcroft, and the recently-released "All the Best."

Six alumni will be recognized for "outstanding achievements,

public service and exceptional service to Washington University." This year's recipients are Dolores Baja-Lasán, Ph.D. (Social Work, 1959),

chancellor of the Philippine Women's University System; John Davis Ezell (Art, 1954), artist and set designer; Mark J. Ginsburg, M.D. (Arts & Sciences, 1973, and house staff, 1981), rheumatologist; W. Patrick McGinnis (Business, 1972), president and chief executive officer, Ralston Purina Co.; William F. Patient (Engineering, 1957), retired chairman of the board, The



Bush: Quarter century of service

See **Bush**, page 6

First for Missouri New supercomputer, lab will be 'bridge to future'

By TONY FITZPATRICK

Two new National Science Foundation (NSF) grants to Washington University will bring Missouri its first science supercomputing center and an astrophysics simulation laboratory. The laboratory, through cyberspace, will enable users to apply the Einstein theory of general relativity to the simulation of neutron stars and black holes; anyone from the highest tier researcher to the merely inquisitive can thus explore a simulated universe.

Wai-Mo Suen, Ph.D., professor of physics in Arts and Sciences, is the principal investigator for the grants, totaling \$4 million, to support collaborative supercomputing research with investigators here and at other major universities.

One is a three-year \$1.8 million grant from the NSF Major Research Instrumentation (MRI) program to purchase a supercomputer and establish a Center for Scientific Computing within the Division of Natural Sciences and Mathematics.

Co-investigators on this grant are Claude W. Bernard, Ph.D., professor of physics; Barbara Pickard, Ph.D. professor of biology; Victor Wickerhauser, Ph.D., professor of mathematics; and Michael E. Wysession, Ph.D., associate professor of earth and planetary sciences.

The four co-principal investigators on the grant are but a handful of University researchers who will access the supercomputer to expedite and enhance their research projects.

The MRI program grant will bring a "massively parallel" computer to the Hilltop campus. A massively parallel computer harnesses the power and production of many computer processors simultaneously to process information and graphics at rapid speed.

"The vision is that, with this computer on campus, we will be able to build a community of users of parallel scientific computing," Suen said. "There is a strong core of researchers here already using massively parallel computing at the national centers, but they become stymied when they have to wait for

See **Supercomputer**, page 6

Wayman Crow Professorship in physics goes to John Clark

John Walter Clark, Ph.D., professor of physics in Arts & Sciences, has been named the Wayman Crow Professor of Physics, effective Oct. 1. A formal installation ceremony will take place in spring 2000.

"John represents a model for an endowed professor," said Edward S. Macias, Ph.D., executive vice chancellor and dean of Arts & Sciences. "He is internationally respected for his research, and he has been an outstanding teacher at all levels. In addition, he has worked hard to strengthen

both the physics department and the University. I'm delighted to name him to this, the second oldest professorship at Washington University."

Clark received a bachelor of science degree in 1955 and a master of arts in 1957, both from



Clark Distinguished theoretical physicist

See **Clark**, page 2

Mouse next in line for DNA sequencing; new network formed

By LINDA SAGE

The School of Medicine will participate in a major new research program to decipher the genetic makeup of the mouse, one of the most frequently used mammals in medical and behavioral research.

The National Institutes of Health (NIH) announced Oct. 5 that it will initiate this project with \$21 million, provided over the next seven months to 10 laboratories that have formed the Mouse Genome Sequencing Network. The network will determine the physical organization of the mouse's 21 chromosomes and will sequence the estimated 3 billion chemical letters in the chromosomes' DNA. It expects to complete a working draft in three years.

Washington University will receive \$2.7 million of this funding and expects to receive a total of \$24.6 million for the first three years. John D. McPherson, Ph.D., assistant professor of genetics, will be the University's principal investigator for the mouse project.

"Because mice and humans share many of the same fundamental biological and behavioral processes, this animal is one of the most significant laboratory models for human disease," said NIH Director Harold Varmus, M.D. "Knowing the genetic make-up of the mouse, and being able to compare it to the DNA of humans and other animal species, will greatly expedite many avenues of research, including assessing predisposition to disease, predicting responses to environmental



McPherson Principal investigator here

agents and drugs, and designing new medicines."

The NIH funding for the Mouse Genome Sequencing Network illustrates the value of the mouse genome to a wide spectrum of biomedical scientists. "Every institute at NIH, with support of the NIH Office of the Director, has made a contribution to the first year of funding for the Mouse Genome Sequencing Network, demonstrating the importance of this work to research progress in virtually every area of biomedical research, from

hereditary hearing impairments to Alzheimer's," said James F. Battey Jr., M.D., Ph.D., director of the National Institute on Deafness and Other Communication Disorders of NIH and co-chair of the Trans-NIH Mouse Genomics and Genetics Resources Coordinating Group.

Research on the mouse genome will occur in two stages, following the strategy now being used by the international Human Genome Project to sequence the genetic blueprint of the human. Scientists working on the mouse genome first will focus their efforts on completing an intermediate working draft version of the animal's genetic instructions. This first stage will be completed no later than 2003. They then will turn their attention to filling any

gaps in the draft and finishing the sequence in high-quality final form by 2005.

"Many scientists have told us that sequence data, even in working draft form, is very useful to their research. For that reason, the Human Genome Project and now the mouse sequencing effort will complete their work in these two stages," said Francis Collins, M.D., director of the National Human Genome Research Institute (NHGRI) of NIH. NHGRI is leading the NIH's participation in the Human Genome Project.

By spring 2000, the Human Genome Project will produce a working draft of the genetic blueprint of the human. By 2003, or possibly sooner, the finished high-quality version of the human

See **Genome**, page 6

Medical School Update

An added benefit

Immune system protein could be critical in kidney disorders and other diseases

By BARBRA RODRIGUEZ

Evolution has an uncanny way of reusing good blueprints, as researchers recently were reminded when they discovered that a protein involved in immune-cell interactions might be important for kidney function.

Andrey S. Shaw, M.D., principal investigator of the research on the CD2-associated protein, said, "Defects in CD2AP may play a critical role in some kidney diseases."

The research is published in the Oct. 8 issue of *Science*. The first authors of the paper are post-doctoral fellow Neng-Yao Shih, Ph.D., and research associate Jun Li, who both work in Shaw's laboratory at the School of Medicine.

Shaw, associate professor of pathology, led a team of researchers who studied the protein. His group originally cloned the gene as a molecule important for T cell function. The researchers were surprised to find that CD2AP also is specifically expressed in the kidney glomerulus, which filters toxins and other substances from the blood.

The researchers found that mice lacking CD2AP had defective glomeruli and died of renal failure. When they analyzed these mice, they found that CD2AP was expressed in the kidney, mainly in a cell known as a glomerular epithelial cell. The glomerular epithelial cell has a complex shape with foot-like extensions that wrap around capillaries of the glomerulus, forming spaces for the flow of blood filtrate that are called slit diaphragms. In the mice lacking CD2AP, the epithelial cells were damaged and the slit diaphragms were lost.

The mice, developed by Shih and Li, died of kidney failure by the time they were 6 weeks old. The researchers, including co-author Jeffrey H. Miner, Ph.D., assistant professor of medicine and of cell biology and physiology, found progressive damage to the foot-like extensions as early as one week after the mice were born.

How could missing CD2AP have such a dramatic effect on the kidneys? To address this question, Shaw revisited a model concerning CD2AP's potential role in T cells of the immune system. He

developed this model with colleagues Michael L. Dustin, Ph.D., associate professor of pathology, and Paul M. Allen, Ph.D., the Robert L. Kroc Professor of Pathology.

T cells defend the body from microbes by interacting with another immune system cell. Shaw previously showed that CD2AP plays an important role in organizing the T cell surface, helping the cell form a molecular bridge with other immune cells.

The molecular bridge forms as a T cell molecule binds to another molecule on the other cell. CD2AP helps position the molecule, CD2, and anchor it at the right place in the membrane. CD2 also serves as a border

guard, keeping proteins in separate regions on the T cell surface.

Shaw and his group were struck by the similarities between CD2 and a recently identified protein called nephrin, which is expressed in glomerular epithelial cells. Nephrin, the major component of the slit diaphragm, functions as a molecular bridge between epithelial cells and as a barrier between two distinct surfaces of the epithelial cell. This suggested to Shaw that CD2AP might function by binding to nephrin.

The gene encoding nephrin was cloned last year and identified as the culprit in the most common type of hereditary

kidney syndrome, congenital nephrotic syndrome of the Finnish type. Occurring in one of every 10,000 Finns, the syndrome results from lack of nephrin and produces kidney damage, as occurs in Shaw's research animals that lack CD2AP.

This similarity suggests that a defect or lack of CD2AP might be involved in some cases of congenital nephrotic syndrome and other kidney diseases. "This opens up a whole area of inquiry, where we wonder how the slit diaphragm is altered in human kidney diseases and whether a predisposition to kidney failure may be related to genetic defects in the slit diaphragm or kidney epithelial cells," Shaw said.

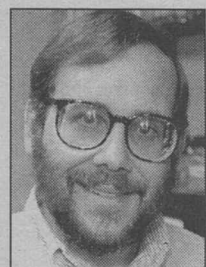
Sanes named Alumni Endowed Professor of Neurobiology

By LINDA SAGE

Joshua R. Sanes, Ph.D., professor of anatomy and neurobiology, has been named the Alumni Endowed Professor of Neurobiology.

"The Washington University Medical Center Alumni Association launched these professorships in 1978 to help attract and retain renowned physicians and scientists," said William A. Peck, M.D., executive vice chancellor for medical affairs and dean of the School of Medicine. "We are

delighted that this sixth chair will honor Joshua Sanes, an intellectual leader in the field of neuroscience."



Sanes: Studies synapses

Alumni professorships combine

unrestricted gifts from medical alumni and former house staff with gifts from friends of the medical school. The minimum endowment for each position is \$1.5 million.

Sanes joined the University in 1980 as an assistant professor. He studies intercellular connections called synapses. These junctions pass information between cells, like the plug between a modem and a computer. A synapse called the neuromuscular junction connects the tip of a nerve cell to a muscle fiber, enabling the nerve to control the muscle. Other synapses solder the brain's 10 billion neurons into circuits that allow us to speak or read or plan movements.

"As far as we know, all of our behavior depends on synapses," Sanes said. "And some neurological and psychiatric disorders — Alzheimer's disease and schizophrenia, for example — seem to involve flaws in synapse formation or function. Knowing how synapses are made is essential to understanding and eventually correcting synaptic derangements."

Signals from the growing tip of a motor nerve cell organize the synaptic region of a muscle fiber. In turn, the muscle signals back to the nerve, turning the tip into a terminal. Signals from the terminal then cause further changes in the muscle. This crosstalk aligns muscle receptors precisely with incoming nerve signals. "We want to know how this incredible arrangement is achieved," Sanes said.

When he began to study the neuromuscular junction in 1976, synaptic development was largely unexplored. Using a variety of techniques, he has identified several molecular components of the synapse and explored their interactions.

His early work focused on a synaptic protein called laminin β -2, which he identified and isolated. In collaboration with the late John Merlie, Ph.D., he cloned the laminin β -2 gene and eventually generated mutant mice that lacked it. His use of these knockout mice proved an invaluable contribution to the field. As well as revealing the normal functions of specific synaptic proteins, it has generated animal models of several neurological disorders.

The laminin β -2-free mice formed disorganized, malfunctioning synapses, providing the first example of a protein that organizes synapses in living animals. The group since has isolated specific parts of laminin β -2 that influence the growth and differentiation of nerve axons and allow them to connect with muscle.

The many other molecules Sanes has studied include agrin, a muscle protein that helps cluster the receptors receiving nerve signals, and dystrophin, a muscle protein that is abnormal in Duchenne muscular dystrophy.

The group now is applying the approaches it used with the neuromuscular junction to synapses in the brain. "We want to identify the constituents and find out how they work," Sanes said. Last year, the researchers reported that a protein called gephyrin is required to form synapses in the spinal cord.



Walking in a patient's shoes First-year Program in Physical Therapy students Geoffrey Nelle (left) and Anne Schmidt (right) practice gait training techniques under the watchful eye of Tammy Burlis, an instructor in the program. Using a gait belt, Nelle helps Schmidt stand in preparation for walking with the support of parallel bars.

\$1.1 million grant helps Castro establish unique Asthma Clinical Research Center

Mario Castro, M.D., assistant professor of medicine, has received a five-year \$1.1 million grant from the American Lung Association to fund an Asthma Clinical Research Center (ACRC). Washington University, Saint Louis University, the American Lung Association of Eastern Missouri (ALAEM) and private physicians have teamed up to establish this center.

"For the first time, Washington University will participate in a large multicenter study spanning almost 20 asthma centers addressing a common clinical problem," Castro said. All of the data will be shared. Johns Hopkins Medical Center will serve as the data-coordinating center by collecting the results from the participating centers.

The collaboration brings St. Louis into a network of 19 asthma research centers across the United States and establishes a unique partnership among St. Louis' two medical schools, the ALAEM and physicians in private practice. Washington University School of Medicine will lead the St. Louis team's clinical studies. Other sites in this "center

without walls" include Barnes-Jewish Hospital, St. Louis Children's Hospital, Saint Louis University Hospital, Cardinal Glennon Children's Hospital, the Clinical Research Center located at Barnes-Jewish West County Hospital and other medical sites convenient to patients.

Robert C. Strunk, M.D., and Edwin B. Fisher Jr., Ph.D., are co-investigators at Washington University. Raymond Slavin, M.D., and Brad Becker, M.D., will participate from Saint Louis University. Two physicians in private practice, Phillip Korenblat, M.D., and Jeff Tillinghast, M.D., also are taking part. The center just hired a nurse coordinator, Mary Ellen Scheipeter.

Participation in this multicenter network will give the St. Louis researchers access to a greater number of asthma patients. "This will give physicians helpful information on how to better manage asthma patients in their practice," Castro said.

Asthma is a chronic, long-term lung disease with no cure. It only can be controlled. Asthma sufferers experience difficulty breathing because their airways swell and constrict.

Many factors can trigger an attack — cigarette smoke, pollen, cold air and household dust. In St. Louis, the strongest triggers are cockroaches and the mites in household dust.

Those at highest risk for asthma include children living in poverty or in the inner city and African-Americans and Hispanics. While 6.3 percent of American children suffer from asthma, the rate is 11 percent to 12 percent in the St. Louis metropolitan area. And 15 percent of children who attend St. Louis City public schools have asthma.

Also, both the number of cases and the number of deaths from asthma are increasing in the St. Louis metropolitan region.

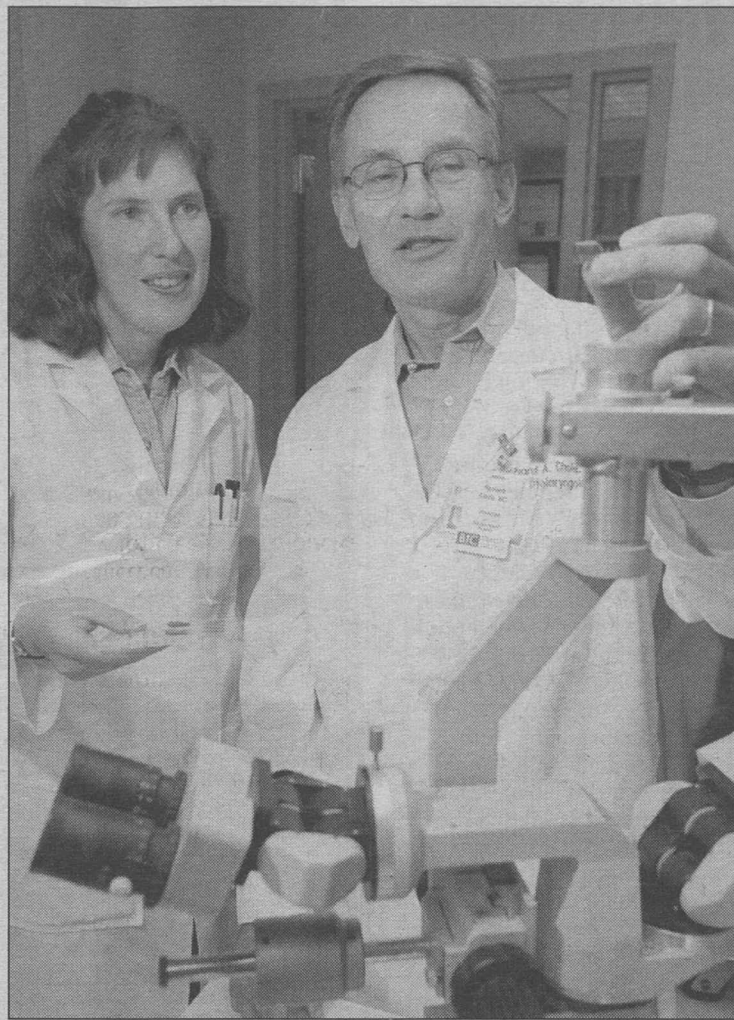
"We have great medications and understand more about the disease, but we are still seeing an increase in morbidity and mortality due to asthma," Castro said.

The researchers will try to develop new ways to help adults and children care for their disease in early life. "Children with chronic asthma that persists into adulthood may have impaired lung function, much like smokers," Castro said. "We want to find effective treatments to intervene as early as possible."

Washington People

As a boy, the last thing Rick Chole expected was to become a surgeon, despite the fact that his father was the first cardiologist in California's San Fernando Valley. "I really was very close to my father and admired him a lot," said Chole, M.D., Ph.D., the Lindburg Professor and head of the Department of Otolaryngology at the School of Medicine for the past two years. "But I thought that his career was at too high a level to attempt."

Chole received Cs and Ds in grade school and found even those grades difficult to achieve, the result of what he now suspects was a mild form of dyslexia. But in junior high, he became interested in math and did well in this



Richard A. Chole, M.D., Ph.D., shows research assistant Ruth Gill a piece of embedded ear tissue.

A keen ear for patients' suffering

Ear surgeon Richard A. Chole, M.D., Ph.D., combines creative research with heartfelt empathy for those who seek his help

BY BARBRA RODRIGUEZ

conceptual subject and in science. Then a high school teacher got him hooked on biology. "We had a biology club and I was its president," Chole said. "I wasn't very socially adept and I wasn't very athletic, so that's where I found my niche."

Chole applied to medical school on a whim while working on a biology degree at the University of California, Berkeley. He was accepted at the University of Southern California in 1965 and left Berkeley after his junior year, without finishing a bachelor's degree.

He entered medical school unsure if he should have gone into research instead, but in the end he found fulfillment becoming an ear surgeon and a hearing disease researcher, both fields that took advantage of his knack for handling hands-on, conceptual tasks.

"Ear surgery is kind of a creative surgery that is mechanical and reconstructive. And sometimes," he added, "you get to help people regain their hearing."

Before Chole specialized in otolaryngology, he undertook a year-long internship at the Los Angeles County Hospital and learned that the high tension and strong personalities of trauma surgery weren't for him. He also spent two years in private family practice, where he developed his skills as a physician.

"Richard brought a holistic approach to patient care and had a marvelous manner with patients, in addition to his great skill as a world-class specialist," said Gerald S. Lazarus, M.D. Chole was Lazarus' personal physician while Lazarus was dean of the medical school at the University of California (UC)-Davis.

In 1972, Chole and his family moved to Minneapolis so he could undertake an otolaryngology fellowship at the University of Minnesota. He also renewed his science interest, obtaining a Ph.D. by performing research between medical rotations. Five years later, the Choles headed back to California, where he would spend the next 21 years in the Department of Otolaryngology at the UC-Davis medical school.

His research focuses on cells called osteoclasts that dismantle bone during normal repair processes. The overactivity of osteoclasts in the ear, however, can destroy critical bones that transmit sound information, resulting in hearing loss and various ear diseases.

Gerbil model

To study cyst-like growths in the ear called cholesteatomas, Chole developed a gerbil model in the 1980s that is still widely used. Cholesteatomas can develop after chronic ear infections, as is true of several other ear diseases. Chole now is developing mouse models to look more closely at genes and how their protein products influence osteoclast activity in ear infections that set the stage for disease. "If we can understand what controls bone remodeling by these cells, we hope to develop techniques to block the development of ear diseases," Chole said.

The potential impact of his work is always at the back of his mind, a trait he said he shares with many physician/scientists. "As physicians, we've cried with a lot of patients, and we live with their suffering all the time," he said. "It just adds a little bit to our interest in getting answers to medical questions."

Chole has done his part to add to medical advances. He has

developed a method of reshaping human cartilage to replace damaged inner ear bones and is co-developer of a tympanostomy tube used to ventilate the ear in patients suffering from repeated ear infections. The widely used tube halves the rate of these infections after the surgery.

In addition to pursuing these advances at UC-Davis, he added administrative and leadership responsibilities to his activities there, serving as chair of the otolaryngology department for 13 years. Lazarus, Davis' medical

"As physicians, we've cried with a lot of patients, and we live with their suffering all the time. It just adds a little bit to our interest in getting answers to medical questions."

school dean, noted that Chole's multiple skills made him an extremely talented, versatile department head.

His keen interest in research and other areas has been noticed as well by those who now work with him at Washington University. J. Gail Neely, M.D., professor of otolaryngology, said the faculty here have been very impressed with Chole since his arrival early in 1998. "On top of being a physician/surgeon and understanding the practice of medicine, he understands its business side and understands science. He is extremely supportive of developing new knowledge and of medical education."

A devout Christian and family man, Chole also has remained active in his faith throughout his career. And when their children were younger, he managed to arrive home by 6 p.m. many nights to help his wife, full-time homemaker Cindy Chole, care for them. His colleagues attribute these and other accomplishments to his keen mind, drive and organizational skills.

"He's a phenomenal individual, and one of the few true triple threats that persist in academic medicine," said Hilary Brodie, M.D., Ph.D., who trained under Chole and became chair of the UC-Davis otolaryngology

department when Chole came to Washington University. "He's an extremely talented surgeon, a creative, excellent scientist and a wonderful teacher," said Brodie, who still seeks Chole's scientific and career advice.

Despite his accomplishments, Chole admits that his career hasn't always been easy. "A physician/scientist is kind of pulled at both ends, and you don't do a really Nobel Prize-winning job at either side," he noted. "But you end up being a link between science and medicine, and it's critical to have some people who do that."

Primary goal

Chole's primary goal at the medical school is creating an environment where young otolaryngologists can pursue this rewarding career choice. Brodie and Chole's other colleagues are certain he will accomplish his purpose. Brodie observed that not a single resident or faculty member has left the otolaryngology department at Davis this decade, and attributed this dedication to the leadership Chole provided there.

Ever modest, Chole credits his faith in God and his outgoing wife with helping him become the person he is today. "I think that she really helps me to come out of my shell and be able to interact with other people better. I would never have been able to end up in a job like this if not for her," he said.

The couple will celebrate their 30th wedding anniversary in December. By then, Chole said he hopes they have a new home under construction so he can renew some favorite hobbies. Besides enjoying photography, he also has rebuilt a 1965 E-type Jaguar from scratch and grows a dozen or so Bonsai trees.

He started tending the miniaturized trees three decades ago in admiration of the patience, spiritual fulfillment and long-term perspective the Japanese gain from nurturing them. Keeping them healthy requires special soils, attention to their environment and regular pruning and shaping. "These miniature trees are never looked at as they actually appear, but as what you imagine that they will become, sort of like a child," Chole said.

"Looking at your life in the context of a bigger plan — it's a wonderful thing to do."

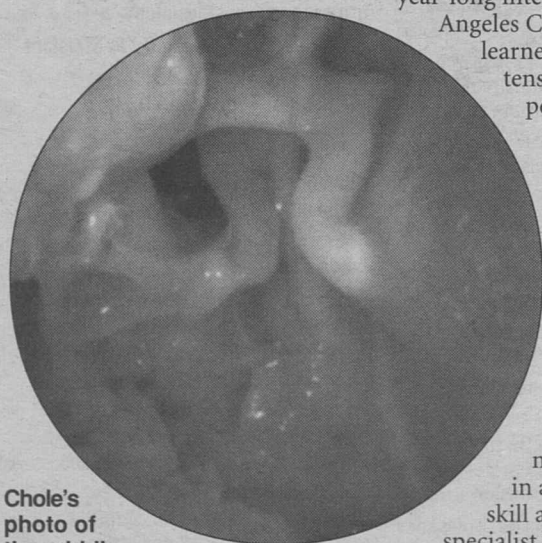
Richard A. Chole

From Davis, Calif.

Education University of California, Berkeley, undergraduate studies; University of Southern California, M.D.; University of Minnesota, Ph.D.

Family Wife, Cindy; children Joe, 27; Tim, 25; Katy, 22; and Melinda, 19

Key achievements Current president, Association for Research in Otolaryngology; author of "A Color Atlas of Ear Disease"



Chole's photo of the middle ear shows the ear drum (right) and attached ear bones that carry sound waves to the inner ear, including the triangular-shaped stapes bone.