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The Hippocrene, a diverse collection of experiences, reflections and artistic creations by members of the Washington University community, debuted this fall. The semi-annual publication was launched by first-year medical students Kathleen Page, Petros Karakousis and Vijay Shankaran, who wanted a creative outlet for faculty and students in addition to existing medically oriented extracurricular activities. The book contains work by members of the occupational therapy program, the Division of Biology and Biomedical Sciences, medical faculty and students.
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Researchers say SIDS may be many syndromes — each with separate causes, characteristics and triggers.

THE COVER

Various colors in the image reveal where receptors for acetylcholine and rapsyn are expressed in cultured fibroblast cells. Red indicates rapsyn, green is acetylcholine receptors and yellow shows where both rapsyn and receptors are in the same location. The experiment, conducted by the late John P. Merlie, Ph.D., provided a major step in understanding how the neuromuscular synapse, the junction between muscle and nerve, is assembled during development or nerve regeneration. For more, see the story beginning on page 12.

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New Alumni Professorship For Mecham

Robert P. Mecham, Ph.D., professor of cell biology and physiology and of medicine, has been named an Alumni Endowed Professor in the Department of Cell Biology and Physiology. Alumni professorships are funded by unrestricted gifts from medical alumni and former house staff and by gifts from friends of the School of Medicine. Six alumni professorships currently exist.

Mecham studies extracellular matrix, the critical material that helps bind together and support structures and tissues of the human body. His laboratory focuses on learning how cells produce elastic fibers, a major component of the extracellular matrix. Many human diseases, including Marfan’s syndrome, emphysema and several vascular diseases, stem from abnormalities in elastic fiber structure.

In addition to his work in the laboratory, Mecham has been extensively involved in teaching. He received the School of Medicine’s Distinguished Teacher Award in 1993 and 1994.

Erlanger: Exemplifying High Standards

Lisa Erlanger, a May 1995 graduate of the medical school, has been named the first Steven Dresler Award recipient. The award honors Dresler, an assistant professor of pathology, who died in 1989.

The award is given to a fourth-year student who best exemplifies the qualities of Dresler, including high academic standards, a commitment to promoting social good, civil rights and civil liberties through social action, volunteerism and high ethical behavior.

During medical school, Erlanger was awarded a Spencer T. Olin Fellowship for Women in Graduate Study and was the student representative selected to meet with First Lady Hillary Clinton during her visit to Washington University last year. Erlanger also helped coordinate the School of Medicine Interviewee Hosting Program and was chairperson of the American Medical Women’s Association recruitment program for women and minorities.

Erlanger currently is doing a family practice residency at Providence Hospital, affiliated with the University of Washington, in Seattle.
Holtzman Named Seldin Professor

Michael J. Holtzman, M.D., has been named the Selma and Herman Seldin Professor of Medicine in Pulmonary Diseases.

Holtzman, director of the division of pulmonary and critical care medicine, studies the molecular and cell biology of the airway epithelium, the layer of cells lining the respiratory tract. He hopes to understand how these cells interact with the immune system to protect the airway from infection and injury.

His laboratory was responsible for initial reports implicating the surface epithelial cell as an active participant in the development of airway inflammation. His group defined the enzymes that generate lipid mediators of airway inflammation. More recently, the lab characterized the role of a molecule called ICAM-1, which directs the interaction between epithelial cells and immune cells. Holtzman’s group also has shown that both of these genes are controlled by a single transcription factor called Stat1. The group is investigating how these molecular controls are switched on and off during airway inflammation in patients with asthma.

Dodson Elected President Of EFA

Edwin Dodson, M.D., professor of pediatrics and neurology, was elected president of the Epilepsy Foundation of America (EFA) in May.

In his two-year term as president, Dodson will guide the organization’s policy and programs, increase educational services, strengthen the EFA affiliates and expand EFA-based mechanisms for funding research.

Dodson, who is associate dean for admissions and financial aid, also is a leading expert on drug utilization in children with epilepsy. He received an EFA grant in 1975 to study the metabolism of antiepileptic drugs in children. The EFA awarded him another grant in 1983 to investigate the effects of various combinations of antiepileptic medications.

He has served on many of the EFA’s committees, and he joined its Professional Advisory Board in 1987. As chair of the advisory board from 1991 to 1993, he launched the largest physician education project the organization has ever undertaken. He joined the EFA’s board of directors in 1989.

Cryer Named Karl Professor

Philip E. Cryer, M.D., professor of medicine and director of the division of endocrinology, diabetes and metabolism, has been named the Irene E. and Michael M. Karl Professor of Endocrinology and Metabolism.

Cryer studies the mechanisms that prevent or correct low blood sugar in patients with insulin-dependent diabetes. He also directs Washington University’s general clinical research center.

Cryer’s research has been instrumental in explaining the physiology of glucose counter-regulation, the mechanisms that normally prevent or correct hypoglycemia, or low blood sugar. His work focuses on the role of the hormone epinephrine and has shown that deficient epinephrine secretion is a major factor in the development of episodes of hypoglycemia in diabetic patients. Hypoglycemia is a common side effect of diabetes treatment that can cause blackouts, seizures and death.

Cryer is president-elect of the American Diabetes Association and is a past recipient of the Banting Medal.

Lorenz Receives Culpeper Award

Robin Lorenz, M.D., Ph.D., assistant professor of pathology and medicine, has received a Charles E. Culpeper Foundation Scholarship in Medical Science for 1995.

The award provides Lorenz with $100,000 a year for three years to fund her research, which examines the development of intestinal inflammatory diseases such as ulcerative colitis and Crohn’s disease.

The funding will enable Lorenz to further define the cells and proteins that play a role in initiating intestinal inflammatory diseases. Her work will focus on identifying the function of the M cell, a cell in the intestinal lining that is thought to be an important regulator of the mucosal immune system. M cells, Lorenz notes, may transport proteins and bacteria through the intestinal lining to the immune system.

Lorenz was selected from more than 50 applicants nominated by their medical schools.
BARNES RETINA INSTITUTE

Specialty Eye Group Serves Metro Area

Physicians of Retina Consultants Ltd. and the Department of Ophthalmology and Visual Sciences have joined forces to establish Barnes Retina Institute, the largest vitreoretinal specialty group in the metropolitan area. The new organization links 10 specialists in a network that has five locations and provides comprehensive vitreoretinal care throughout the St. Louis and central Illinois region.

Eight ophthalmologists of Retina Consultants Ltd. and two from Washington University will conduct their medical practices under the auspices of the Barnes Retina Institute. All of the physicians involved have either a part-time or full-time faculty appointment with Washington University.

Some 75 employees will serve patients at locations throughout the metropolitan area. Patients can see a physician affiliated with Barnes Retina Institute at Washington University Medical Center/Barnes Hospital, or at offices in North County, South County and West County in St. Louis, and in Mount Vernon, IL.

The institute will be an attractive partner for corporate-sponsored clinical research and will offer patients an opportunity to enroll in the latest research projects involving retinal diseases. The strong teaching and medical education traditions that have been a vital part of both Retina Consultants and the Department of Ophthalmology will be continued in the new Barnes Retina Institute.

Doctoring The St. Louis Rams

The Department of Orthopaedic Surgery has been selected to provide team medical services for the St. Louis Rams professional football team.

The department and its sports medicine specialists will work together with other physicians at the School of Medicine to provide comprehensive medical care on a daily basis and in emergency situations. Such services include pre-season physicals, pre- and post-game evaluations, and physician presence at all practices, training camps and games. Players and their family members requiring inpatient care will be treated by Washington University faculty members at hospitals within the BJC Health System, which is affiliated with the medical school.

"I think this is terrific for the Rams and for Washington University," says Richard H. Gelberman, M.D., head of the Department of Orthopaedic Surgery. "We are honored that the team has entrusted Washington University with its health needs, and we will see to it that the team gets the highest level of care possible."

The core medical team includes:

Robert A. Shively, M.D., assistant professor of orthopaedic surgery, who will travel with the team. He also cares for the Washington University athletic teams as well as 12 area high school teams.

Rick W. Wright, M.D., instructor of orthopaedic surgery, who also will travel with the team.

Bernard T. Garfinkel, M.D., clinical professor of medicine, who served as the medical director for the St. Louis Cardinals football team until they moved to Phoenix.

Garfinkel will be assisted by his associate, James F. Loomis Jr., M.D., a clinical instructor of medicine.

Richard H. Gelberman, M.D., Fred C. Reynolds Professor of Orthopaedic Surgery, will oversee medical services for the Rams. Gelberman recently relocated to St. Louis from Harvard University, where he treated the hand and wrist injuries of the New England Patriots and the Boston Bruins.
Room To Grow

The Alzheimer's Disease Research Center (ADRC) and the Memory & Aging Project (MAP), which are part of the Department of Neurology, recently moved to The Health Key Building at 4488 Forest Park Blvd.

The new space comprises 5,300 square feet and houses both administrative offices and the clinic. The ADRC and MAP previously were located in Barnes Hospital's Queeny Tower.

The administrative area of the center has 18 offices and includes a file room that houses a large videotape library, a conference room and a reading room. The clinic features a waiting area and six testing rooms, four of which are for patient examination. Three of the exam rooms are equipped with video cameras for taping patient assessments.

Executive Director Kathleen Mann Keepke, Ph.D., says the new site benefits patients because it is easily accessible and because there is ample room to conduct all ADRC-related ancillary testing, which previously was located throughout the Medical Center.

In addition to the new facility, ADRC Director Leonard Berg, M.D., professor of neurology, has received an $11.2 million, five-year center grant from the National Institute on Aging for continued support of the center. First funded in 1985, the ADRC was one of the first established in the United States. A second five-year award followed in 1990.

"The funding will allow us to obtain more pieces of a very large puzzle that must be put together to develop more effective treatments for the disease," says Berg, who also chairs the medical and scientific advisory board of the national Alzheimer's Association.

In Support Of Brain Research

DENNIS W. Choi, M.D., Ph.D., Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology, testified in June before the U.S. Senate Special Committee on Aging on "Breakthroughs in Brain Research: A National Strategy to Save Billions in Health Care Costs."

The hearing was scheduled "to identify how advances in neurological research can result in significant cost savings to the health care system." Proposals in the House and Senate to cut the National Institutes of Health's $11.3 billion budget were later rejected.

Choi told the Committee that stroke, which afflicts half a million Americans each year, is the third leading cause of death in the Western world and the leading cause of adult disability. Physicians currently are unable to prevent stroke-induced brain damage, but Choi said medical research is bringing this possibility within our grasp.

"We must keep our commitment to medical research," he said. "What we would save by slashing federal funding for research does not compare to the massive losses we currently sustain due to disease."

Choi was among 11 other panel members who testified, including experts on Alzheimer's disease, Parkinson's disease and spinal cord injury, and relatives of celebrities — including the brother of Christopher Reeve — who have suffered brain and spinal cord damage.
Nomads In The Brain

REMOVING deadly brain tumors defuses a bomb but only leaves "normal" brain tissue riddled with migrating tumor cells. Research here shows that these cells can generate new tumors and that the drug Taxol, an experimental treatment for brain cancer, speeds the movement of brain tumor cells.

The most common primary brain tumors are the gliomas. Glioma cells do not metastasize to other parts of the body, but they leave the tumor when it is removed by surgery or radiation, causing death from generalized brain dysfunction.

Daniel L. Silbergheld, M.D., assistant professor of neurological surgery and anatomy and neurobiology, has established human glioma cultures from surgical samples and devised ways to monitor the amoeba-like cells as they wander over the surfaces of plastic dishes.

The cultured cells were unable to migrate when exposed to cytochalasin B, a substance that prevents the assembly of the cellular skeleton. This skeleton is made of microscopic tubules that assemble and disassemble as the cell moves.

Taxol, an anti-cancer drug, locks microtubules in place, preventing the cellular skeleton from disassembling. Although Taxol killed many of the cultured glioma cells, it made the survivors migrate faster than ever, in a dose-dependent fashion.

Silbergheld says physicians should shift their focus away from visible tumors. "Tumor recurrence and patient deterioration may be due to cells in normal tissue rather than to part of the lump being left behind," he says.

A World-Class Cancer Center

THE National Cancer Institute has awarded the School of Medicine a three-year, $814,000 planning grant that will be used to guide the assembly of the Washington University Cancer Center on the Medical Campus. The grant is the first step toward being named an NCI-designated cancer center, a title that would formally recognize the School of Medicine as a national center of excellence in cancer research and patient care.

"This planning grant gives us an opportunity to develop an outstanding center for the care of cancer patients in the Midwest and beyond, and to enhance our strengths in cancer research and education," says William A. Peck, M.D., executive vice chancellor for medical affairs and dean of the School of Medicine. Peck is principal investigator of the planning grant.

The center will administrate and coordinate cancer-related activities throughout the Medical Center. Its goal is to promote multidisciplinary research and patient care, to enhance and centralize patient services and to strengthen public outreach efforts for cancer prevention and control, says Daniel C. Ihde, M.D., professor of medicine, who helped prepare the planning grant.

The center of excellence in cancer care and oncology research will be put into place over the next three years. The medical school then will apply for an additional grant, called an NCI "core" grant. Receiving the core grant would automatically establish the center as an NCI-designated cancer center and would provide additional funds to support existing research and facilities.

Currently, there are about 55 NCI-designated cancer centers, with the closest one in Chicago.

Of Mice And Man

MARK F. Jacquin, Ph.D., research professor of neurology, has received $6.8 million to explore the ways in which the body's surface affects nervous system development and how the mature brain produces the sense of touch.

The grants — a $5.2 million program project grant and a $1.6 million grant from the National Institute of Dental Research — have been renewed continuously since 1985.

Jacquin's team uses rodents as models, focusing on the connections between whiskers and the brain. Jacquin says rodents rely on whiskers to navigate through their environment the way humans rely on their eyes.

Previously, Thomas A. Woolsey, M.D., professor of neurology and neurosurgery, discovered that each whisker on a rat's face is represented by a cluster of neurons in the brain called a barrel. When a particular whisker bends, a nerve conveys messages to the corresponding barrel, allowing the brain to link information about the environment with the location from which it came.

The whisker-barrel system is a convenient model for studying brain development. Moreover, the human brain also contains maps of the body's surface. "It is highly likely that the rules that dictate brain development in rodents also apply to humans," Jacquin says.
Aging In The Balance: Exercise Reduces Tendency To Fall

EXERCISE can reduce the risk of falling in elderly people, especially if the exercise is aimed at improving balance, researchers here have found. The multicenter study describes the combined results of eight independent clinical trials that measured the value of several treatments, including exercise, for reducing the risk of falls in older people. The School of Medicine was the coordinating center for the project, called the FICSIT study (Frailty and Injuries, a Cooperative Study of Intervention Techniques). J. Philip Miller, A.B., professor of biostatistics, was the principal investigator of the coordinating center; Michael Province, Ph.D., associate professor of biostatistics, was the co-principal investigator.

Volunteers aged 60 and older performed one or more of the following types of exercise: weight training, stretching, endurance training and balance training. Participants whose exercise regimen included balance training reduced their hazard of falling by about 25 percent. The most beneficial form of balance training was Tai Chi, an ancient form of martial arts that involves slow, controlled movements. Overall, participants who performed any form of exercise reduced their hazard of falling by about 13 percent.

Although the study pointed to balance training as being especially beneficial, Province says all of the physical components addressed in the study - balance, strength, endurance and flexibility - are important in determining one's tendency to fall.

Preventing falls is especially important considering their impact on health and economics. Every year, about 30 percent of people over 65 years old experience a fall, the researchers write. Roughly 10 to 15 percent of these falls result in serious injuries such as hip fractures.

Protein Provides Clue To Possible Cause Of Glaucoma

INVESTIGATORS have identified a protein that leads them to believe that a common form of glaucoma may be caused by an autoimmune disorder. Glaucoma affects 2 percent of Americans over age 40 and is the second most common cause of irreversible blindness. The disease damages nerve cells in the retina, and as the disorder progresses, patients first lose peripheral and then central vision. Approximately 25 percent of Americans with the disorder have a form of glaucoma in which the eye pressure is not elevated, so-called normal pressure glaucoma (NPG).

Unlike primary open angle glaucoma (POAG), which is associated with high pressure in the eye, it is unclear whether NPG patients benefit from medications that lower intraocular pressure, says principal investigator Martin B. Wax, M.D., associate professor of ophthalmology and visual sciences. Earlier studies conducted by Wax and others had shown that patients with NPG often have antibodies circulating in the eye. The researchers found that patients with NPG make antibodies to a naturally occurring protein in the retina called rhodopsin, a key protein that is involved in the signal the retina sends to the brain in order to see.

Wax says it is still unclear whether these antibodies are directly involved in the disease process, or whether they are a byproduct of another mechanism entirely. His next step is to look for therapies.

The investigators developed a test to detect anti-rhodopsin antibodies in patients' blood. In nearly half of the NPG patients, anti-rhodopsin antibody levels were more than twice as high as the highest level in any POAG patient.

"We don't believe that all normal-pressure patients have this rhodopsin immunoreactivity, but it does appear that a significant subset of patients does, and we view this as an important clue to the diagnosis and potential treatment of their blindness," Wax says.
without WARNING

Researchers Search For Clues To Halt Abdominal Aortic Aneurysms

by Caroline Decker
Hey balloon gradually and painlessly over time and can burst unexpectedly at any moment. Death usually follows within minutes.

Few ailments associated with aging strike as suddenly or are as dangerous as a ruptured abdominal aortic aneurysm, which occurs when the artery wall weakens and stretches to an abnormally large size. They develop in the abdominal portion of the body's largest artery, the aorta, which carries blood from the heart to the intestines, kidneys, pelvis and legs.

Because most abdominal aortic aneurysms develop "silently," they often go undetected until they rupture, causing massive hemorrhage. Even when abdominal aneurysms are found early, while they are still small, no therapy exists to halt their growth. Major surgery to replace the artery wall is the only treatment for a large aneurysm.

Research at the School of Medicine has identified a new lead in the search for the causes of abdominal aortic aneurysms. The discovery may open the door to new treatments for small abdominal aneurysms.

Scientists here have found an enzyme that they suspect plays a key role in weakening the abdominal aorta, leaving the vessel prone to rupture. The finding, reported in the July issue of the Journal of Clinical Investigation, may lead to ways to block the enzyme and prevent abdominal aneurysms from rupturing.
William Parks, Ph.D., associate professor of medicine and cell biology, and Robert Thompson, M.D., have identified an enzyme — 92-kD gelatinase — that they suspect plays a key role in weakening the abdominal aorta. The enzyme is one of a family of 11 enzymes called metalloproteinases. Parks' studies have established the critical role of metalloproteinases in wound healing.

Robert Thompson, M.D., assistant professor of surgery, holds a synthetic, V-shaped graft that is used to repair an aortic aneurysm. The graft is stitched to the aorta at one end and to the two iliac arteries at the other. Once in place, it carries blood to the legs.

The enzyme breaks down elastin, a structural protein that helps strengthen arteries. The researchers found that the enzyme, called 92-kilodalton gelatinase, is elevated in abdominal aneurysm tissue removed from patients. "We think the enzyme is not only involved in the initial development of abdominal aortic aneurysms, but may actually be necessary for their growth," says Robert Thompson, M.D., assistant professor of surgery, and the report's lead author.

In follow-up studies in laboratory rats, Thompson and his colleagues have shown they can successfully prevent the development of abdominal aneurysms by blocking 92 gelatinase with several commonly prescribed antibiotics. They plan to test the drugs in patients with small abdominal aneurysms.

"Our hope is that we will eventually be able to prescribe medication to stop the progressive degradation of elastin in the artery wall," Thompson says.

Elastin allows the aorta to expand and contract as the heart pumps blood throughout the body. Because elastin fibers are strong and flexible, the aorta can tolerate blood pressure fluctuations without dramatically altering its shape. But once the vessel's elasticity is reduced, the force of the heartbeat can cause the aorta to slowly stretch and bulge, resulting in an aortic aneurysm.

Elastin Breakdown

About 15,000 Americans die each year from ruptured abdominal aneurysms. Those at greatest risk are over age 65 with a history of cigarette smoking. Symptoms — when they occur — may include stomach or back pain or a pulsating abdomen when the patient lies on his back. Symptoms are taken seriously by physicians because most patients do not develop any warning signs until their aneurysm is on the verge of bursting. A careful examination by an experienced physician or an ultrasound exam also may detect small abdominal aneurysms before patients develop symptoms.

As abdominal aneurysms grow, their risk of rupture increases. If the vessel ruptures, the mortality rate is a sobering 95 percent. Emergency surgery to repair a ruptured abdominal aneurysm also carries a significant mortality rate — 50 to 70 percent. Physicians often recommend elective surgery when the abdominal aneurysm, which typically measures an inch in diameter, grows beyond 2.5 inches.

Thompson and his co-workers zeroed in on 92 gelatinase because it was known to degrade elastin. The enzyme is one of a family of 11 enzymes called metalloproteinases, which degrade connective tissue proteins. Earlier research by other investigators had suggested that metalloproteinases may be important in the development of aneurysms, but which one was not known.

Thompson, a vascular surgeon, began his aneurysm research when he joined the School of Medicine faculty two years ago. He came to Washington University, in part, because of the faculty's expertise in metalloproteinase and elastin research.

Earlier studies by metalloproteinase authority Howard Welgus, M.D., professor of medicine, identified the proteins degraded by metalloproteinases; he also has shown that metalloproteinases are produced by the inflammatory cells called macrophages.

Gregory Goldberg, Ph.D., professor of medicine, first isolated and cloned 92 gelatinase in 1989. And research by Robert Senior, M.D.,
Moog Professor in Pulmonary Medicine, later established that 92 gelatinase breaks down elastin. Studies by Robert Mecham, Ph.D., Alumni Endowed Professor in the Department of Cell Biology and Physiology, have uncovered the structure of elastin and how elastic fibers are assembled.

Collectively, their research laid the groundwork to study the role of 92 gelatinase in breaking down elastin in abdominal aortic tissue. Thompson teamed with metalloproteinase expert William Parks, Ph.D., an associate professor of medicine and cell biology. Parks' studies have established the critical role of metalloproteinases in wound healing.

Metalloproteinases play a crucial role in breaking down proteins in the body even before a baby is born, Parks says. Metalloproteinases break down proteins in the uterus, which enables a developing embryo to burrow its way into the uterine lining. As a fetus develops, excess skin between its web-like hands and feet is believed to be pared away by metalloproteinases. And without metalloproteinases, a simple cut or a skinned knee would heal much more slowly. "So, even though metalloproteinases are destructive, they also play a very beneficial and needed role," Parks says.

Thompson and Parks searched the family of metalloproteinases for an enzyme that breaks down elastin and is produced in aneurysm tissue. "We focused on the idea that for an enzyme to be important in aneurysm disease, it had to degrade elastin," Thompson says. "And since aneurysms are usually localized to one portion of the aorta, we also thought that the protein would be produced in aneurysm tissue rather than circulating in the bloodstream, though circulating factors may contribute to the breakdown of the artery wall."

In the study, the researchers took samples of abdominal aortic aneurysm tissue from patients undergoing elective surgery to repair the defect. They compared the samples with abdominal aortic tissue samples removed from normal patients and patients with atherosclerosis. The latter group was included to determine whether 92 gelatinase also is elevated in atherosclerotic disease. Atherosclerosis — or hardening of the arteries — may be a predisposing factor for the development of aortic aneurysms, the researchers speculated.

They found elevated levels of 92 gelatinase in aneurysm tissue compared with abdominal aortic tissue samples taken from the other patients. Levels of 92 gelatinase were twice as high in the aneurysm tissue compared with atherosclerotic tissue, and 10 times higher compared with the normal aortic tissue.

"The study raises our level of confidence that this enzyme is important in aneurysms, but probably not necessary for the development of atherosclerosis," Thompson says.

When researchers stained the tissue samples and looked for evidence of 92 gelatinase under the microscope, they found no presence of it in normal tissue and only spotty traces of it in some atherosclerotic tissue samples. In all aneurysm samples, however, the presence of 92 gelatinase was clear.

The researchers also were able to trace the secretion of 92 gelatinase to macrophages, an inflammatory cell of the immune system typically found in aortic aneurysm tissue. The macrophages, the researchers determined, produce the messenger RNA that directs the production of 92 gelatinase. "We were able to show that the messenger RNA for 92 gelatinase is made by the macrophages," Thompson says.

Taken together, the results suggest that chronic macrophage production of 92 gelatinase significantly contributes to the breakdown of elastin in abdominal aortic aneurysms, the researchers say.

Potential For Treatment

Within the wall of aneurysm tissue the researchers found lymphocytes and macrophages, indicating that aneurysm is not only a chronic inflammatory response but also an immune response.

Thompson and Parks then set out to determine whether they could successfully block 92 gelatinase. Earlier studies had shown that tetracycline derivatives are potent inhibitors of metalloproteinases. So the team chose to test their effectiveness in laboratory rats. "The drug selectively blocked 92 gelatinase," Thompson says, "but it did not prevent an inflammatory response."

The macrophages still congregated at the aortic wall and even sat side-by-side with the elastin, but the structural protein was not being degraded. "Presumably because we've blocked the enzyme's action," Thompson explains.

The researchers used tetracycline doses comparable to those prescribed clinically to treat infection. But follow-up studies indicate that even lower doses may effectively block 92 gelatinase.

Thompson and his co-workers now hope to determine whether tetracycline derivatives can block 92 gelatinase in patients who will undergo elective surgery to repair an abdominal aneurysm. They plan to give patients the drug several days prior to surgery to determine whether it can reduce 92 gelatinase levels in aneurysm tissue.

If it works, the researchers hope to follow up with a study testing whether the drugs can prevent the growth of small abdominal aneurysms.

Tetracycline compounds are inexpensive and have few side effects. But Thompson and his colleagues also are exploring the use of tetracycline derivatives that have the gelatinase-inhibiting effect without the antibiotic effect. Patients taking such a drug, which so far looks promising, would not have to worry about antibiotic resistance, a side effect of long-term antibiotic use.

A treatment for small abdominal aortic aneurysms may encourage more physicians to examine their older patients for signs of a developing aneurysm or to suggest routine ultrasound screening for those patients over 65. "That would allow us to find the small aneurysms and treat them medically, but just as important, we could identify the large aneurysms that now are being missed and get them repaired before they rupture," Thompson says.
John Merlie always got an early start on Saturdays, so colleagues would drop by to chat as they arrived at work. If they wanted advice, Merlie was a willing listener. If they needed help, Merlie would get the job done. But on May 27, they found an empty office—John P. Merlie, Ph.D., professor of molecular biology and pharmacology, had died of a heart attack at his home a few hours before.

The neuroscience community was stunned by Merlie's death at age 49. Zach Hall, director of the National Institute of Neurological Disorders and Stroke, wrote in the July 21 issue of Science that it was "doubly shocking because John was in midstride of what many thought the most important work of an already distinguished career."

During the previous six months, Merlie had seen the success of a difficult four-year project, helped win a prestigious program project grant from the National Institutes of Health and published a landmark paper in the journal Nature.

Merlie was prying the nervous system apart molecule by molecule. "For a long time that was considered an avant-garde approach," says Jeff W. Lichtman, M.D., Ph.D., professor of anatomy and neurobiology. "When John began these studies, molecular neurobiologists were considered great optimists who had little chance of making progress."

Merlie studied the neuromuscular synapse, the junction between muscle and nerve. He wanted to know how the synapse is assembled during development or nerve regeneration. "He was trying to understand a complicated and elegant cellular process," says Eugene M. Johnson, Jr., Ph.D., Norman J. Stupp Professor of Neurology. "He was building a body of work brick by brick."

Merlie planned to apply his findings to the brain, where synapses between neurons play key roles in learning. Understanding synapse formation may hasten treatments for neurologic disorders such as Alzheimer's disease, where synapse loss is tied to devastating symptoms.
The acetylcholine receptor, left, is made of five subunits. The cut-away drawing shows the receptor's ion-transporting channel, which opens rapidly when the two alpha subunits both bind to acetylcholine molecules. (With permission from "Chemical Signaling in the Brain," by Jean-Pierre Changeux. Copyright ©1993 by Scientific American, Inc. All rights reserved.)

Because synapses in the brain are difficult to study, many researchers use the more accessible neuromuscular synapse as a model.

**Receptor Assembly**

Merlie became interested in the synapse in 1973, while working in Paris with Jean-Pierre Changeux, discoverer of the nicotinic acetylcholine receptor. Located on the muscle side of the neuromuscular synapse, the receptor receives commands from nerves. These chemical messages take the form of acetylcholine, which transforms the receptor into a channel for sodium and potassium ions. The muscle contracts when thousands of channels open.

Merlie's early work, at the Salk Institute in San Diego, the University of Pittsburgh and then Washington University, focused on how the receptor is put together. "John was one of the first to realize the importance of understanding the mechanism of receptor assembly," says Stephen Heinemann, a neurobiologist at the Salk Institute.

The receptor looks like a tubular flower with five petals: two of a protein called the alpha subunit and...
one each of beta, gamma and delta. Shortly after birth, receptors are made
with an epsilon subunit in place of gamma.

To assemble this Rubik's cube, the
muscle cell makes the four types of
subunits, adorns them with sugar, then
nearly folds each protein. At some
point, it adds lipid and phosphate.
After the correct assortment of
subunits congregates into a receptor,
the product is packaged and shipped
to the muscle fiber surface, where it
inserts itself through the cell mem-
brane.

"John mapped out a number of
these assembly steps, applying the
newest information in cell biology," says
Merlie's closest collaborator,
Joshua R. Sanes, Ph.D., professor of
anatomy and neurobiology. "This was
probably the first protein in the
nervous system that had been studied
with this approach."

Merlie's papers describe biochemi-
ical properties of the acetylcholine
receptor, the identification of an
intermediate in the assembly of the
alpha subunit, the synthesis of the
receptor on membrane-bound ribo-
somes, the discovery that modifying
the subunits with sugar is necessary for
assembly, and the binding of lipid to
subunits.

Control Of Gene Transcription
Merlie became an assistant professor of
pharmacology at the School of
Medicine in the spring of 1983. At a
symposium that summer, he became
better acquainted with Sanes, who was
mulling over the distribution of
acetylcholine receptors. By the 12th
day of a mouse's 18-day gestation
period, receptors are dotted randomly
over the surface of a muscle fiber. On
day 13, they respond to the arrival of a
neuron by clustering at the developing
synapse, like iron filings attracted to a
magnet.

During the next 20 days, a cluster
doubles in size as new receptor
molecules are added. So receptors sit
shoulder to shoulder in the 0.1 percent
of the muscle fiber surface that lies
beneath the nerve terminal. "One of
the questions we are interested in,"
Merlie said in 1991, "is why one patch
of the surface has synaptic proteins
and the rest of the surface does not."

Sanes, Merlie and other investi-
gators have uncovered at least two
mechanisms for concentrating recep-
tors at the synapse. First, the nerve
tells the muscle to make receptors at
the synapse and to stop making them
elsewhere. Second, muscle proteins
tether receptors to the synaptic region
of the muscle membrane.

Sanes and Merlie proposed the
first mechanism in 1985 and then
tested the idea as technologies
improved. Embarking on a transgenic
program in 1987, Merlie began to
introduce altered genes into mice.
Most genes consist of a stretch of
DNA that codes for a protein and a
preceding stretch, called a promoter,
that binds proteins that regulate the
gene. So if the promoter is detached
from its usual gene and joined to one
that generates an easily detectable
product, it is possible to tell when the
usual gene would normally be tran-
scribed.

Using this approach, the collabo-
ators obtained direct evidence for
differences between synaptic and
nonsynaptic nuclei in 1991. They bred
cows containing the promoter of the
epison subunit attached to a gene that
makes nuclei react with a blue dye
when it is active. Looking at single
muscle fibers, they observed that the
synaptic nuclei became blue, whereas
the nonsynaptic ones did not. "That
really nailed down our hypothesis that
synaptic nuclei selectively transcribe
the receptor genes," Sanes says.

Because Merlie was interested in
the nerve signal that regulates this
transcription, he and M.D./Ph.D.
student Gerald Chu cultured muscle
cells from the genetically altered mice.

Lacking contact with nerve, this
system could reveal whether a protein
from nerve influenced transcription.

The researchers focused on a
protein called ARIA (acetylcholine
receptor inducing activity), which
previously had been purified from
chicken brain. They found ARIA at
the neuromuscular synapse, showing
that it was in the right place to
influence muscle. When they added
ARIA protein to cultured muscle cells,
the epsilon subunit became more
abundant. When they added it to
muscle cells derived from the genetically
altered mice, "we got blue nuclei
all over the place," says Chu, whereas
there were hardly any blue nuclei in
the cells that were not exposed to
ARIA. Therefore ARIA may be the
substance from nerve that turns on
receptor genes in synaptic nuclei."

Toward An Artificial Synapse
Merlie also studied a protein from the
interior surface of the muscle fiber
membrane, which he later named
rapsyn (receptor associated protein of
the synapse).

Because rapsyn's distribution
mirrors that of the acetylcholine
receptor, it was thought to tether
receptors at the synapse.

In 1987, Merlie's group collaborat-
ated with Jonathan B. Cohen, Ph.D.,
then professor of anatomy and neuro-
biology, to clone the rapsyn gene and
study the protein. "We realized after a
while that we could then try to
reconstruct some aspects of a synapse
in a cell that ordinarily doesn't make a
we could try to decide what the
minimal requirements were and how
some of these proteins functioned in
making a synapse."

Merlie and others had cloned the
acetylcholine receptor genes by that
time. This allowed his group, in
collaboration with Joe Henry
Steinbach, Ph.D., professor of anesthesi-
ology, to introduce the gene copies
into cultured fibroblast cells, which
normally do not make receptors. The
fibroblasts scattered acetylcholine
receptors over the cell surface. But
when copies of the rapsyn gene also
were supplied, the receptors clumped
together. "This suggests that [rapsyn]
can induce acetylcholine receptor clustering,” Merlie explained in 1991.

Postdoctoral fellow Elizabeth D. Apel, Ph.D., currently is using the fibroblast system to explore the relationship between rapsyn and a protein called dystroglycan, which is part of the supportive scaffolding in a muscle cell.

The Knockout Effort

In 1991, Merlie decided that “if we really want to know what a protein does during the development of a synapse, it is going to have to be in a live animal that is unable to make that protein.” So he embarked on an ambitious project to delete specific genes in mice.

Because the prospect of success was so uncertain, “we decided to make three knockouts in parallel — rapsyn, laminin B2 and agrin,” Sanes explains. In 1989, he and Merlie had identified laminin B2 as a component of the basal lamina, which covers the muscle fiber like a sausage skin. They suspected it played a role in the formation or stabilization of synapses. Agrin, like ARIA, is a signal from nerve that promotes receptor clustering.

They started with the agrin knockout, but their first success was with laminin B2. The mouse pups looked normal at birth but died two to four weeks later.

Two-week-old normal mice had well-differentiated synapses. Sacs of acetylcholine gathered near the end of the nerve terminal, ready for discharge, and the terminal was neatly capped by a helper cell called a Schwann cell. On the other side of the synapse, the muscle fiber membrane had many infoldings.

But nerve axons at the neuromuscular synapses of the knockout mice failed to develop the usual pretzel-shaped branches. And the acetylcholine sacs were scattered randomly around the terminal. Processes from the Schwann cells poked into the synapse, blocking the gap like roots in a drain, and there were few folds in the muscle fiber membrane.

These structural peculiarities had dire consequences for the flow of information, electrical recordings revealed. The collaborators concluded in Nature on March 16, 1995, that “[laminin B2] is important in synaptic differentiation... and that a molecular genetic analysis of synaptogenesis will be feasible in mammals.” This landmark paper provided the first example of a substance that organizes synapses in living animals.

The rapsyn knockout was next off the production line. Analysis of the mutant mice, which died on the day of birth, proved that rapsyn is necessary for clustering receptors and for construction of the subsynaptic protein scaffold.

Just before Merlie died, the team obtained the agrin knockout, which had previously proved elusive. “John’s last six months were probably the best of his life,” Sanes says. “This huge knockout effort had paid off, and our program project grant was assured.”

The five-year, $5.5 million grant was awarded to Sanes for research with Merlie, Lichtman and William D. Snider, M.D., Ph.D., associate professor of neurology. “So the project will go on,” Sanes says, “even without the best molecular neurobiologist at the School of Medicine.”

John Merlie’s work continues through members of his laboratory. They are, front row, L to R: his son, John Merlie, Jr., Medha Gautam, Elizabeth Apel and Michelle Elam; second row, Jacque Mudd, Dianne Barry and Barbara Klocke; third row, Andrea Missias and Wei-xi Athena Guo; fourth row, Zhican Qu and Mark Grady. Not pictured are Gerald C. Chu, Mia Nichol and Malu Gamez Tansey.
Reconstructive surgeons strive for functional improvement when applying their craft to repair oral cavities that have been ravaged by cancer. They also are faced with the task of ridding their patient of disease and performing a reconstruction that causes minimal deformity and disability — a particularly challenging call when working with cancers of the head and neck.

But the real goal in such reconstructive surgeries, says microvascular surgeon Timothy R. Jones, M.D., is to replace the tissue that is removed with similar tissue. Jones, who is an assistant professor in the division of plastic and reconstructive surgery, has found that tissue from the
Colon is much like that in the mouth and well-suited to reconstructive oral surgery. Not only is it thin, supple and durable, enabling it to facilitate speech and swallowing, the tissue is lubricated, which is necessary when resurfacing the oral cavity.

"This tissue is the most similar there is to what we are removing," says Jones. "With new technology, from endoscopic surgery to microvascular surgery, surgeons can transfer specific tissues from other areas of the body to make reconstruction as similar as possible to what was originally present. That's probably the most beneficial thing about this procedure."

Tissue from the colon is removed through an incision in the abdomen, then split lengthwise along the surface and sewn into the defect inside the mouth.
Timothy R. Jones, M.D., has developed a procedure known as free colon transfer, which is applicable to a variety of oral cancers and can be performed by most microvascular surgeons.

The procedure Jones has developed is known as free colon transfer; he has performed five such surgeries since 1992. The technique involves removing a segment of colon from the abdomen, splitting it lengthwise along the surface, and sewing the flap into the defect inside the mouth, much as a carpet is laid on a floor.

Although Jones does not consider the procedure experimental, he says it still is in the preliminary stage of development. “An essential concept in reconstruction is choosing the right procedure for the right person, because there is no perfect reconstruction,” he explains. “It’s a situation in which you have several options to choose from, and the goal is to select the option most appropriate for the patient’s needs.”

Until now, the tissue most commonly used to refine the oral cavity was taken from the skin of the forearm. For the most part, Jones says the tissue was well-suited to the task because it is thin. The big disadvantage, he notes, is that the tissue is not a lubricated surface like that inside of the mouth, and people with hairy forearms must endure having hair grow inside of their mouths. Another drawback, he says, is that people with poor circulation to the hands can have complications because an artery from the hand also is retrieved when the forearm tissue is transferred.

“One great advantage of the colon is the abundance of tissue available—the large intestine is so plentiful that it can be taken with essentially no side effects to the patient in terms of bowel function,” he says. “The tissue is thin, secretes mucus and provides a smooth lining that can be draped over the jawbone, allowing construction of a denture. A common problem among oral cancer patients is fitting them with teeth and giving them ways to chew food.”

Tissue from the gastrointestinal tract has been used before for head and neck reconstruction but with limited success. The small intestine is less suitable because its surface is irregular, and it secretes excess mucus; the lining of the stomach did not work because it secretes acid which can cause ulcers in the mouth.

Applying The Technique

Jones’ first free colon transfer was performed on Shirley Acton of Edwardsville, IL. Acton had a large oral cancer that had invaded the fleshy part of her right cheek and spidery through the upper and lower jawbones, part of her tongue and right tonsil.

Unlike traditional treatment plans, she received six weeks of radiation therapy prior to surgery. Jones says usually surgeons remove the cancer first and then give radiation. He reverses the process, he says, because radiation therapy applied to new tissue adversely affects its function.

“Radiation therapy is a necessary part of the treatment, but the problem with radiation is that it not only kills the cancer cells but also kills normal cells,” he says. “There are little, mucous-secreting glands throughout the intraoral lining, but after they are irradiated, their ability to secrete saliva is reduced. This causes dry mouth in patients, which is one of the problems I have tried to address by administering radiation before surgery.”

Surgery is long—Acton’s was 17.5 hours—because several procedures are taking place: cancer removal, colon resection and oral reconstruction. Two surgical teams are involved—one for the abdominal procedure and one for the head and neck. James W. Flesman, Jr., M.D., assistant professor of general surgery, heads the team that works on the abdomen.

Before surgery, Acton received several doses of antibiotics in the form of oral rinses and intravenous solutions to sterilize her mouth and large intestine. Brimming with bacteria, the mouth and the large intestine must be sterilized to prevent post-operative infection, Jones says.

Before tissue from the large intestine can be considered for transfer, patients are examined by colonoscopy to ensure their colons are free of polyps, which can be indicators of cancer, and other disease. So far, only one patient has not qualified for the procedure due to severe diverticulosis.
The size of the tumor determines the amount of colon taken for transfer. Jones says the large intestine is about six centimeters in diameter, but it distends when split lengthwise. "For reconstruction, usually you don't need a lot of length, but more width," he says. "If you split the intestine longitudinally along the surface and open it, it provides at least 12 centimeters of tissue."

To gain access to the diseased tissue in Acton's mouth, surgeons cut an incision through her lower lip, around the chin and down the neck, splitting her jawbone so that the lower portion of her face opened like a book. The cancerous tissue was removed, and tissue from the colon was retrieved, measured and sewn in place.

"One of the tricky parts is gauging how taut to make the new tissue," Jones says. "Mobility is important, so we don't want it too tight, plus, the intestine really has the capability to distend. None of the reconstructions has been too tight so far. In fact, on two people we've had to go back and remove redundant tissue."

Despite the length of the operations, Jones says all of the patients have recovered quickly and healed without complications. "They were all out of the hospital in less than two weeks," he says. "I think they healed so well because the tissue has a good blood supply, and we are able to reduce the level of bacteria, and, hence, the chance of wound infection with antibiotics."

**The Patient's Perspective**

Although her surgery took place three years ago, Acton, who is now 60, continues to see Jones regularly for check-ups. She also visits the dentist routinely to have work done on the prosthetic upper denture she wears, since both of her jaws were shortened in order to remove all of her cancer. The cancer also caused her to lose part of the palate (which allows the voice to vibrate) and part of her tongue.

Acton says what was most difficult after the surgery was waiting for her mouth to heal so that she could wear dentures and start talking. She was nourished through a feeding tube for eight months and could not wear dentures until it was removed.

Acton says she no longer has the capability to push food down her throat with her tongue, so she must wash it down with liquid. Still, she eats most everything, with the exception of fried or barbecued pork, which she says is dry and difficult to swallow. "It takes me a while to eat," she says. "But food tastes the same to me as it did before surgery."

Acton says Jones explained to her that tissue from her colon would be transferred to her mouth, and that she was the first patient to undergo the procedure. "The doctors were very good about explaining everything and making me and my family feel comfortable," she says. "I would advise anyone contemplating this type of procedure not to be afraid and have it done. It's an adjustment, but one that you can live with."

**Work To Be Done**

Although Jones says the free colon transfer is a definite improvement over other methods, he continues to refine the technique. One area of interest is the pharmacologic manipulation of mucous-secreting glands. Jones wants to know if such glands can be controlled with medications to produce more mucous and if medications could affect the type of lubrication in the mouth. He also recently performed the colon removal endoscopically rather than with the traditional 10-centimeter incision above the naval.

At this time, Jones is not aware of other physicians in the United States doing the procedure. However, a surgeon in Taiwan who heard a presentation by Jones on the surgery has performed several free colon transfers and been pleased with the outcomes. Intraoral cancers are prevalent in Taiwan and are believed to result from people chewing a substance similar to smoking tobacco here.

"The technique is applicable to a variety of oral cancers, and most microvascular surgeons would have no trouble performing it," says Jones. "These blood vessels are big for a microsurgeon, and there is plenty of length to the vessels. I think it's really just now getting introduced — it's not into the mainstream yet."

When Jones discusses surgical options with his patients, he says he is honest and tells them his technique is new in the way it is being applied. "Actually, the operation itself is rather straightforward in terms of removing the colon," he explains. "Colon is commonly removed when it is involved with cancer. What I'm doing is removing colon which is normal and using it in the mouth. People seem to have accepted it very well; they really have put their trust in me."

"The real key with intraoral cancer is early detection. If cancer is detected early, the prognosis is much better, treatment is less extensive, and we don't have to do extensive surgery and radiation."

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Shirley Acton, who had a large oral cancer removed three years ago, was Jones' first patient to undergo a free colon transfer.
Scientists Find That Different Cases Have Different Causes

by Diane Duke

Sudden infant death syndrome (SIDS) — the very mention of which evokes fear in parents and prospective parents alike — visited the Mulhall family four years ago. Their infant son, Nathaniel, became a victim to the unexplained syndrome when he was just three days old.

So two-and-a-half years ago, when Tyler Mulhall's health began to deteriorate two days after his birth, his parents, Michael and Sheryl of Rochester IL, feared that history might be repeated.

Tyler went immediately into a high-risk nursery, where he received glucose and endured many tests as doctors tried to determine the cause of his sudden and rapid decline.

"I was very nervous," Sheryl recalls. "We stayed that night at the hospital, and they didn't bring him in to me because he wasn't hungry. The next day, he was in the nursery and he started turning pale and was having trouble breathing."

The familiar scene frightened her as she recalled Nathaniel: "He seemed healthy when he was born, but then he started not wanting to eat. We brought him home on the second day and the next morning, I found him dead in his crib."
"We're sort of chipping away at what used to be called SIDS and giving these cases real diagnoses."

Arnold Strauss, M.D., studies how defects in particular enzymes involved in the breakdown of fatty acids cause diseases such as SIDS. He estimates that faulty enzymes account for about 5 percent of SIDS deaths nationwide.

Findings by Bradley Thach, M.D., left, and James Kemp, M.D., indicate that soft bedding may cause at least 25 percent of SIDS deaths. Thach and Kemp study rebreathing, a form of accidental suffocation, and have suggested that a variety of types of bedding could suffocate infants by trapping exhaled air.

Unlike Nathaniel, Tyler was able to receive effective treatment. He was referred to the care of Arnold Strauss, M.D., professor of pediatrics, and Robert Steiner, M.D., a pediatric geneticist and instructor of pediatrics at the School of Medicine. Strauss and Steiner study how defects in particular enzymes involved in the breakdown of fatty acids cause diseases such as SIDS. They determined that Tyler's condition was caused by a genetic mutation of the enzyme Medium Chain Acyl-Coenzyme A Dehydrogenase, or MCAD, which is linked to fatty acid metabolism.

That discovery, along with others that have been made relating to SIDS, leads Strauss and other pediatric experts to believe that what is called SIDS may actually be a large number of syndromes, each with its own causes, characteristics and triggers. "Some of the causes are better defined than others, but this is certainly among the best defined," Strauss says of the MCAD gene mutation. "We're sort of chipping away at what used to be called SIDS and giving these cases real diagnoses."

Strauss, who also is a professor of molecular biology and pharmacology, began applying his fat metabolism research to SIDS in 1987. He knew that when MCAD is faulty it cannot convert fatty acids into energy, and the heart and liver are adversely affected. He later cloned the MCAD gene in his laboratory; more recently he has identified the MCAD genetic mutation, known as G583A, which can kill infants only days old. Tyler was found to carry this mutation.

Most of the time, children with MCAD deficiency function normally because they get their energy from food intake, Strauss says. But in cases like Tyler's, when an infant gets sick and misses meals, the child may develop low blood sugar, liver failure and begin vomiting. The lack of energy to the heart and liver is compounded by a toxic build-up of fats. If the child does not receive a quick, intravenous dose of sugar, the result often is death.

Strauss' laboratory has identified numerous faulty forms of MCAD as well as deficiencies in other enzymes that are needed to break down fats and also can cause SIDS. Collectively, Strauss says, these faulty enzymes are responsible for about 5 percent of the 7,000 SIDS deaths that occur in the United States every year.

A Serendipitous Finding

Strauss' finding of the G583A mutation in Tyler came at the same time that he learned of another family who had lost a child under similar circumstances. Both families had lost their firstborn children when they were three days old, and both were found to carry the G583A mutation.

Tyler will take medication for the rest of his life to help with the breakdown of fats. He also must have frequent feedings and be carefully watched when he is sick, even with a cold. But the Mulhalls are thankful. "If it weren't for this discovery, I'm sure he wouldn't have made it," Sheryl says of her son, who is now healthy.

Strauss, whose work has led to an
Exploring The Physiology Of SIDS

Working to uncover the mysterious mechanisms behind one of the most common types of SIDS are Bradley Thach, M.D., professor of pediatrics, and James Kemp, M.D., assistant professor of pediatrics.

In the 1970s, Thach began studying apnea in infants. Apnea, a period during which breathing stops, often is characterized by color change, choking, gagging and limpness. Thach was interested in what initiates apnea and airway obstruction in infants. Many believed that apnea and airway obstruction might be one of the most common causes of death in SIDS.

He began exploring the mechanisms of recovery when an infant experiences apnea, wanting to find out why some infants recovered their breathing and others did not. Most infants automatically revive themselves and resume breathing by using what is known as the gasping reflex. They take in a quick, powerful breath that reoxygenates their blood and saves their lives.

In the late 1980s, Thach began working with Kemp, who also had an interest in airway problems and mechanics. When a woman from Defiance MO, came to them after one of her twins died while lying face down on a pillow, the two researchers began
to develop a test to determine whether bedding that came in contact with an infant's face could produce fatal asphyxia.

Using mechanical and animal models, the researchers simulated infant breathing on two polystyrene-filled cushions. These models enabled them to measure the effects of softness, malleability, airflow resistance and rebreathing of oxygen-poor air.

In a study published in The New England Journal of Medicine in 1991, Kemp and Thach warned parents that continuing to use polystyrene-filled cushions could endanger their infants' lives.

The researchers studied the deaths of 25 infants, most of whom had died while lying face down on polystyrene bead-filled cushions. Autopsies had been conducted on 23 infants, and 19 of the deaths were attributed to SIDS. However, Kemp and Thach's findings indicated that the majority of deaths probably were due to rebreathing, a form of accidental suffocation.

The study provided the first evidence that directly linked the cushions to the infants' deaths, Thach says.

The researchers concluded that if an infant lies face down with nose and mouth resting on the cushion, the material can mold around the infant's head closely, preventing access to fresh air. This forces the child to rebreathe expired air, which contains low levels of oxygen.

A year later, based in part on Kemp and Thach's work, the Consumer Product Safety Commission banned polystyrene-filled cushions after they were cited in the deaths of 30 infants nationwide.

Back To Sleep

As Kemp and Thach introduced the idea of rebreathing as a mechanism of SIDS, other countries began campaigning for parents to take steps to reduce SIDS risk factors. In New Zealand, where SIDS rates were two to three times higher than the rest of the world, health officials identified a number of risk factors. Among them: putting infants face down to sleep, smoking during pregnancy and not breastfeeding.

Soon, New Zealand, Australia and Holland launched Back to Sleep campaigns, followed by Great Britain and Norway. As a result, the SIDS rates in those countries have been reduced by 50 percent.

Health officials in the United States initially were skeptical of the data when it was published in New Zealand and Australia. But as more countries experienced similar results, the United States began to consider new ways to reduce the incidence of SIDS.

Kemp and Thach then published a study showing that soft bedding may cause at least 25 percent of SIDS deaths. Using several testing methods, they suggested five types of bedding that could suffocate infants by trapping exhaled air. They have since concluded that a variety of bedding may be implicated in face-down SIDS deaths.

Their research helped launch a U.S. Back to Sleep campaign in 1994 that urged parents to put babies to sleep on their backs as well as eliminate soft bedding. This campaign was sponsored by the American Academy of Pediatrics, the National Institute of Child Health and Human Development, the Sudden Infant Death Syndrome Alliance and the Consumer Product Safety Commission.

Studies since the campaign kick-off show the number of parents putting infants to sleep on their backs in the United States has increased from 25 percent to 68 percent. Data still is being collected, but it appears that SIDS may be occurring with less frequency. In St. Louis, where Kemp and Thach conducted their research, there were 26 SIDS deaths reported in 1990; in 1994, there were 12.

"I think the implications of the 'Back to Sleep' campaign are very important," Thach says. "This intervention has eliminated one type of SIDS — one factor — and allows us to see more clearly the other types of contributing factors. Preventing SIDS is a concept that until very recently was unthinkable. Most of us thought this would not happen in our lifetime."
In Response To Disaster

by J. Andy Sullivan, M.D.

I BEGAN Wednesday, April 19, with an hour’s workout, then started seeing patients at 8:00 a.m. I went to get my mail around 9:00, and on the way back heard a loud explosion. Looking toward downtown Oklahoma City, I saw a huge cloud of gray, concrete-like smoke.

I ran to The University Hospital and saw that the glass in the main lobby had been broken out. I went up to the roof from where I could see downtown, about a mile away. Black smoke poured from the area, and helicopters converged. I realized that a disaster had occurred and that many patients would be coming to our hospitals.

By 9:30, plans were in place. All patients who could leave had been sent home; elective surgery had been canceled, and the emergency rooms were prepared. The first patients to arrive at the Children’s Hospital suffered lacerations, blast injuries, fractures and head injuries. The initial wave brought us almost all of the patients we would receive that day. Being a teaching hospital, we had a large number of attendings and senior residents available instantly to care for patients, and we met the challenge.

At 11:00, with all our initial patients stabilized, I went to my clinic where I learned that medical personnel were being asked to help at the bomb site downtown. A hospital police officer drove a colleague and me to the scene.

It was like driving into a war zone. Parts of cars were strewn about; glass was blown out of all the buildings, and the huge Murrah Building was lying in a shambles. Many people were standing around cut and bleeding. Debris was strewn everywhere.

Many more people than were needed were there, and no one was clearly in charge. A doctor across the police line told us to select two medical personnel to go with us to the bomb site. As we walked, I questioned why in the world I was headed toward a building that had just exploded and might have more bombs in it.

After an hour helping at the blast site, I determined that triage had been established and that patients could be evacuated to hospitals, leaving little to be done at the site. The risk seemed high for me to be there, and it did not seem that there was much useful that I could do.

I was back in my clinic watching coverage when a colleague — Dr. David Tuggle — informed me that a victim had been found alive, trapped in the building’s basement. By his analysis, the only way to save her was to amputate her leg to free her.

With an amputation set, disposable scalpels and borrowed tennis shoes, I returned to the bombed-out Murrah Building. I was led to a stairwell and then down a ladder into the basement. I encountered one of my orthopaedic residents and requisitioned the hard hat he wore. From a fireman, I borrowed a flashlight. Concrete dust filled the air as we walked in rubble, water and debris, stepping over wires, pipes and chunks of concrete.

The victim — Dana — lay at the end of a long crevice. Getting to her was like exploring a cave. A huge concrete beam had fallen along
her right side, landing just at her right knee. It supported the collapsed floors above in a triangular shape, creating a small pocket in which she had survived. She was covered in white dust, lying on her back in six inches of water. Only one person at a time could approach her in the tiny space.

A colleague attempted to start an I.V., but was unsuccessful. The floors above were unstable, and one fireman kept his hand on the concrete beam. If he felt movement, and that we the disaster.

I made a circular saw and removed a piece of rebar that blocked my access to her knee. We made one last attempt to free her but couldn’t and caused her great pain. The firemen positioned a harness under her so we could pull her out quickly.

I crawled back in and discussed the situation with Dana. She was tearful, but understood the necessity. She agreed to the surgery. I was worried that she might not survive much longer, because she was hypothermic, hypotensive and having difficulty breathing. We administered Versed®, afraid that Demerol® would suppress respiration. Versed® had the advantage of being hypnotic and amnesic.

I used a scissors to remove the leg of Dana’s jeans. Then, lying on top of her, I twisted the two ropes to cut off the remaining circulation to the leg. Using the disposable blades and an amputation knife, I worked my way through the knee’s ligaments, tendons, muscles and vessels. The tourniquets worked, and Dana was pulled out onto a spine board and evacuated immediately to a safer and training, are decisive and action-oriented. Making the decision to perform the amputation was difficult but made easier by Dr. Tuggle, who supported the opinion that there was only one choice.

The operation was made more difficult by the conditions, but it could have been done by anyone with knowledge of the anatomy. The true heroes of the day were the police, firemen and others who worked under definable hazard to locate survivors and help them.

I think the city and the hospitals performed superbly in response to the disaster. And while I hope nothing similar ever happens again, the bombing clearly demonstrated the need for teaching hospitals with their well-trained depth, emergency medicine programs and designated trauma centers that can react instantaneously. Many such programs are placed in jeopardy by spending cuts that seem practical until something like the tragedy of the Oklahoma City bombing occurs.

\*Editor's Note: J. Andy Sullivan, M.D. ’69, is professor and Don H. O'Donoghue Chair, Department of Orthopaedic Surgery and Rehabilitation at the University of Oklahoma College of Medicine. The opinions expressed here are his own. He will be one of two recipients of the Weigelt-Wallace Award, an international recognition honoring physicians for extraordinary dedication and sacrifice on behalf of medicine and mankind. Established by an anonymous Texas benefactor, the award includes a $50,000 honorarium.\*
MORE than 200 School of Nursing alumnae, who graduated from 1927 through 1969, came from 24 states to attend the reunion luncheon at the Frontenac Hilton in St. Louis on June 10, 1995. It was the first time in many years that the group had come together for such an event.

Graduates from 1945 gather around Dorothea "Dottie" Cooper Hammer, who modeled their student nurse uniform.


Gloria Dieu McCanna, '45, presented a gift on behalf of the 50th year anniversary classes to the School of Medicine, accepted by Dean William A. Peck, M.D.

Bee Whitney Schulz, a 1936 graduate, was an enthusiastic song leader.
Graduates from 1946

Irene Metheny Morrison and Lois "Lou" Long Jacobs, class of 1946, introduced and congratulated the Class of 1945 on its 50th anniversary.

Graduates from 1947

Hazel B. Duncan, (seated, far right) Class of 1927, was recognized as the earliest graduate in attendance. Next to her are Ella Brase Lange, '30, and Edna Rose Heman, '31. Standing (L to R) Class of 1934 members, Ruth Danielsen, Grace Freund Susman and Mary Weiss Barnhart, along with William A. Peck, M.D., executive vice chancellor for medical affairs and dean of the School of Medicine.

Genevieve "Gennie" Koch Mason, '57, Eudora Winterrowd Schilsky, and Sue Schultz, both '56, reminisce over photos.
Blath Named WUMCAA President

Richard Blath, M.D.

Richard A. Blath, M.D. '71, assumed leadership of the Washington University Medical Center Alumni Association (WUMCAA) when he took over as president on July 1, 1995.

Blath, a private practitioner in St. Louis who specializes in urology, is chairman of the Department of Surgery at Christian Hospital Northeast and Northwest, a division of BJC Health System. He also is on the medical staffs of DePaul Health Center, St. Luke's and Missouri Baptist hospitals.

"Prior presidents, Dr. Ortbal and others, have set a very high standard—I'll be trying to emulate them and continue their tradition," Blath says of the year ahead.

One of those traditions has been the support of medical student organizations and community service projects. Last year, the Alumni Association contributed approximately $21,000 to these community service projects, which provide medical students with valuable experience in community settings as well as assisting the schools and clinics in which they serve.

The projects involve medical students in educating public school students and clinic patients about such topics as drug abuse, reproductive health, AIDS prevention, prenatal care and domestic violence.

Dr. Blath also will head the reunion class gift drive for the Class of 1971.

"We hope to raise $100,000," Blath says of the drive, adding that he would like to top the $130,000 raised by the Class of 1970.

These funds will expand the alumni-funded scholarship programs which ease the financial burden of students graduating from medical school.

Blath earned his undergraduate degree at Miami University in Oxford OH. After completing his medical degree at Washington University, he served as assistant resident in general surgery at Vanderbilt University Hospital in Nashville TN and as both resident and chief resident in urology at the School of Medicine and Barnes Hospital. He served two years in the United States Air Force and is a fellow of the American College of Surgeons.

Reaching New Heights

The School of Medicine's annual fund drive — the yearly solicitation of support for the school — ended at the close of June after an outstanding year. A total of $1,291,628 was raised for fiscal year 1995 from medical, healthcare administration, occupational therapy, physical therapy and nursing alumni and former house staff. According to the Annual Fund Chairman, John Davidson, M.D. '52, FHS, "Participation and giving to the School of Medicine increased this year thanks to the unflagging efforts of the Eliot Society Membership Committee, the reunion gift chairs and medical and allied health student phonathon callers." Alumni gave $767,927, increasing total dollars to the Annual Fund by 16 percent this year.

Part of the increase is attributed to the inspiration of the Eliot Society "Chairmen's Challenge," an effort to enlist 110 new members in the Eliot Society. The challenge was met, with 115 new members joining during the year. Issued by Dr. and Mrs. Phillip E. Korenblat and Dr. and Mrs. Nicholas T. Kouchoukos, longtime supporters of the school, the challenge matched gifts to the Annual Fund up to $50,000. Additionally, 366 current Eliot Society members renewed their memberships. Total membership in the Eliot Society numbers 481 for the year.

The Reunion Classes of 1935, 1940, 1945, 1950, 1955, 1960, 1965, 1970, 1975, 1980 and 1985 generously supported the Annual Fund through their respective gift drive activities. Of special note, the Class of 1970 raised nearly $130,000 in five-year pledges for an endowed student scholarship in the class's name. The 25th reunion gift effort, a program initiated last year by the...
Class of 1969, was led by a steering committee of six classmates. The committee included: Joann L. Data, Ronald J. Gaskin, Stephen A. Kamnetzky, Paul A. Mennes and William T. Shearer. David Ortblas chaired the effort.

**New Leadership**

The leadership and support obtained through our dedicated volunteers have made this a special year for the School of Medicine's Annual Fund. Thanks to the countless alumni who contributed their special talents and strengths to make the Alumni and Development Office's programs successful.

Special thanks to Nicholas T. Kouchoukos, M.D. '61 and Philipp E. Korenblit, M.D., FHS, who have served six years as Eliot Society co-chairmen. They will be succeeded by Ira J. Kodner, M.D. '67 and Gordon W. Philpott, M.D. '61. Kodner is professor of surgery at the medical school and director of the division of colon and rectal surgery at The Jewish Hospital of St. Louis. Philpott is the Edison Professor of Surgery and professor of radiology at the medical school. He is the associate director of surgery at Jewish Hospital.

John Davidson, M.D. '52, completes his fifth year as Annual Fund Chairman and will be succeeded by Emily Smith, M.D. '68.

**Officials of Johnson & Johnson present two gifts totaling $435,000 to support research being conducted by Robert D. Schreiber, Ph.D., Alumni Professor of Pathology and professor of molecular microbiology; Kathleen C. Sheehan, Ph.D., research instructor in pathology, and Philip D. Stahl, Ph.D., Edward Mallinckrodt, Jr., Professor and Head of the Department of Cell Biology and Physiology. From left: Sheehan; Jeffrey C. Geesin, Ph.D., of Johnson & Johnson's Wound Healing Technology Resource Center; William A. Peck, M.D., executive vice chancellor and dean; Stahl; Edward S. Kimball, Ph.D., of Johnson & Johnson's Janssen Research Foundation, and Schreiber. Schreiber's project is titled "Definition of the Molecular Basis of TNF/IL-1 Mediated Immunosuppression: Potential Development of a New Family of Immunosuppressive Agents." Stahl's project is called "New Ligands for the Macrophage Mannose Receptor and Inflammation."**

**New Officers Elected At Annual Meeting**

The annual meeting of the Washington University Medical Center Alumni Association (WUMCAA) was held on Friday, May 12, 1995, with David W. Ortblas, M.D., presiding.

Dr. Ortblas reported on the activities of the past year and presented the slate of nominees for new officers and Executive Council members for 1995-96. Unanimously elected, the new officers and members are:

- Vice President - Barry Milder, M.D. '73;
- Secretary-treasurer - Gordon Philpott, M.D. '61.

Council members to serve three-year terms: Robert C. Packman, M.D. '56, James E. Marks, M.D. '65, Kenneth Rotkoff, M.D. '75, Jennifer Wray Cole, M.D. '84, Anne Goldberg, M.D., former house staff.

New out-of-town members, who serve one-year terms, are:
- C. Garrison Fathman, M.D. '69;
- Robert Kolodny, M.D. '69; John Eisenberg, M.D. '72; Robert Fry, M.D. '72 and former house staff, and Robert Telfer, M.D. '65 and former house staff.

Barry Siegel, M.D. '69, and Dolores Tucker, M.D. '74, were elected to serve two-year terms as representatives to the Alumni Board of Governors.

New ex-officio members will include: Senior class president, Scott Gilbert; Annual Fund Chairman, Emily L. Smith, M.D. '68, and Associate Dean of Medical Education, S. Bruce Dowton, M.D.
Frank B. Norbury, MD '48, received his bachelor's degree in biology from Illinois College in Jacksonville in May. His college education was interrupted by World War II, when the Army sent him to medical school after two years of undergraduate school. He retired from the practice of internal medicine in 1989, and when he learned that he could complete his bachelor's degree with 30 hours, he went back to the classroom at age 70. When asked by a classmate what he was going to be, Norbury said, "I've already been."

Ron Evens, M.D.
Robert R. Goodin, MD, FHS '64-'66, is the 1994-95 president of the Kentucky Medical Association.

Michael Adams, MD '67, was recently awarded membership in The American College of Physician Executives, an educational and professional organization of 9,500 physicians in medical management.

Paul Lange, M.D.

Paul H. Lange, MD '67, is the 1994-95 president of the Kentucky Medical Association, recently awarded membership in the Executive, an educational and professional organization of 9,500 physicians in medical management.

'L80s

Robert Harmon, MD '70, recently named senior vice president and medical director of MetraHealth Center for Corporate Health in Oakton VA.

James John Bemberg, HAP '75, received the U.S. Public Health Service, Surgeon General's Exemplary Service Medal, for his outstanding leadership skills as administrative officer and for his ability to work with all types of individuals from both the public and private sectors. Former Surgeon General Joycelyn Elders bestowed the honor during her last days in office.

Mitchell P. Fink, MD '77, recently appointed Johnson and Johnson Professor of Surgery at Harvard Medical School and surgeon-in-chief at Beth Israel Hospital in Boston. He and his wife, Jan, will soon celebrate their 24th wedding anniversary.

Blair R. Suellentrop, HAP '77, serves as president and CEO of Complete Health in Birmingham AL.

Augustine Attiah, MD '79, practices private pulmonary medicine and critical care in Dallas. He writes that he has been chief of medicine at Charter Medical Hospital for the past two years.

Cheryl Keshner, OT '79, resides in Atlanta, where she is married, the mother of three children and has a private practice serving the school system.

'80s

Thomas W. Loeb, MD '80, writes that he is happily married and the father of two sons, living on Long Island and practicing plastic surgery in Manhattan.

Luci Belnick, MD '85 and Jeff Cohen, MD '85, are settled in Orlando FL, with their three children. Belnick is a faculty internist at Orlando Regional Medical Center, and Cohen is in private practice in nephrology.

Claire Skaggs Smith, OT '85, resides in Denton MD, with her husband and two children. She works with disabled children in the public school system.

Lyn McDivitt Duncan, MD '86, is assistant professor of pathology at Harvard Medical School and a dermatopathologist at Massachusetts General Hospital. Her daughter, Micki, is six; son Elias was born Dec. 19, 1994.

Kelly Greene, MD '87, sends word that she and her husband, Pat Offnek, MD, recently had a second son, Bobby, who joins brother Sean, now two. Both practice in the Seattle area.

Lawrence Gassner, MD '88, reports that he has joined a group of internists in Phoenix following several years of teaching at Maricopa Medical Center. He and his family plan to make the desert their home: "Winters are great, but it's a little toasty in the summer."

Mark Plumb, MD '88, is finishing a pulmonary fellowship in Milwaukee and then will enter private practice there. He and his wife, Chris, have two children.

Tom MacKenzie, MD '89, and his wife, Annie, have two children — Miles, and the newest addition to the family, Caden. He is on the faculty at the University of Colorado's Division of General Medicine and is working on his MSPH.

'90s

Bill Schwab, MD '90, PhD, works at Washington University Medical Center hospitals and enjoys playing with "his four beautiful and talented kids when he's home."

Edmond D. Hardin, Jr., HAP '92, has joined Chi Systems, Inc., a healthcare management consulting firm in Ann Arbor, as senior consultant.

Stephanie Brickner Jones, MD '92, is one of three authors of the book, Medical School Admissions: The Insider's Guide (Mustang Publishing, 1995). The book offers frank and practical advice from recent graduates to the 30,000 applicants vying for the nation's 17,000 openings. Jones is chief resident in anesthesiology at Barnes Hospital and mother of a 7-month-old son.

Jennifer L. Babb, OT '93, remains in St. Louis, working at Christian Northwest Hospital and investigating opportunities for earning an MBA.
Jennifer L. Forsberg, PT '93, works in outpatient physical therapy for a Green Bay WI hospital and serves as an athletic trainer for the local rugby team. She recently was elected to the nominating committee for her district of the Wisconsin Physical Therapy Association.

**IN MEMORIAM**

Gervais D. Smith, MD '22, died January 21, 1995, in Springfield MO. He was 98. He maintained a medical office in Bolivar MO for 66 years, following the direction set by his father. Survivors include his wife of 53 years, a son and two grandchildren.

Roland W. Stuehner, MD '23, died June 26, 1994, at the Madison House in Kirkland WA, at the age of 94. A specialist in general surgery, he had offices in St. Louis' University Club Building and was an assistant professor of surgery at St. Louis University. His survivors include four children.

James Roy Amos, MD '32, died January 13, 1995. He was 92. He worked in public health in Missouri and South Dakota and was a great supporter of the Boy Scouts of America. He is survived by his wife, three of his four children, 14 grandchildren and 21 great-grandchildren.

Christopher H. Martin, MD '33, died in his sleep on November 26, 1994, in Connecticut. He practiced medicine in Boulder CO and was a founder of the Boulder Medical Center.

Margaret Ann Ellis Crowe, NU '39, died June 1, 1995, at her home in Cape Girardeau MO. During the '50s, she helped to organize the nursing education program at Southeast Missouri State University.

Gene B. Starkloff, MD '39, died January 11, 1994, at Mari De Villa Nursing Home in west St. Louis County. He was 79. Starkloff was a pioneer in the treatment of the obese with intestinal bypass surgery. He was the son of the late Max C. Starkloff, MD, former city health commissioner after whom St. Louis' city hospital was officially named. Among his survivors are two daughters and three grandchildren.

Joyce M. Brueggeman, NU '42, died of complications from Parkinson's disease on April 21, 1995. She was a longtime faculty member of Washington University School of Nursing.

Alvin Goldfarb, MD '43, assistant professor emeritus of clinical surgery, died March 30 at his Creve Coeur MO home, apparently of a heart attack. He was 75. He retired in 1993 and attained the emeritus title in 1994. Among his survivors are two daughters.

W.G. Klingberg, MD '43, of Tulsa, died May 25, 1995, from heart failure. He was 79. He became the first chairman of the Department of Pediatrics at West Virginia University in 1960 and is considered the father of pediatrics in that state. He is survived by his wife, four of his five children and seven grandchildren.

Charles Jacobs, MD '45, died May 7, 1995, of leukemia. He had been an ear, nose and throat specialist in Ferguson MO, for 43 years. Jacobs was professor emeritus and taught throughout his career. Among the survivors are his wife, four children and 10 grandchildren.

Joan Gillen Iknayan, NU '51, died unexpectedly in Garden City KS, on November 5, 1994, while visiting relatives. She lived in Robinson IL, and leaves behind a husband, two daughters, two sons and two grandchildren.

Barbara Nancy Voegel, MD '57, died March 25, 1995, in Alton IL, after a lengthy illness. She had practiced pediatrics in Alton for 25 years.

Peggy Gaither Dismuke, NU '66, died at her home in Farmington MO, on May 3, 1994. She had retired as psychiatric nurse consultant for the Southeast Missouri Mental Health Center in Farmington in 1992. She is survived by her husband, James.

Susan Irish Virkler, NU '66, died on Wednesday, December 7, 1994, after a long fight with cancer. She was 50. She had been deeply involved in civic and political activities in Charlotte NC. Her survivors include her husband and two children.


John P. Merlie, PhD, professor of molecular biology and pharmacology, died on Saturday, May 27, of heart failure at his home in Olivette MO. He was 49. A memorial service was held on May 30.

Merlie, who received his doctorate in molecular biology from the University of Pennsylvania in 1973, had been at Washington University since 1983 despite several offers to become department chair at other universities. He devoted his career to the study of synapses, the connections between nerve cells and cells that receive their messages. For more about his work, see the feature story in this edition.

Merlie is survived by his wife, Margaret Brunk Merlie; three sons in St. Louis, John Paul Merlie, Chris Merlie and David Louis Merlie; his parents, Louis and Elvira Merlie of Vineland NJ; a brother, Richard Merlie of Spring Green WI, and a sister, Luann Linsalata of St. Louis.

Isaias Spilberg, MD, associate professor of medicine, died June 5, 1995, at Barnes Hospital after a long illness. He was 58. He joined the faculty in 1968 and at one time directed the rheumatology center and the Arthritis Foundation Clinical Research Center. Among those surviving are his wife and son.
Mark your calendars now and plan to meet your classmates in St. Louis at Reunion '96!

CLASSES OF:

Registration materials will be mailed in January.

MAY 9-11, 1996
A sapphire necklace, center, produced by Marc Hammerman, M.D., Chromalloy Professor of Renal Diseases in Medicine, was among the creations on display at the School of Medicine's Anne F. Dillon Faculty/Family Art Show in June. Encircling Hammerman's piece are necklaces made by Razine M. Wenneker, wife of Alvin S. Wenneker, M.D., associate professor of clinical medicine.