Managing Pain
First-year medical students now can get a portion of their neural science education from HyperBrain, a Macintosh-driven LaserDisc program in which the computer displays instructions, diagrams and text, and the LaserDisc — titled “Slice of Life” — provides 50,000 high-definition images. Four complete stations are available in the Media Computer Center in the library, and students have the luxury of scheduling their own time for instruction. Lessons are not necessarily linear: “There are many ways in, and you can go forward, backward or explore any subject in greater detail,” says Ed Walter, media librarian. According to Thomas A. Woolsey, M.D., course director, response to HyperBrain has been good. “In talking to students, my impression is that they are better prepared,” he says in support of the new teaching tool incorporated in response to student enthusiasm.
On The Cover:

We all share the experience of pain, but each of us may sense it differently and respond to it uniquely. Treating pain requires an open mind and the broad-based, multidisciplinary approach practiced at the School of Medicine's Pain Management Center. The graphic interpretation of pain on the cover is by Colorado artist Greg Michaels.

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A star athlete, brilliant student and natural leader exerted a powerful influence on the school.

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Imagine learning to speak without knowing how words sound. That is the challenge deaf children face, one that takes intensive training to meet. Now, early results of a study at the Central Institute for the Deaf (CID) show that cochlear implants may make the skill of speaking a little easier for deaf children to acquire.

For three years, investigators at CID measured deaf children's progress in learning to speak and understanding speech. Those with cochlear implants were significantly better at both tasks than were children using either conventional hearing aids or tactile aids, which convert sound into vibrations on the skin.

"We have no doubt that auditory speech perception is improved by a cochlear implant and that some aspects of speech production are accelerated," says Ann Geers, Ph.D., principal investigator and director of clinical services at CID. She cautions, however, that the conclusions are preliminary because the study is not complete. The researchers have compiled results from 18 of 48 children in the study.

Only about 10 percent of profoundly deaf children in this country learn to talk, Geers says, because few have access to the intensive training and highly skilled teachers required. If the early findings hold, cochlear implants could make that training less difficult and therefore more accessible, she says.

The study is the first to compare the effects of cochlear implants with other devices by looking at children who are all in the same educational program, says Jean Moog, co-investigator and principal of the CID school. "That allows us to separate the effects of the device from the effects of training," she says.

Cochlear implants pick up sound through an external microphone and relay it to a speech processor. The processor transmits to a decoder surgically implanted in the skull behind the ear. The decoder then stimulates an array of electrodes implanted in the ear's cochlea, and the electrodes excite the auditory nerve. Because the device cannot reproduce as many frequencies as an ear, the sounds it makes are less clear than normal hearing. "The cochlear implant is not making children hear the way you and I hear," Geers says. "It's a whole new sensation. These children are trying to learn language based on very limited information."

Of the 18 children who have finished one year or more of the study, all showed roughly equal abilities to distinguish basic speech patterns — hearing the difference between one-, two- and three-syllable words. But on tests that required perception of different sounds, implant children showed a marked advantage, Geers says.

Children with implants also produced more understandable speech. In a test that measured the number of understandable utterances out of 50, the researchers found that implant children improved by 45 percent, compared to about 10 percent for tactile aid and hearing aid children. "The bottom line is how much of a child's speech we can understand. That appears to be fairly dramatically affected by the implant," Geers says.

Although cochlear implant results look promising, the researchers intend to finish the study before making definite conclusions about the implants' effects. "We're interested in cochlear implants, and we're optimistic, but we're not yet ready to begin recommending them on a regular basis," Geers explains.

"We believe that if deaf children can learn to talk, they can be more independent because they won't need an interpreter. It opens up all kinds of social, economic and work opportunities if they can communicate with anyone," Moog adds.
Peek and Sanes Are AAAS Fellows

William A. Peck, M.D., and Joshua R. Sanes, Ph.D., have been honored with election to the rank of fellow by the American Association for the Advancement of Science (AAAS). A fellow of the association is defined as a "member whose efforts on behalf of the advancement of science or its applications are scientifically or socially distinguished."

Peck, vice chancellor for medical affairs and dean of the medical school and president of the Washington University Medical Center, was named for his "distinquished research in bone and mineral metabolism and for leadership in developing an internationally acclaimed center of clinical investigation at Washington University."

Peck is an internationally recognized expert in the study and treatment of osteoporosis, a progressive bone disease that is believed to affect more than 20 million Americans—usually women—who suffer bone loss and who may have severe skeletal and health problems. His contributions to academic medicine include clinical patient care, research, teaching and administration.

A native of Connecticut, Peck is a graduate of Harvard University, where he earned his undergraduate degree cum laude in 1955. He received his medical degree with honors from the University of Rochester School of Medicine in 1960. He joined the Washington University faculty in 1976 as Simon Professor of Medicine and physician-in-chief of the Jewish Hospital of St. Louis.

Sanes was elected as a fellow "for many insights into the mechanism of synapse formation." His research is directed toward learning how synapses form in the vertebrate neuromuscular system. His lab is investigating what molecules neurons use to recognize each other, leading to the highly complex patterns of synaptic interconnections that form during development.

Born in Buffalo, Sanes received bachelor's degrees in biochemistry and psychology from Yale and a doctorate in neurobiology from Harvard. He joined Washington University in 1980 as an assistant professor of physiology and biophysics and was named professor of anatomy and neurobiology in 1988.

Olin Fellows Named

The selection committee for the Spencer T. and Ann W. Olin Fellowships for Medical Scientists recently announced the names of fellows selected for 1991. According to Philip D. Stahl, Ph.D., director of the Division of Biology and Biomedical Sciences, the Washington University students selected are:


Recognized for superior achievement in biomedical research, Olin Fellows look forward to outstanding careers in medicine. Most are engaged in pursuing combined M.D./Ph.D. degrees and already have gained national recognition for their research.

The fellowships are funded by a $30 million commitment to the Division of Biology and Biomedical Sciences made in 1986 by the Spencer T. and Ann W. Olin Foundation. The gift supports students in the Medical Scientist Training Program (MSTP). The MSTP combines a solid education in clinical skills with training in basic research techniques. The program at Washington University School of Medicine is one of the nation's most prominent, attracting young people of exceptional talent from around the world. Through support of the program, the fellowships are instrumental in helping to fill the continuing shortage of physicians who pursue careers in biomedical research.

The gift also supports an annual Olin Symposium that focuses on biomedical research and assists in the training of students in the M.D./Ph.D. program.
Can Effects Of Stroke Be Safely Limited?

Drugs called NMDA antagonists can prevent brain damage caused by stroke, but they have not been used for that purpose because of toxic side effects. Now it may be possible to block those side effects, thereby allowing doctors to use NMDA antagonists to prevent stroke damage, say scientists here.

The team's paper in the journal *Science* reports that scopolamine—a drug used widely as a motion sickness remedy—is one of several drugs that prevent the toxic side effects of NMDA antagonists, thereby making them safer for use in stroke therapy.

"This is a fascinating line of research," says author John W. Olney, M.D., professor of psychiatry, "that has taken several surprising turns." Among the NMDA antagonists that Olney and his colleagues have been studying, the best known is phencyclidine (PCP), also called "angel dust." Neuro-scientists were surprised to find in the early 1980s that PCP, an illegal street drug that causes psychotic symptoms, can powerfully protect the brain against stroke.

Then, in 1989, Olney and his collaborators reported that PCP and related drugs, in addition to protecting many nerve cells against stroke damage, also have a neurotoxic action that damages some nerve cells. And now Olney and his colleagues have found that the neurotoxic action can be eliminated by several common drugs, such as scopolamine and pentobarbital.

These new findings raise an important question: Can the drugs that prevent the neurotoxic side effects also prevent the psychotic side effects? "There is indirect evidence providing a basis for optimism on this point," Olney says. "However, the final answer to this question must await future human studies because the expression of psychotic symptoms is a peculiarly human trait."

Currently, no effective treatment to limit brain damage caused by stroke exists. According to the National Institutes of Health, stroke is the third leading cause of death in the United States. Of the 500,000 Americans who suffer a stroke each year, nearly 30 percent die and 20 to 30 percent are permanently disabled. Olney is hopeful that this research will facilitate the development of effective and safe treatments for stroke, but he cautions that extensive clinical trials will be needed before such treatments can become generally available.

Farmer Directs Development

Randy L. Farmer has been appointed assistant vice chancellor and director of medical alumni and development programs, according to an announcement by David T. Blasingame, vice chancellor for alumni and development programs.

Farmer came to Washington University in 1988, joining the office of corporate and foundation relations. He was named director of that office in 1989.

How, Not Just How Much

One of two newly licensed vaccines used to protect infants from bacterial meningitis produces antibodies that are less effective at binding to the surface of bacteria, say scientists at the medical school.

Study of the vaccines, HibTITER, PedvaxHIB, and PRP-T, shows that though each vaccine produces enough antibodies to prevent *Haemophilus influenzae* type b (Hib) infection.

PedvaxHIB, prepared by Merck Sharp & Dohme, produces antibodies that bind to the bacterial polysaccharide capsule less avidly than antibodies elicited by the other Hib vaccines.
Although both the Praxis and Merck vaccines protect against bacterial meningitis, the vaccines achieve protection in fundamentally different ways. After a single injection of the Merck vaccine, two-month-old infants elicit high antibody concentrations, which are enough to protect them, Granoff says. The Praxis vaccine may require two or three injections to fully protect an infant. "Children who get the Praxis vaccine are not fully protected until after six or seven months of age," Granoff says. "The Merck vaccine achieves protection in a single dose at two months."

But Granoff says there is a price for the speedy antibody response elicited by the Merck vaccine. "The overall quality of the antibody achieved by the Merck vaccine at seven months is inferior to that elicited by the Praxis vaccine," Granoff says. The difference relates to the Merck antibody's decreased ability to bind to the bacterial surface and initiate the process by which other proteins in the blood kill bacteria.

By measuring antibody avidity, or how well an antibody binds to antigen, Granoff has shown that it takes almost seven times more antibody elicited by the Merck vaccine to kill bacteria. Granoff says these results do not indicate that Merck's vaccine is inferior. "The point is that the vaccines elicit much higher antibody concentrations in most children than required for killing the bacteria," he says. "The fact that it takes seven times more antibody doesn't really matter as long as the antibody concentrations are sufficient."

The Merck vaccine, Granoff notes, has an advantage if a baby is at high risk of disease, like those who attend day care or have older siblings. "The advantage of protecting an infant with a single, early injection is considerable," he says. "On the other hand, if a baby is not at high risk for being exposed to infection, then the other vaccines that induce a higher affinity antibody might be more desirable. Ultimately, I think all three vaccines will be effective."

Granoff believes the study should influence how vaccines are tested in the future. Traditionally, scientists have monitored a vaccine's effectiveness by measuring how much antibody is produced. If a new vaccine produces as much antibody as an old vaccine, it has been considered equivalent to the old vaccine. These studies neglect the avidity of the antibody, Granoff says. "I think we need to be at least thinking about whether measuring total antibody concentrations is sufficient or whether other measurements, such as antibody avidity, should be added to the vaccine evaluation process."

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Lee N. Robins Is Named University Professor

Lee N. Robins, Ph.D., professor of social science in psychiatry and director of the Masters Program in Psychiatric Epidemiology, has been named University Professor of the Social Sciences at the university, Chancellor William H. Danforth has announced.

University professorships are held by distinguished scholars whose work overlaps disciplines and schools. In her new role, Robins will continue her responsibilities at the School of Medicine and will play an extensive role within the Faculty of Arts and Sciences.

"Robins is one of the most distinguished social scientists associated with Washington University," notes Martin H. Israel, dean of the Faculty of Arts and Sciences. "As University Professor and a member of the newly formed Committee on Social Thought and Analysis, she will play a significant role in shaping the social sciences curriculum at the university."

The Committee on Social Thought and Analysis was created earlier this year to supervise an interdisciplinary curriculum that draws on faculty from various departments in the social sciences, humanities and the engineering, law and social work schools.

Robins, who is internationally recognized as a leader in studies of behavioral disorders in children, has been a member of the School of Medicine faculty since 1954. While establishing her professional career in sociology and epidemiology in the psychiatry department, she has held adjunct appointments in the sociology department and the Institute for Urban and Regional Studies on the Hilltop Campus. Much of Robins' work has centered on the effects of drug use, alcoholism and other familial disorders on child development.
A Marker For Type II Diabetes

Research here has identified the first genetic marker for non-insulin-dependent diabetes, a disease that affects millions of Americans.

Investigators studied genetic patterns in 16 French families in which some members had a form of non-insulin-dependent diabetes, also called Type II diabetes. They found that about half of the diabetics inherited a particular form of the glucokinase gene. Glucokinase is an enzyme critical for stimulating the production of insulin, the chemical that allows glucose to enter body cells.

“We have shown that a person is more likely to inherit a specific form of the glucokinase gene if they have one kind of Type II diabetes,” says M. Alan Permutt, M.D., professor of medicine in the division of metabolism. “Although we studied a subset of Type II diabetics, we think the results may apply to all Type II diabetics.”

The results strongly suggest that a mutation in the glucokinase gene could contribute to causing Type II diabetes, but the investigators have not yet identified the defect itself, Permutt says. The findings could lead to tests using this gene as a marker to predict diabetes and, with further understanding of the genetic influences, could eventually lead to gene therapies.

Type I diabetes, or insulin-dependent diabetes, is usually diagnosed in childhood. It is caused by an inability to produce adequate amounts of insulin. Type II diabetes is the more common form and normally appears in middle age. Its cause is unknown, but obesity and genetic influences have been identified as risk factors. The diabetics in Permutt’s study had a particular kind of Type II diabetes, distinguished by patients who first showed symptoms before age 25.

Researchers have searched for genetic markers for Type II diabetes for years. But the task has been difficult because the disease is probably caused by many genes. “This is step number one in uncovering what causes Type II diabetes. One importance of the finding is that it indicates that this approach of studying candidate genes is going to pay off,” Permutt says. “This will be encouraging to other scientists working in this field.”

The next step, he says, is to find the mutation involved and find out how frequently the mutation occurs in the general population of Type II diabetics. “We’d like to be able to isolate the gene and then show that it makes a defective enzyme,” he says. The study appeared in the March 12 issue of Nature.

Crawford’s Achievements Honored

Susan Crawford, Ph.D., professor of biomedical communication and director of the Library and Biomedical Communications Center, has received the President’s Award and the Marcia C. Noyes Award of the Medical Library Association (MLA).

The President’s Award is given annually to an individual who has made exceptional contributions that have enhanced the profession. The Noyes Award, the association’s highest honor, recognizes an individual who has made lasting and outstanding achievements. The awards cite Crawford’s “universal contributions to the profession in the areas of service, research, and publishing” that have given stature and credibility to health sciences libraries on both the national and international levels.

Crawford has authored or edited more than 120 publications and has received many national honors for her work. During her 11-year tenure at Washington University, she has been instrumental in planning and funding the medical school’s new Library and Biomedical Communications Center.

This highly automated center houses one of the most distinguished medical collections in the country.

School Rescues Fellowships

The School of Medicine’s Executive Faculty has voted to provide as much as $80,000 to continue funding the Summer Medical Student Research Fellowship Program that recently was placed at risk by a loss of the Basic Research Science Grant (BRSG) from the Public Health Service — the program’s principal support.

According to Milton J. Schlesinger, Ph.D., professor of molecular microbiology and administrator of the fellowships for the past seven years, the summer program provides first-year students with an opportunity for hands-on experience in a research lab and direct contact with a faculty member early in their medical school careers.
"This decision by the Executive Faculty shows that they believe the program to be essential to both education and research here as well as to steering young careers," Schlesinger says.

Until the recent NIH budget cut in the BRSG, the program managed to accommodate almost all students applying for summer fellowships — the rest were supported by NIH training grants or other medical school funds. That meant 36 students engaged in research in laboratories here during the summer of 1991. Each received a $1,800 stipend and produced a written report of the experience. Some saw their names on published papers, and a few had a direction set for their life's work.

In 1992, Schlesinger says, only enough money was going to be available to fund a maximum of 10 fellowships. Public Health Service funds for such grants have been reduced across the board and are being divided among a greater number of programs, he explains.

But then the Executive Faculty rescued the program. Most of the funding now will come from the medical school's departments under a formula weighted for the number of students participating and the departments' individual abilities to pay.

As a result, Schlesinger says, it will be possible to accommodate all 39 applicants on file with a $2,000 stipend for their 1992 summer research programs.

Two Awards, Honor To Raichle

Neurologist Marcus E. Raichle, M.D., is the recipient of two awards for his ground-breaking research on the function of the human brain. He also has been elected to the prestigious Institute of Medicine of the National Academy of Sciences.

One of 50 new members of the institute, Raichle investigates how the brain performs daily tasks. He aims to create a brain atlas that maps regions of the brain responsible for such functions as language and attention.

Raichle was presented with the 1992 Decade of the Brain Medal by the American Association of Neurological Surgeons on April 13 at the group's annual meeting in San Francisco. The medal commemorates the "Decade of the Brain 1990-2000," enacted by Congress to enhance public awareness of the benefits of brain research. The medal is awarded annually to a distinguished neuroscientist in recognition of notable contributions to this research.

He also received the Silvio O. Conte Decade of the Brain Award from the National Foundation for Brain Research at the organization's third annual Decade of the Brain Symposium on May 19 at the National Press Club in Washington, D.C. The foundation presents the award annually to a person who has demonstrated leadership and excellence in the advancement of the brain sciences.

Syposium Explores Project Implications

A March 24th symposium sponsored by the Program for Women in Science in Medicine featured three women experts as speakers on the topic: "The Genome Initiative: Recent Advances and Implications for Human Health Care." Helen Donis-Keller, Ph.D., who holds an appointment in genetics and psychiatry here, discussed the overall scientific goals of the federally-sponsored Genome Initiative and reported on progress in her laboratory. Mary-Claire King, Ph.D., professor in the School of Public Health, University of California, Berkeley, described epide-miological and genetic mapping approaches for pioneering family studies on genetic factors in breast cancer. And Patricia King, J.D., professor of law at Georgetown University Law School discussed the social and ethical implications of mapping the human genome.

"This is the first time in our history that the government has undertaken to explore such implications at the same time basic scientific studies are under way," she noted.
The 20 million Americans affected by kidney disease face a number of related hazards including hypertension, severe anemia and the toxic effects of waste products that build up when kidneys fail. But one of the most serious complications associated with chronic kidney disease, especially in patients maintained on chronic hemodialysis, is secondary hyperparathyroidism—a condition that can result in bones so brittle that they snap with one miscalculated step.

Secondary hyperparathyroidism occurs when calcium levels in the blood fall below normal and cause an increase in activity of the parathyroid gland, which produces parathyroid hormone (PTH). Overproduction of PTH causes mineral metabolism to go awry, robbing calcium from bones to maintain calcium levels in the blood. The result is the painful and debilitating bone disease osteitis fibrosa, which makes bones brittle.

This complication, which also increases risk for kidney stones, osteoporosis and gastrointestinal problems, has baffled researchers for decades. But after 30 years of work, a promising new compound may be able to reverse secondary hyperparathyroidism and minimize damage done to bone.

When calcium levels in the blood drop even minutely, sensors in the parathyroid glands located at the base of the neck respond immediately by secreting PTH. The hormone binds to bone cell receptors known as osteoblasts, which send a message to the resorbing cells, osteoclasts, and calcium returns to the blood.

"The secretion of PTH is a protective response that mobilizes calcium from the bone to normalize calcium in the blood," says Eduardo Slatopolsky, M.D., Joseph Friedman Professor of Renal Diseases in Medicine. "But there is a price to pay, because overproduction of PTH causes further destruction of the skeleton. The bones become brittle and break, and they don’t heal well because the bone is abnormal."

Slatopolsky, who has spent his career studying secondary hyperparathyroidism, currently is investigating a compound he says may be key in reversing the devastating condition. The compound, called 22-oxacalcitriol (OCT) was developed in Japan and is an analog of vitamin D, which...
controls the metabolism of calcium and phosphorus in the body. OCT acts in a manner similar to that of the active component of vitamin D, called calcitriol, that inhibits production of PTH and controls the severity of secondary hyperparathyroidism.

In animal studies comparing OCT and calcitriol, Slatopolsky says OCT appears to have all the benefits of calcitriol but none of its negative side effects. In some patients with secondary hyperparathyroidism, calcitriol can cause hypercalcemia (high calcium in the blood), metastatic calcifications or occlusion of the coronary and peripheral arteries, gangrene and eventually loss of extremities.

“We can give very large doses of OCT to suppress PTH secretion and the effect on calcium metabolism is minimal, next to nothing,” says Slatopolsky. “We are trying to develop clinical protocols to see if we actually will be able to suppress PTH in humans. If so, this probably will be the drug of choice.”

Slatopolsky’s team has used OCT successfully to reverse secondary hyperparathyroidism in uremic dogs and rats. He anticipates similar experiments using OCT in humans later this year in Japan, where the developer of OCT, Chugai Pharmaceuticals, is located.

Chugai and Washington University have patented the OCT compound, and Slatopolsky has received a $500,000 grant from the company to conduct further investigations on how various organs of the body metabolize the vitamin D derivative. Currently, his laboratory is studying how calcitriol and OCT suppress the synthesis and secretion of parathyroid hormone on the molecular level. Alex Brown, Ph.D., assistant research professor in medicine, and Jane Finch, research associate, are conducting a series of experiments in rats with kidney failure to understand the mechanisms by which OCT suppresses secondary hyperparathyroidism.

Slatopolsky says OCT succeeds where calcitriol fails because it is metabolized differently by different organs of the body, specifically the gastrointestinal tract and skeletal system. Both calcitriol and OCT bind to receptors in the parathyroid gland and suppress the synthesis and secretion of PTH. But in the intestine and in bone, where there are also receptors for calcitriol, there is virtually no response produced by OCT.

“In the parathyroid glands, OCT is equal to calcitriol, but in the intestine its action is minimal,” Slatopolsky says. “It depends on the site we’re talking about whether it’s more active, equally active or less active than calcitriol. There are a lot of unknowns that we don’t understand.”

Slatopolsky’s work has been instrumental in defining specific aspects of renal failure and developing bedside therapies to treat it. He is recognized as a leader in the study of mineral metabolism in patients with chronic renal failure. In 1982, he was the first to begin intravenous use of calcitriol in conjunction with renal dialysis to suppress secretion of PTH. Until then, calcitriol had been given orally in small doses. Although oral doses increased calcium absorption, they weren’t enough to control the production of PTH.

“When you have renal failure, the number of receptors for calcitriol in the parathyroid gland drops,” Slatopolsky says. “But with higher concentrations of calcitriol, which we achieve through intravenous infusion, we can regulate the number of receptors, and the effect of calcitriol is magnified for improved suppression of PTH.”

When renal failure plays havoc with the ability of individual parathyroid cells to recognize calcium, it is referred to as a “shift in set point.” As a result, Slatopolsky says, higher blood calcium concentrations must be present for the...
Slatopolsky's lab, Alex Brown, Ph.D., prepares samples for an assay.

parathyroid cells' sensitive secretion mechanism to recognize calcium the way normal cells do.

"The sensitive mechanism we have (to recognize calcium) is lost to renal failure," he says. "The number of receptors drops, the set point is shifted to the right, and there is a blunting effect that causes you to need much more calcium. We can return the set point to normal because the abnormal set point, in part, is due to the lack of calcitriol."

Still, there is a limit to how far calcium levels can be increased without causing adverse effect. Disease (such as metastatic calcification or hypertension) or symptoms (such as headache, nausea and vomiting) can result when calcium levels soar too high and other mineral levels, such as phosphorus, are left unchecked.

Early in his career, Slatopolsky showed that the phosphorus retained by patients with renal failure plays a significant role in the development of secondary hyperparathyroidism and resulting bone disease. With kidney disease, the body loses its ability to rid itself of the phosphorus normally eliminated through urine. Phosphorus, a mineral we consume in our diets daily, impairs the metabolism of vitamin D by suppressing the action of the enzyme, 1-hydroxylase, responsible for converting vitamin D into calcitriol.

In the past, phosphorus levels were controlled with diet and with aluminum-based phosphate binders, otherwise known as stomach antacids, which trapped the phosphorus and allowed its removal through excretion. Problems developed when researchers discovered that patients with kidney failure retained aluminum in the bones. Aluminum retention can lead to the painful bone disease osteomalacia and can cause death from aluminum encephalopathy.

Aluminum-based phosphate binders have since been replaced with calcium carbonate that eliminates phosphorus from the body but also substantially increases calcium levels. The problem, Slatopolsky says, is that with the increased calcium levels patients can't tolerate sufficient doses of calcitriol to suppress PTH.

Slatopolsky's experiments with OCT began about three years ago after its companion compound, calcitriol, was found to be effective in differentiating malignant cells and in suppressing the abnormal growth of skin fibroblasts. Slatopolsky was hopeful that OCT would work similarly on abnormal parathyroid cells, so he went to Japan to request the compound for testing.

Slatopolsky says OCT is one of the most promising of about 50 vitamin D analogs being studied worldwide in the search for effective suppressors of parathyroid hormone. Also exciting is OCT's potential for treating malignancies and skin disease. Studies in Japan have shown that OCT reduced breast tumor cells in rats by 60 percent. When used in combination with a common form of chemotherapy, tumor cell reduction was even more dramatic. "This has the potential to open new horizons for treatment of cancer, because it suppresses cell growth and induces cell differentiation," says Slatopolsky, who looks forward to exploring the many possibilities presented by what might become medicine's next multi-purpose drug.
The Search For A Speedy And Accurate Assay To Diagnose Heart Attacks

by Juli Leistner

Every year, millions of Americans feel the frightening symptoms of a possible heart attack: crushing chest pain, sweating, nausea. For 1.5 million, the symptoms are a sign of the real thing. Half a million of them will die from their heart attacks.

Physicians have a well-equipped arsenal of treatments for the nation's number-one killer, but in the critical early hours of an attack, they still must rely on judgment to distinguish false alarms from hearts in trouble. For two decades, physicians have tested for the appearance of a particular blood enzyme as a sure sign of heart damage. But the enzyme appears later, often only after the time window during which treatment must begin to minimize damage. Researchers are now sharpening their analytical skills to find earlier markers. Soon they may have easy, fast tests to diagnose within an hour and even help monitor the effectiveness of treatments.

When patients come to the hospital emergency room with the classic symptoms, a heart attack may seem unmistakable. But making a positive diagnosis is not always easy: Characteristic chest pain can be caused by indigestion; 40 percent of heart attacks escape discovery from electrocardiograms, and some patients with abnormal EKGs have healthy hearts. The result: About four in 10 patients are difficult to diagnose, says Paul Eisenberg.

As the heart is choked of oxygen, creatine kinase, or CK, leaks out of dying heart cells and into the bloodstream. Sobel, now director of cardiology and Tobias and Hortense Lewin Distinguished Professor in Cardiovascular Disease, and Roberts, currently head of cardiology at Baylor University, recognized that one form of the enzyme — MB CK — is derived almost exclusively from heart tissue and that rising blood levels were therefore a reliable sign of heart damage.

Sobel and Roberts developed assays for MB CK that gradually became the standard for diagnosing heart attacks, says Allan Jaffe, M.D., professor of medicine and director of cardiac intensive care at Barnes. But the original tests were cumbersome and time consuming.

Then in the mid-1980s, Jack Ladenson, Ph.D., professor of medicine and pathology, developed a monoclonal antibody that recognized MB CK. The finding was destined to make testing for MB CK clinically practical, because monoclonal antibodies lend themselves to fast, automated analytical tests. The university licensed the monoclonal technology to several companies, and automated tests have since become available.

"When you use the antibody that Ladenson developed, inaccuracies that occur with some other assays and could lead to confusion in their interpretation essentially don't occur. And it is much faster than the old test," Eisenberg says.
Ladenson's lab staff gave the new antibody a name they considered worthy of its powerful potential: "Conan," after Arnold Schwarzenegger's hulking film character.

The commercial tests take place in a machine roughly the size of a microwave oven. An automated arm places a drop of serum on a paper slide coated with Conan. MB CK in the serum binds to Conan and sticks to the paper. The machine flushes the slide with a solution containing a second, label-carrying antibody. Another flush adds a fluorescent marker to the label that the machine reads to produce a measurement of MB CK. Eisenberg estimates that about half the hospitals in the United States now use automated assays. He expects most to incorporate them within a few years.

Although Conan is a significant advance, problems remain. Besides heart attacks, elevated MB CK sometimes also results from hypothyroidism, renal failure, and diseases involving chronic muscle damage.

But, says Eisenberg, "the major limitation with MB CK is physiological: It takes several hours for it to leak out of your heart muscle and into the blood in a high enough concentration to measure. So even if you had the fastest assay in the world for MB CK, it's not going to permit diagnosis of a heart attack immediately."

At the same time, current treatments such as clot-busting thrombolytic drugs hinge on treating patients as soon as possible and within one to four hours of the start of an attack.

"So you are stuck with a bit of a dilemma: The test that will confirm a heart attack generally becomes positive only after you would want to start therapy," Eisenberg says. That's a dilemma worth avoiding because thrombolytic therapy carries an unavoidable but nevertheless acceptable risk of bleeding, according to Jaffe.

As a result, Conan is used primarily as a confirmation and to guide the later stages of care rather than to help decide on the initial care. For patients whose symptoms are not clear cut, emergency room physicians must decide two things, Jaffe says: "Who can you send home, and if you decide to admit a patient into the hospital, what level of care does that patient need? At present, people still use their best judgment about how to do that."

Researchers are now using the Conan strategy as a model to come up with even better markers, says Dana Abendschein, Ph.D., a research associate professor of medicine in the cardiology division.

Abendschein, Sobel and Jaffe are testing for sister forms of MB CK — called MM CK "isofoms" — to diagnose heart attacks even earlier, perhaps within one or two hours. The MM CK "tissue isofom" leaks from dead heart cells into the bloodstream, where subtle chemical changes occur to create two additional isofoms. Abendschein and his colleagues find that levels of the tissue form rise quickly in relation to the other forms during the early stages of heart attacks. A recent study found the rise a reliable marker for heart attack in 95 percent of 50
patients. MM CK’s limitation is that it is not specific to heart damage because it can come from tissues other than heart muscle.

The Washington University researchers also are using the MM CK isoform tests to determine when clot-busting drugs have opened blocked coronary arteries. “When we give one of the clot-dissolving agents like t-PA or streptokinase, we currently have no way of knowing whether the blood clot dissolved except by doing an angiogram,” Eisenberg says.

When blood flow is restored, a flood of enzymes washes out. By measuring the rate of appearance of the tissue form, Jaffe, Abendschein and Sobel have found that they can detect reopening of the heart artery within an hour of the onset of treatment 90 percent of the time. Abendschein directs a core laboratory for the multicenter Thrombolysis in Myocardial Infarction (TIMI) clinical trial, which is investigating the utility of isoform analysis for rapid diagnosis of coronary reopening in patients given clot-dissolving drugs.

Another possibility for fast diagnosis and detecting reopening of arteries is myoglobin, a protein involved in muscle contraction. It also leaks from damaged heart tissue very early. Ladenson has made a monoclonal antibody for myoglobin that is the basis of another automated assay, now close to commercial release. Studies so far show myoglobin to be helpful but slightly less accurate than other tests. However, it is also cleared from blood so quickly that it is useful only in patients who get to the hospital very quickly, Eisenberg says. In addition, the protein is not specific to heart damage.

On the other end of the time scale, the protein troponin, a structural part of muscle cells, leaks into blood over a period of days. Ladenson has made an antibody for one type of troponin that he thinks may be specific to the heart. The assay now under development would be useful in patients who come in for treatment extremely late, he says. Clinical tests on troponin are just starting.

“Troponin might be an important test when you have a false positive MB CK. That’s a small portion of patients, but it represents a diagnostic problem when it comes up. Having something else that’s very cardiac specific would be helpful there,” says Eisenberg.

Plasma from a patient suspected of having suffered a heart attack is loaded into a vial, then sampled by the immunoassay analyzer.

The researchers predict that physicians will eventually use a combination of these tests. “As the testing becomes more readily available and rapid, it might eventually be possible to take a small tube of blood and do a battery of tests. We are already beginning to look at combinations of markers considered together,” Abendschein says.

Bedside diagnosis with one, quick blood test is the ultimate goal, Eisenberg says. “At the same time, we’d like to have something that’s 100 percent cardiac specific. None of these current tests is perfect. All of them still require an element of clinical judgment.”

Rapid assays, Eisenberg predicts, probably will not guide the initial decisions of emergency department physicians but will help to more efficiently treat patients whom they decide to admit to the hospital. “The real impact will be two things: One is that patients who don’t have a heart attack will get excluded and moved out of intensive care faster; the other area is in noninvasive detection of a heart artery being reopened. There is more enthusiasm there than anywhere else,” he says.
In a sense, pain drives medicine. It's the signal that something is wrong, that tissue is being damaged. Pain sends people to doctors for expert care. So it is necessary.

But pain is elusive. It can't be seen or imaged. Despite increasing medical precision, measuring pain remains a subjective process. Experience teaches us that cuts and sores heal; pain will go away. Once it is gone, it cannot be recalled accurately.
Sometimes, however, pain grows to overwhelm a life. When it won't moderate and it won't stop and it begins to color all perception and interfere with relationships and daily living, then it becomes more than a warning and more than a symptom. Then it is a disorder all its own that requires the attention of specialists like those at the Washington University Pain Management Center.

As an example, consider the case of Mary Jo Rubio. Working as a visiting nurse in January of 1985, she cared for an elderly patient lying in a bed particularly close to the floor. When Rubio straightened from her task, she knew she had hurt her back. Every day since — for more than 2,700 days now — the pain has been with her. Rubio says the pain never has been less than 4.0 on a 10-point scale. Like most chronic pain sufferers, her pain has depressed her and laid waste to her plans. It has changed her relationships and dictated her choices.

When the intervertebral disk she ruptured was surgically removed 10 days after the initial event, the pain changed, but it didn't go away. In the time between the initial damage and April 1991 when Rubio got to the then new Pain Management Center, she visited 10 different physicians and tried everything that was offered to her — from deep body massage through relaxation techniques to powerful pain medications — all without substantial effect. "You just grab for anything you can to find relief," she says. "I worked and worked to find comfort."

Relief only came in any real measure when her entire experience of suffering was analyzed, then treated, using the multidisciplinary approach employed by Robert Swarm, M.D., and his colleagues at the Pain Management Center. Swarm, coordinator of the center and an instructor in anesthesiology, says Rubio's experience is unique in detail but not unusual in type. "Every case is different," Swarm says, "but when the pain is chronic, the problem is always complex." Chronic pain is defined as any pain which has continued...
for more than six months. Then, there is "always an emotional component," and the need for a broad-spectrum evaluation of the patient's condition that sets a multidisciplinary course for treating it.

According to neurobiology, pain begins when nociceptors (the name given to the nerve cells dedicated to sensing pain) are stimulated. They communicate impulses to the spinal cord and then to the brain, where suffering starts. Finally, pain behavior is displayed, Swarm explains. The perception of pain equals suffering, he says, and suggests that perhaps the center he oversees could be called the "Suffering Management Center," since that's what is treated there. "We don't treat nociception; we try to manage suffering — the whole experience," he says.

When a patient like Mary Jo Rubio first comes to the center — having been referred from general practitioner to specialist and then to the center — an early step is to rate the severity of the suffering. Patients are shown a horizontal line 10 centimeters long and asked to point to the spot that represents the level of perceived pain. The left end of the line is "0" and no pain; the right end is "10" and the most extreme pain imaginable. The physician then measures from the left in centimeters and reads a numerical value — say 4.2 or 6.7 — for the pain. "Our goal is to move down that line to the left," Swarm says.

In the effort to move down the line, the pain center's collaborators keep foremost the question: "What is likely to be helpful?" Called in to consult might be a psychiatrist to help ease the depression that so often accompanies chronic pain, a clinical psychologist to refocus attention away from the pain, a dietician to assist with weight control and dietary choices, a physical therapist to retrain muscles and treat movement dysfunction and an occupational therapist to help the patient with activities of daily living. Coordinating the treatment and administering medication and nerve blocks as appropriate is the anesthesiologist with additional specialty training in pain management.

Pain is so complex that it is difficult to describe in general terms. So pain center personnel employ classifications to make sense of the challenge. At its simplest, their model consists of two kinds of pain and three types of patients.

For the clinician who treats pain as a disorder, it can be either nociceptive or neuropathic. Nociceptive pain originates with the ongoing stimulation of the nerve cells dedicated to sending signals of chemical, thermal or mechanical damage to tissue. Neuropathic pain is the result of damage to nerves. For there to be neuropathic pain, there need not be continuing tissue damage — the nerves themselves have sustained damage and continue to send signals of pain after the acute injury has healed, Swarm explains. "Physicians have been slow to recognize such neuropathic pain and to acknowledge that it is as real as any other," he says.

Patients seen in the pain management center include those with:

**ACUTE PAIN** — Often post-surgical patients or victims of trauma, these patients have had pain for hours, days or weeks. Frequently, their pain is due to insult to nociceptors, though even these patients may have pain of neuropathic origin. "Most but not all acute pain patients respond to opioid medications at conventional levels," Swarm says, explaining that opioid medications work in the manner of morphine by blocking the transmission of pain signals to the brain. Opioids depress...
Working with nociceptors — nerve cells dedicated to sensing pain — Edwin W. McCleskey, Ph.D., studies pain one cell at a time. When we feel pain, he says, that’s not just regular nerve cells being overstimulated. It’s nociceptors, nerves that don’t fire at all until the stimulus reaches a noxious level.

The job of the nociceptor can be divided into three parts: 1) The painful stimulus is transduced at the tip of the nociceptor into a series of electrical impulses called action potentials. 2) The action potentials travel the length of the cell’s axon to the spinal cord. 3) The arrival of the action potentials at the spinal terminal causes the release of a chemical neurotransmitter that activates a second neuron leading to the brain.

Aspirin subtly inhibits the tip of the nociceptor. Local anesthetics stop transmission along the nociceptor’s axon. Opiates, by far the most selective and effective pain suppressors, inhibit communication between nociceptors and the secondary neuron.

Nociceptors don’t work in isolation. Stimulated, they also release signaling substances that communicate with the immune system. Then the permeability of blood vessels increases, redness appears, and new defenses are called to the fray. Activated immune system cells exude histamine and serotonin, sensitizing adjacent nerves. McCleskey, assistant professor of cell biology, says the expanding sensitization is at the root of chronic nociceptive pain, when there’s more pain than there is apparent tissue damage.

In an effort to understand and control pain, McCleskey strives to fill out the biological mechanism by which opioids work. He has shown that morphine and its analogs restrict the ability of one nerve to “talk to” another by inhibiting molecules called calcium channels that control neurotransmitter release. When a pain signal originating at the nociceptor and destined for the brain arrives at the synapse, transmission can be inhibited by morphine.

In that regard, morphine mimics the endogenous opioid system first described in the ’70s. McCleskey says that system of natural pain control is remarkably specific: “It affects pain from the main site, but lets through other sensations.” As an example of its intricacy, he points to studies of soldiers with serious war wounds who, under the stress of combat, continued with their tasks, issuing utterances such as, “I feel it, but I don’t care.” The endogenous opioid system was putting down their pain.

The endogenous system is also the reason acupuncture works. By creating small pain, the acupuncturist’s needles stimulate the release of endogenous opioids into the central nervous system and bloodstream. And when we rub near a sore spot, we’re working to accelerate the release of endogenous opioids by additional nerve impulses.

McCleskey faces several challenges in his effort to comprehend the roots of pain. Endogenous opioids are among the smallest and simplest hormones in the body, as short as five amino acids. Morphine, that mimics them so well, is an organic, ringed compound. Why they bind to the same site remains a question. Beyond that, no one has yet isolated nociceptors outside the body, so they are particularly difficult to study. McCleskey is at work on a method that will sidestep the problem of identifying them by creating a culture of nerve cells containing identified nociceptors.

The work’s potential dividends are huge. If the mechanism by which nociceptors operate to create the experience of pain can be mimicked outside the body, it may be possible to screen for drugs that more effectively control pain. A larger arsenal would be of tremendous medical benefit.
the transmission of the pain signals between the peripheral nerves and the spinal cord. Traditionally, such analgesics (pain blockers) have been administered via injections every three to four hours.

Swarm and his colleagues use such injections but also employ more powerful techniques including the epidural application of local anesthetics or opioid analgesics. An epidural is so-called because pain medication is delivered outside or above (“epl”) the “dura” (the outermost layer of tissue surrounding the spinal cord). They also sometimes use local anesthetics to block the nerves that transmit pain signals, and they may control the nociceptors at the site of the tissue damage by delivering anesthetics to the injured skin and muscle.

In some cases, patients are given control of their own pain management via patient controlled analgesia (PCA) devices that use a portable pump to deliver carefully measured pain-quelling doses of medication.

The relief of acute pain is clearly humanitarian, Swarm says, but equally important is the opportunity it provides. Patients free of pain turn, cough and breathe deeply sooner after surgery than those who suffer intensely. They also can become involved in their physical therapy more quickly, and evidence is growing that they heal faster. Complications and possible side effects are possible with strong pain therapy, but they must be weighed against the risks of untreated pain, such as pneumonia, the effects of immobility and perhaps chronic, severe pain, Swarm says.

Pain center personnel also push the frontiers of pain therapy by treating pre-surgery patients—dulling nociceptors at the site of the future incision on the basis of increasing evidence that such early intervention potently reduces post-surgical pain.

**CHRONIC NON-CANCER PAIN** — Some patients with chronic non-cancer pain suffer from vascular disease and ischemia of the lower extremities that leads to nerve damage. Others are diabetics with the complication of peripheral neuropathy—pathological changes in the nervous system. But 50 percent of such patients suffer back pain. Most of it, Swarm says, is the result of a work-related injury or acquired through degenerative arthritis of the back, as in Mary Jo Rubio’s case.

The original source of the pain is sometimes replaced with reflex sympathetic dystrophy (RSD)—a relatively common but poorly understood neuropathic condition that centers an exquisitely painful region on the site of earlier trauma and sometimes evolves into cold, swollen extremities that subsequently become useless.

In many such cases, a physical therapist consults in the treatment. Jay Diamond, M.H.S./P.T., a pain-center collaborator from the Irene Walter Johnson Rehabilitation Institute, says he takes a four-step approach to physical therapy for chronic pain sufferers. First, he learns from patients what body area hurts, when it hurts and what diminishes the discomfort. “I try not to dwell on their pain but on their decrease in functional activity as well as what they want to do that they presently cannot do,” he says. Then he performs an exam, observing both the quantity and quality of movement. He identifies postural and structural misalignments and muscle lengths and strengths that contribute to a diagnosis for the particular movement dysfunction. Finally, an exercise program is devised to restore proper mobility.

“If a patient says his back is killing him every time he stands up, then I watch him stand,” Diamond says. The goal: to get him to move correctly, using proper body...
"The philosophy of 'no pain, no gain,' does not hold," says physical therapist Jay Diamond, M.H.S./P.T., of the Johnson Rehabilitation Institute. Diamond trains patients to move correctly, using proper body mechanics to reduce their pain.

Helping them requires breaking the loop between how they think about their futures and their pain-restricted behavior. It may require logical argument and it may require encouraging them to test their limitations, Ristvedt says.

He also helps patients cope with their pain by directing their attentional mechanisms away from the pain. A common exercise is to ask the patient first to concentrate fully on his or her pain for a matter of minutes. Then the patient is asked to focus entirely on something else — a book, a sight, a favorite hobby — for the same length of time. The distraction, Ristvedt says, can be instructive; many patients can use distraction techniques to learn to differentiate between what he calls "OK pain," or tolerable pain, and "not OK pain."

Employing relaxation techniques he eases tension. Biofeedback helps patients gain local control over their muscles. And Ristvedt intervenes in some of the social aspects of pain behavior to address the friction that sometimes develops when the contribution by the patient is restricted.

CHRONIC CANCER PAIN — Swarm says that 60 percent of cancer patients will suffer moderate to severe pain with their disease or its treatment at some time. At best, he adds, only 50 percent of those will have their pain adequately relieved, even in developed countries.

That's more the fault of uninformed physicians than it is a problem of resistant pain. Swarm says: "The appropriate use of oral opioid medications will control pain for well over 90 percent of cancer pain patients. Of course, you can't just give these patients morphine and send them off; you must anticipate and treat the side effects and repeatedly adjust the dosage. Access to analgesics is very important for cancer patients." For the five to 10 percent whose cancer pain persists, Swarm may employ nerve blocks or more potent routes of analgesic administration.

Bonnie Henry, R.N., clinical nurse specialist in the Pain Management Center explains the team's overall approach: "We don't just prescribe pain medication. We search for the source of the pain through a broad, multidisciplinary evaluation. If we can't eliminate the cause, then we devise a management plan, provide the necessary support and give psychological help in coping with it. Even though all the pain may not be gone, we can bring back a level of functioning these patients thought they'd never have again."

Does that approach work? Listen to Mary Jo Rubio comment as she slides a cake into the oven: "They've been the only people who ever helped me. I do whatever they tell me. I can get pretty sad thinking about the future, but they help with the pain and they help me avoid that depression."
A rare photo of Barry Wood, M.D., shows him at his desk. The inscription: “To Ken King, my last clinical teacher,” is a reference to King’s time as chief resident, during which he reported daily to Wood on all admissions.

BY M. KENTON KING, M.D.
Precisely 50 years ago, William Barry Wood, Jr., came to Washington University as Busch Professor and Head of the Department of Internal Medicine. He had been recruited by Philip Shaffer, with assistance from Evarts Graham. He was destined to stay for 13 years and to achieve great prominence in academic medicine.

Barry Wood was born May 4, 1910, in Milton, Massachusetts. His father was a Harvard graduate and a cotton broker. Barry attended Milton Academy, where his talents as a star athlete in several sports, a brilliant student and a natural leader first became evident. It was a foregone conclusion that he would attend Harvard (1928-1932), and his record there was unbelievable. He earned nine varsity letters as a quarterback, center on the hockey team, star shortstop and first baseman and captain of the football team. He was a unanimous choice as All-American quarterback. He earned a tenth letter in tennis. He graduated summa cum laude and was first marshal of the senior class.

During his student days at Harvard, Barry worked with L.J. Henderson in the fatigue laboratory, studying the effects of strenuous exercise on the leukocyte count. He found that the count frequently doubled in short-distance runners, but quickly returned to normal. In football players, with more sustained exertion, the count might increase by a factor of three or four and remain elevated for hours. With this work began a lifelong scientific interest in the role of the leukocyte.

When Barry was a boy, his family spent a part of each summer in Maine at a camp shared with three other families. It was there that he met Mary Lee Hutchins, or Leal. She was at Vassar while he was at Harvard, and soon after graduation, the two married. During his senior year, Barry had written a book titled *What Price Football*. The royalties from the book, written by an All-American quarterback, helped finance the first few years of marriage.

After graduation from college, Barry decided to go to medical school at Johns Hopkins despite strong contrary advice from a number of “Boston Brahmin Physicians.” He felt that it would be good to get away from Boston, where he had spent nearly all of his life. Leal’s father was a physician who had trained at Johns Hopkins, and he had often spoken of what a wonderful place it was. Barry and Leal lived near the Hopkins Hospital. Leal went to Goucher and then to The Hopkins School of Public Health while Barry was a medical student. Both often spoke of these as among their happiest days.

In medical school, Barry worked in the laboratory of W. Mansfield Clark, investigating oxidation-reduction potentials. One summer he took a clerkship at The Boston City Hospital, where he was exposed to stimulating clinical teachers: Soma Weiss, William Castle and Chester Keefer. Although tempted to go into biochemistry upon graduation, he decided instead to pursue clinical medicine and went on to internship and assistant resident appointments at Hopkins, on the medical service headed by Warfield Longcope.

While still a resident physician, Barry, encouraged by Longcope, visited Oswald T. Avery at the Rockefeller Institute in New York. He was fascinated by Avery’s account of the whole story of the pneumococcus capsule and the polysaccharides. Upon completion of his residency, he returned to Boston as a fellow in the bacteriology department of Hans Zinsser. Zinsser was chronically ill, so Barry was assigned to work with John Enders. Wood and Enders developed a laboratory model of pneumococcal pneumonia in rats, based on earlier work by Nungester. Thus, Wood was launched upon studying the role leukocytes play in recovery from pneumococcal pneumonia.

Wood returned to Johns Hopkins for two years (1940-42) with the title of assistant in the department of medicine. In 1942, at the age of 32 and only six years after receiving his M.D. degree, he accepted the position of professor and head
of the Department of Medicine at Washington University. He was, in his own words, “flabbergasted” at the offer. He was only three years beyond house-officer training, and the heavy professional responsibilities would make it difficult to do research. His mentors at Hopkins advised against taking the position, but the attraction of the offer, and especially the challenge, were too great to resist.

Washington University, too, had gambled tremendously, handing one of the most important positions in its medical school to a young man whose bibliography contained fewer than 10 papers (four more were published after the appointment had been announced). The gamble, however, paid off handsomely, perhaps beyond the dreams of those who engineered it, as Wood later became a leading figure in academic medicine in this country.

In St. Louis, Wood was wise enough to hang back just a bit while learning the ropes from Harry Alexander, Alfred Goldman and Sam Grant. These experienced clinicians guided him and quieted those who worried about the green young man. Wood also adhered strictly to the admonition of his wife, Leal, never to mention Johns Hopkins. But Barry learned fast, as all who came to know him in St. Louis realized. He built a fine department, attracting an excellent young faculty including William Daughaday and a steady flow of superior house officers including early chief residents Edward Reinhard, Llewellyn Sale, Jr., Robert J. Glaser, Ernest Rouse and Bernard Garfinkel. Wood became an exceptional clinician, a tremendously stimulating teacher at the bedside and a leader among the senior faculty.

Why was Barry Wood a great man? He was highly intelligent and well-educated, but so are many others. He worked very hard. He had a captivating personality and was well-liked by almost everyone, but such traits are not rare. These qualities only formed the foundation of his makeup.

Those who knew Barry Wood well agree that he was different from anyone else they had ever known. He was born to lead. He had a special knack for making every patient, every case, seem fascinating. Boredom was unknown to him. His enthusiasm for quality was highly infectious. He increased the self-esteem of those around him by expressing confidence that they would perform well, and so they usually made a special effort to do so. He applauded their successes generously. He spoke to all persons with remarkably equal attention and respect, especially students and young people; deans and presidents received equal, but not extra, attention. If Barry was talking to a student in a crowded room, and a stream of dignitaries filed by, his eye contact and his attention remained totally with the young person until the conversation ended. This quality greatly impressed scores of young people.

Barry never, ever initiated comment about his athletic career. Others frequently brought it up, mentioning this or that great feat on the gridiron against Army or Yale. He would smile, pull at his ear lobe, and offer a comment such as, “That was a long time ago.”

During 13 years in St. Louis, Wood published 47 scientific papers, including 21 in the *Journal of Experimental Medicine*, two in the *Journal of Immunology*, and two in *Science*. He managed to make time for research despite a great many competing activities. He continued to work on the mechanism of recovery from pneumonia, including the importance of surface phagocytosis and became interested in the pathogenesis of fever. He was
Milton Eisenhower, then president of Johns Hopkins University, put his finger directly on the point, saying: "He was wise because his spirit was uncontaminated, because he knew no violence, or hatred, or envy, or jealously, or ill will. I believe that it was this purity that chiefly made him the (man) we so much revere ... it was a rare good fortune that brought to such eminence a man so reserved, so unassuming, so retiring, so gracious to high and low, and so serene."

And from Barry's housekeeper, Rosa Capers, who joined him after Leal's death: "Doctor Wood always made me feel so important." In one line she expressed what so many had felt.

Robert J. Glaser, M.D., a long-time friend and colleague of Barry's, who served as dean of two U.S. medical schools (Colorado and Stanford), as director of two major medical foundations (Henry J. Kaiser Family Foundation and The Lucille P. Markey Charitable Trust) and is a Washington University trustee, interviewed Barry on tape shortly before his death.  

Summarizing Wood's position in American medicine, Glaser says: "In his era Barry Wood was one of the most respected individuals in American academic medicine. Those who knew him at Washington University regarded him as a superb clinician, a stimulating teacher, and a productive investigator. Nationally, he was widely respected as a wise councillor and role model. His tragic death took from the scene a man who, in my opinion, was a giant in the best sense of the word."

Barry Wood died suddenly on March 9, 1971, in Boston, where his career had begun. He was there to attend a dinner honoring the retirement of Nathan Pusey, president of Harvard University.

*This tape is in the medical library in the "Leaders in American Medicine" series, sponsored by Alpha Omega Alpha. Also available from the AOA office, 525 Middlefield Road, Suite 130, Menlo Park, CA 94025.


Editor's Note: The author worked daily with Barry Wood for six years, in both St. Louis and Baltimore. He and Mrs. King (June) lived in his family home, north of Baltimore, for portions of three summers, while the Wood family was vacationing in Maine.  

Wood is shown with students on the ward in what was called a "student laboratory." In the bow tie is Robert J. Glaser, M.D.
The largest School of Medicine class in seven years — 130 students — graduated earlier this year after taking part in the National Resident Matching Program. More than three quarters of the graduating students, fully 76 percent, will be doing their postgraduate training at one of their top three choices of institutions. And 56 percent will train at their first choice.

Internal medicine remained the most frequent choice among residencies, selected by 43 of the School of Medicine graduates. That figure represents a percentage equivalent to the previous class, when 33 percent also opted for residencies in medicine. Choices reflecting increased popularity this year were surgery and residency programs described as "transitional" before specialties such as anesthesia. Pediatrics and radiology also remained popular choices.

Fifty-seven of the new physicians will stay in Missouri for their postgraduate training, 48 of them at Washington University or affiliated institutions. Other common destinations: California (13 students), Illinois (10), Massachusetts (9) and Texas (9). The complete list follows. Some names may be listed more than once because of preliminary and transitional residencies.

**ALABAMA**
*Birmingham*
University of AL Hospital
General Surgery
Terrill, Stephen G.

**ARIZONA**
*Phoenix*
Good Samaritan Hospital
General Surgery
Kunes, Margaret L.
St. Joseph's Hosp./Med. Ctr.
Internal Medicine
Beck, Brenda C.

**CALIFORNIA**
*Fresno*
UCSF/Fresno Valley
Transitional
Stein, Steven J.

*Los Angeles*
UCLA Med. Ctr.
Pathology
Shibuya, Robert B.
Radiology - Diagnostic
Heiss, Steven G.

*Sacramento*
Univ. of CA-Davis Med. Ctr.
Medicine-Primary
Redmond, Gregory S.
Obstetrics-Gynecology
Lee, Jon G.

*San Francisco*
CA Pacific Med. Ctr.
Internal Medicine
Cortland, Dawn D.
Medicine - Preliminary
Baranski, Karen J.
Ophthalmology
Shin, John C.

*San Diego*
U.S. Naval Hospital
Transitional
Kortebein, Patrick M.
Miller, Jeffrey S.

**Stanford**
Stanford Affiliated Hospital
General Surgery
Morris, Jonathan A.

**COLORADO**
*Denver*
University of Colorado
Anesthesiology
Stein, Steven J.

**CONNECTICUT**
*Norwich*
Yale-New Haven Hospital
Anesthesiology
Rhim, Sunghee
Medicine-Primary
Rhim, Sunghee
Obstetrics-Gynecology
Pustilnik, Terri B.
 Pediatrics
Pappano, Dante A.

**FLORIDA**
*Tampa*
University of South Florida
Pediatrics
Davis, Grace V.

**GEORGIA**
*Atlanta*
Emory University
Obstetrics-Gynecology
Spector, Michelle
Transitional
Blatt, Andrew N.

**HAWAII**
*Honolulu*
Tripler Army Med. Ctr.
Pathology
Frank, David R.

**IOWA**
*Des Moines*
VA Medical Center
Surgery - Preliminary
Ghouri, Ahmed F.

**ILLINOIS**
*Chicago*
Cook County Hospital
Emergency Medicine
McCrae, Paula C.

Loyola Medical Center
Gen. Surgery - Prelim.
Stokes, Ill. Sam

McGaw Medical Center
Internal Medicine
Stosor, Valentina
Vinci, Lisa M.

Anesthesiology
Sample, Madison

Pediatrics
Patterson, Lee V.

University of Chicago Hospitals
Pediatrics
Suggs, Adrienne H.
Waggoner, Darrel J.

Radiology - Diagnostic
Funaki, Brian S.

**EVANSTON**
Evanston Hospital
Transitional
Shin, John C.

**LOUISIANA**
*New Orleans*
Tulane Univ. School of Medicine
General Surgery
Thomas, Jr., Thomas V.
Peter Fishbach (at right) congratulates a trio of friends on their residency appointments during Match Day. From left, the three are Carlos Arcangeli, David Ritter and Patrick Kortebein.

St. Johns Mercy Med. Center
Transitional
Garcia-Ferrer, Francisco
Heiss, Steven G.
Martin, David P.
Rothman, Mark C.

Family Practice
Hoekzema, Grant S.
Newell, Astrid F.

St. Louis Childrens Hospital
Pediatrics
Altsura, Rachel A.
Bacharier, Leonard B.
Hershey, Andrew D.
Hershey Khurana, Gurjit
McGuire, Mary C.
Thio, Kwee Liu Lin

St. Mary’s Health Center
Medicine-Preliminary
Sample, Madison

St. Louis University
Pediatrics
McHaney, Mark B.
Washington University
Neurology
Carnes, Kenneth M.
Gorman, Douglas S.
Neurosurgery
Ojemann, Jeffrey G.
Ophthalmology
Garcia-Ferrer, Francisco
Otolaryngology
Cho, Judith E.
Urology
Arcangeli, Carlos G.

MINNESOTA
Minneapolis
Hennepin County Med. Ctr.
General Surgery
Collert, Mary E.
Univ. of MN Hosp. & Clinics
Internal Medicine
Canaday, David H.
Holman, Russell L.
Mandal, Robert W.
Rochester
Mayo Graduate School
Anesthesiology
Martin, David P.

NEW HAMPSHIRE
Lebanon
Dartmouth-Hitchcock Med. Ctr.
Radiology-Diagnostic
Reinhart, Robert D.

NEW JERSEY
Newark
UMDNJ - NJ Medical School
General Surgery
Brenner, Bruce M.

NORTH CAROLINA
Chapel Hill
University of NC Hospitals
General Surgery
Szwarc, Michael F.

Durham
Duke Univ. Medical Center
Internal Medicine
Desai, Sanjay A.
Quackenbush, Robert C.

NEBRASKA
Lincoln
Lincoln Med. Education Foundation
Family Practice
Treptow, Craig L.

NEW YORK
New York
Mt. Sinai Hospital
Internal Medicine
Schwartz, Jonathan
Surgery - Preliminary
Lederman, Eric D.
NY University Med. Ctr.
Internal Medicine
Fedor, Matthew C.
Presbyterian Hospital
Internal Medicine
Chapman, Jeff T.
Pediatrics
Moon, Anne M.
St. Lukes-Roosevelt Hospital
General Surgery
Ornstein, David K.

Rochester
Strong Memorial Hosp.
Internal Medicine
Bennett, Norman E.

OHIO
Cincinnati
Univ. of Cincinnati Hospital
Pediatrics
Finn, Gregory K.
Rankin, Denise M.
Zupan, Andrew A.

Cleveland
Mt. Sinai Medical Center
Emergency Medicine
Eitel, Janice R.

Columbus
Ohio State University
Ophthalmology
Spraul, Joseph W.

OREGON
Portland
OR Health Science University
General Surgery
Lum, Sharon Shou Jen

PENNNSYLVANIA
Bethlehem
St. Lukes Hospital
Transitional
Reinhart, Robert D.
Philadelphia
Chestnut Hill Hospital
Transitional
Antell, Andrew G.
Hospital of the Univ. of PA
Internal Medicine
Donahue, John K.

Temple University Hospital
Medicine - Preliminary
McCrae, Paula C.
University of Pennsylvania
Radiation Oncology
Antell, Andrew G.

Pittsburgh
University Health Center
Internal Medicine
Gudeman, Susan J.
Medicine - Preliminary
Chen, Diana M.
Obstetrics-Gynecology
Blomquist, Joan L.

TEXAS
Dallas
Baylor Univ. Medical Center
General Surgery
Kwa, Julie A.
Ritter, David W.

Univ. of Texas -SW Med. School
Anesthesiology
Ghouri, Ahmed F.
Ophthalmology
Lai, James Z.
San Antonio
University of TX Health Science Ctr.
Obstetrics-Gynecology
Pfanstiel, Ingrid R.
Wilford Hall USAF Med. Ctr.
General Surgery
Johnt, Daniel M.
Kasemsap, Pachavit
Psychiatry
Skop, Brian P.

VIRGINIA
Charlottesville
University of Virginia
Orthopedic Surgery
Hakala, Brian E.
Pathology
Kolar, Brian J.

WASHINGTON
Seattle
Virginia Mason Hospital
General Surgery
Bradshaw, Barton G.

CANADA
Montreal
Anesthesiology
Ghouri, Ahmed F.
Ophthalmology
Lai, James Z.
San Antonio
University of TX Health Science Ctr.
Obstetrics-Gynecology
Pfanstiel, Ingrid R.
Wilford Hall USAF Med. Ctr.
General Surgery
Johnt, Daniel M.
Kasemsap, Pachavit
Psychiatry
Skop, Brian P.

Temple
Texas A&M - Scott & White
Anesthesiology
Thompson, Paul A.

VIRGINIA
Charlottesville
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Orthopedic Surgery
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Alumni Report

1992

WELCOME ALUMNI

REUNION

1992
The '92 Reunion Alumni Award recipients (left to right): Harry S. Jonas, M.D. '52, (Alumni Achievement Award); Brent M. Parker, M.D. '52, (Alumni Achievement Award); Bernard Becker, M.D., (Distinguished Service Award); John D. Davidson, M.D. '52, (Alumni/Faculty Award); Frederick D. Peterson, M.D. '57, (Alumni/Faculty Award); William M. Landau, M.D. '47, (Alumni/Faculty Award) and Robert D. Utiger, M.D. '57, (Alumni Achievement Award).

Alumni Achievement Awards

Harry S. Jonas, M.D. '52, is the director of the division of undergraduate medical education and secretary of the Liaison Committee on Medical Education (LCME) of the American Medical Association. Prior to accepting that position in 1987, he was associated with the School of Medicine at the University of Missouri in Kansas City for 21 years, the last nine as dean. Under Jonas' leadership, that medical school achieved the respected status it enjoys. His dedication to quality medical education took him to the position of national influence he now holds. In recent years he has been site visit secretary for the LCME to major medical schools and has provided consultation to a number of educational institutions. His students remember Jonas as a "very special dean" who knew each of them personally and was always accessible. They search for superlatives with which to express their admiration for him, calling him "an incredible teacher" and "an extraordinary clinician." Colleagues describe him as one who "has used his remarkable energy and abilities to make significant contributions to his profession and his community and yet has time for family and a host of friends."

Brent M. Parker, M.D. '52, is professor emeritus of medicine at the University of Missouri at Columbia, where he teaches part-time. For six years he was chief of staff and associate dean for clinical affairs at the University Hospitals and clinics. Parker spent 14 years at Washington University as assistant and associate professor of medicine, co-director of the cardiology division and director of the Adult Cardiac Catheterization Laboratory. From 1957 to 1959 he served as section chief of cardiology at the Veterans Administration Hospital, University of Oregon.

Among the honors he has received are the Arthur E. Strauss Award from the St. Louis Heart Association and the Preventive Cardiology Academic Award from the National Heart Lung Blood Institute. He has been repeatedly recognized for his superb teaching, receiving the Outstanding Teacher Award at the University of Missouri in 1974, the Golden Apple Award in 1975, and the Teacher of the Year in Cardiovascular Disease Award from the American Heart Association, Council on Clinical Cardiology in 1986. He is more than an admired and respected professor; he is a treasured friend whose contacts with his students endure long after graduation.

Robert D. Utiger, M.D. '57, is clinical professor of medicine at Harvard Medical School and deputy editor of the "New England Journal of Medicine." From 1979-89 he served as director of the clinical research unit at the University of North Carolina School of Medicine, where he was Verne S. Caviness Professor of Investigative Medicine. Before going to North Carolina, Utiger was professor of medicine at the University of Pennsylvania.
School of Medicine, where he was chief of the endocrine section of the department of medicine.

Utiger became interested in research while in medical school and subsequently has made major contributions to the field of endocrinology. His research has focused on the interrelationships between the pituitary and thyroid glands, and he pioneered in the development and application of assays for thyroid-stimulating hormone and other hormones of the pituitary-thyroid system. Through his exemplary editorial work, Utiger is a national influence for the highest standards in the publication of information for the medical profession.

His peers describe him as a “very fine clinician,” “a modest person with a delightful sense of humor,” and a “thoroughly dedicated researcher and teacher.”

Alumni/Faculty Awards

John D. Davidson, M.D. ’52, is associate professor of clinical medicine at the School of Medicine and director of the division of hyperbaric medicine at St. Luke’s Hospital. He combines these responsibilities with a busy private practice.

He is particularly interested in hyperbaric oxygen therapy and in the effect of hyperbaric oxygen and growth factors on healing in ischemic wounds. He has been influential in the resurgence of interest in this therapy, which has the potential for significantly reducing healing time.

He has been active in the alumni association, serving as chairman for his class reunions. Giving many years of service as a member of the Executive Council and its committees, he is currently chairman of the Annual Fund and a member of the Eliot Society Membership Committee and the Alumni Board of Governors.

Davidson is a respected family physician and cardiologist, often treating several generations of the same family. He takes genuine pleasure in working with students who find in him a valued model and mentor. Colleagues and patients describe him with superlatives: “tremendously caring and thoughtful,” “very conscientious and hard-working,” “very dedicated to his patients, his family and his community.”

William M. Landau, M.D. ’47, is professor of neurology at the School of Medicine. From 1970 to 1991 he was head of the department of neurology, and from 1974 to 1991 also co-head of the combined department of neurology and neurological surgery.

Landau is widely respected for his clinical acumen and for his significant investigation of the motor system, which has been his abiding research interest. He is internationally known for his critical analysis of neurological research and for applying to his own work the same exacting standards. His somewhat satirical papers on “neuromythology” have been said to express the scientific conscience of neurology.

He is equally reputed locally as an incisive critic of political and social issues and a spirited participant in community affairs. He has been admiringly characterized as a person “who does not shun battles and is notorious for starting them, if they involve causes about which he has strong convictions.”

His stature as a teacher was honored by the senior medical students with their Teacher of the Year Award in 1987.

Frederick D. Peterson, M.D. ’57, is associate professor of clinical pediatrics at the School of Medicine and has maintained a thriving private practice for over 30 years.

Peterson is a clinical faculty representative to the Executive Faculty. He also has been instrumental in helping to establish the Community Office Practice Experience (COPE), which has revolutionized the manner in which ambulatory pediatrics is taught to residents by providing training in the office of a practicing pediatrician. He gives generously of his time and expertise to those he teaches, and they especially value his ability to critique in a way that is both effective and kind.

Peterson is devoted to the highest standards of patient care and has made significant contributions to patient care review. He has brought skill and sensitivity to that work, successfully negotiating a variety of challenging and difficult tasks.

To his many patients and their parents Peterson is an extraordinarily able and beloved physician who inspires confidence and trust. His colleagues say he takes his role as physician and teacher very seriously, is “articulate and tactful” and “a joy to work with.”

Distinguished Service Award

Bernard Becker, M.D., is professor and emeritus head of the Department of Ophthalmology at the School of Medicine. He headed the department from 1953 to 1988, becoming world-renowned for his research on glaucoma. And he led the department to an international reputation for exceptional research and teaching. Concurrently, he attained a reputation as a supportive leader who encouraged each individual’s professional growth.

Becker is the co-author of a classic text on glaucoma diagnosis and therapy. His publications include several other books, book chapters and hundreds of journal articles. He was the first editor-in-chief of the Journal of Investigative Ophthalmology. He is the recipient of several of the most prestigious awards in ophthalmology, both in this country and in Europe.

At Washington University, Becker devoted many hours of service as chair of the Library Campaign Steering Committee, providing leadership for planning and construction of the new Library and Biomedical Communications Center.

Becker’s influence has been far-reaching. Described by his friends as “quiet and modest,” his work has benefited many patients, medical students, and colleagues and has brought honor to the School of Medicine.
Ruth Moenster, assistant to the director of medical alumni programs, greets Philip Shahan, M.D. '42. In the background is Hannele Haapala, annual fund director.

Alan L. Brodsky, M.D. '67, converses with Mrs. Ira J. (Barbara) Kodner.

Reunion class gift chair W. Edward Lansche, M.D. '52, with his wife, Dee.

Mrs. David (Dee) Desper; Michele Flicker, M.D. '76, and David Desper, M.D. '77.
William A. Peck, M.D., vice chancellor for medical affairs and dean, presents the Distinguished Service Award to Bernard Becker, M.D.

Mrs. Paul (Charlotte) Hagemann and Paul O. Hagemann, M.D. '34, with Alumni Achievement Award recipient Harry S. Jonas, M.D. '52.

William A. Abele, M.D. '47 (standing), visits with Burnet W. Peden, M.D. '47; Jack W. Newport, M.D. '47, and Mrs. Jack (Patsy) Newport.

Mrs. Robert (Susan) Fry; Robert Fry, M.D. '72 (reunion class social chairman); Kenneth J. Lisberg, M.D. '72, and Nancy Stengle.
Mrs. Philip (Jean) Shahan and her husband, reunion class social chairman Philip T. Shahan, M.D. '42, in conversation with C. Barber Mueller, M.D. '42.

I. Jerome Flance, M.D. '35, who won the Alumni/Faculty Award in 1990, shares his thoughts with John D. Davidson, M.D. '52, who won the same award this year. Davidson also served as reunion class social chairman.

Penelope G. Shackelford, M.D. '68, incoming president of the Washington University Medical Center Alumni Association, speaking at the banquet after accepting the gavel.

William A. Peck, M.D., vice chancellor for medical affairs and dean, in the company of Washington University trustee Robert C. Drews, M.D. '55, and Robert L. Virgil, Ph.D., executive vice chancellor for university relations.
Chancellor William H. Danforth, M.D., shares a moment with Robert D. Utiger, M.D. '57, Alumni Achievement Award recipient.

Mrs. John M. (Molly) Slaughter and John M. Slaughter, M.D. '42.

Mrs. Helman (Evelyn) Wasserman; Helman C. Wasserman, M.D. '32; Gerald Wool, M.D., '62, and Mrs. Gerald (Sandra L.) Wool. Wasserman served in the dual role of both social and gift chair for the 60th reunion class.

J. Keller Mack, M.D. '32; Mrs. Eugene (Margaret) Bricker; Eugene M. Bricker, M.D. '34, and Ruth Benjamin enjoying the evening.
Ira J. Kodner, M.D. '67, president of WUMCAA, presides at the alumni awards banquet.

Ira J. Kodner, M.D. '67, congratulates Jon Morris, president of the class of '92, following the official welcome of graduating students into the alumni association.

Randy L. Farmer, Ed.D., assistant vice chancellor and director for medical alumni and development programs, visiting with Mark H. Gregory, M.D., and Mrs. Mark (Patricia) Gregory, Ph.D., director of corporate and foundation relations in the Office of Medical Alumni and Development.

Reunion class gift chairman Gene H. Grabau, M.D. '42, responding for his classmates after their recognition at the awards banquet. He also welcomed the class of '92 into the alumni association.

Beverly Logan-Morrison, M.D. '82, who served as both social and gift chair for her reunion class, renewing acquaintances with Karen L. Goodlett, M.D. '82.
Mrs. Birkle (Mary Lea) Eck; Birkle Eck, M.D. '42; Mrs. George Watkins; George Watkins, M.D. '42; Mrs. Ewald (Ort) Busse, and Ewald (Bud) Busse, M.D. '42.

William M. Landau, M.D. '47, recipient of the Alumni/Faculty Award and reunion class gift chair, greets classmates.

Robert Kingsland, M.D. '37, reunion class chairman, and Mrs. (Shirley) Kingsland.

Photography enthusiast George Sato, M.D. '47, served as reunion class social chairman.

Melrose Blackett, M.D. '82, and Kenniston Carr, M.D. '82.
Mrs. Raymond A. (Ann) Ritter; Raymond A. Ritter, Jr., M.D. '62, (reunion class social chair), and Alan Bisno, M.D. '62.

Mrs. Asa (Dorothy W.) Jones and Asa C. Jones, M.D. '42.

C. Barber Mueller, M.D. '42, and Mrs. (Jean M.) Mueller.

The brothers Adler: Benard C., M.D. '37, and Morton W., M.D. '37, enjoying the reunion.
Louis J. Novoa added a touch of personal style to his traditional garb during commencement exercises held Friday, May 15. The leis were rumored to be symbolic of Novoa's impending marriage in the Hawaiian Islands. The School of Medicine conferred 15 M.D./Ph.D. degrees, five M.D./M.A. degrees and 110 M.D. degrees.
A diagram of what we call pain shows that only the outermost layer of the model — pain behavior — can be observed. But the complex process of experiencing pain begins with the stimulation of nociceptors, nerves dedicated to sensing painful stimuli. For more about pain and its management, see the feature story in this issue.