Demystifying Depression
Illuminated partly by the green light of a laser, Medical Scientist Training Program student Patrick Jay measures the diffusion of membrane proteins on the surface of a cell using fluorescence photobleaching recovery (FPR). A spot on the cell, which has a specific population of its membrane proteins labeled with a fluorescent marker, is illuminated with a laser beam. The fluorescence in the spot is then eliminated—photobleached with an intense pulse of laser light. The fluorescence recovers as labeled protein molecules from nearby diffuse into the bleached spot. The rate of fluorescence recovery corresponds to the rate of protein diffusion. FPR has been used to study the behavior of ion channels and receptors that are important in synapse formation. The FPR apparatus is in the lab of Elliot Elson, Ph.D., professor of biochemistry and molecular biophysics.
Circuit Of Sadness

PET studies reveal the brain circuits involved in depression's unshakable feelings of inadequacy and worthlessness.

A Promising Alternative

Using strict biocompatibility as their keystone, physicians produce a new breast implant that does not interfere with mammography.

The Clinical Connection

After a major contribution to clinical medicine, a bench-science team returns to study basic questions.

On The Cover:

More than just the "blues," depression affects eating, sleeping and the ability to function. Neurologists, psychiatrists and radiologists are collaborating to trace the neural circuits that operate in the persistent feelings of failure, loss, guilt and death that characterize the disease. The photographic representation of depression is by Tom Heine.
New Center To Study Nerve Cell Injury

A new center is being established to develop strategies to protect the brain and spinal cord from injury due to disease or trauma and to promote recovery after injury has occurred.

The center — known as the Center for the Study of Nervous System Injury at Washington University School of Medicine — is the result of an $8 million, five-year collaborative agreement between the university and Hoffmann-La Roche Inc., in Nutley, N.J. Dennis W. Choi, M.D., Ph.D., professor and head of the medical school’s neurology department, will serve as the center’s director.

“This alliance presents a remarkable opportunity for a pharmaceutical company and an academic institution to make use of their similar interests and different strengths to advance the understanding of neurological diseases and to generate new, more effective treatments,” says William A. Peck, M.D., vice chancellor for medical affairs and dean of the School of Medicine.

Under the terms of the agreement, Hoffmann-La Roche will contribute $1.6 million for each of the next five years to support the center. In addition to financial support, Hoffmann-La Roche will provide technical expertise and patent law services and also may develop pharmaceutical products which result from the collaboration.

According to Choi, scientists working in the center will focus on preventing, limiting and reversing damage to cells in the brain or spinal cord. “The center is taking a somewhat untraditional approach,” Choi explains. “Researchers hoping to develop new therapeutic approaches usually target a specific illness, such as Alzheimer’s disease or stroke. By studying the problem of nerve cell injury across disease boundaries, we hope to learn enough about underlying common principles to devise new therapies.”

Drug Blocks Spread Of Flu Virus

Despite concerted effort, diseases attributed to viruses have remained much more difficult for medical science to treat than those caused by bacteria. But recently, a team of researchers here developed a compound that in laboratory tests is 95 percent effective at blocking the spread of one strain of influenza virus. It is a glimmer of hope for the future.

The compound is a peptide (a small chain of amino acids) which stops the influenza virus from spreading by disabling the Velcro-like spikes the virus uses to grab hold of and infect a healthy cell, says Milton J. Schlesinger, Ph.D., professor of molecular microbiology.

Although the peptide may be years away from clinical application, Schlesinger says this approach may provide a basic plan of attack against many viruses including rabies, herpes and respiratory syncytial virus (RSV), a virus harmful to infants. Schlesinger reports in a recent issue of Virology that the peptide inhibits formation of influenza virus in infected cultured cells.

With the flu epidemic a lingering memory in many parts of the United States, attempts to find effective agents other than vaccines to block the virus’ spread have been increased. That isn’t likely to happen, Schlesinger
say, because decades of research on viruses have led to a relatively small armamentarium compared to the wealth of antibiotics that bacterial research has produced.

The difficulty lies in designing a drug that kills viruses without injuring their host cells. Because most viruses contain a small number of genes, they commandeer many gene products required for their replication from the host cell. Consequently, drugs aimed at viruses also may stop normal cellular functions, Schlesinger says.

Engineering a drug that kills the virus without killing its host is an arduous task. However, the molecule Schlesinger designed does just that. The peptide blocks the attachment of the Velcro-like spikes to the flu virus. Without its spikes, the virus can't get into a cell, Schlesinger says.

Normally, each spike is anchored to a “pocket” inside the virus. The molecules that Schlesinger and his collaborators study are believed to fit into this pocket, preventing the spikes from anchoring. “If the pocket is filled, new viruses will no longer appear, and that will be the end of the infection,” Schlesinger says.

Further studies are needed to determine the effectiveness of the approach. Schlesinger recently received a four-year, $800,000 grant from the National Institutes of Health which will fund the design of smaller, more potent molecules to stop a variety of viruses. The initial research was partially funded by Monsanto-Searle.

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**Biostatistics Celebrates Jubilee**

As part of the celebration of 25 years of dedication to education, research and consultation for the medical school community, the division of biostatistics hosted a workshop on study design and brought five distinguished speakers to campus from around the world late in 1991. The workshop, aimed at investigators at the medical school currently contemplating submission of a clinical research proposal, dealt with the practical and scientific issues of designing the study and strategies for writing a successful proposal.

The speaker series brought to campus Newton E. Morton, Ph.D., director of the CRC Research Group in Genetic Epidemiology, Southampton General Hospital, Southampton, England; Paul Meier, Ph.D., Ralph and Mary Otis Professor of Statistics, University of Chicago; Charles F. Sing, Ph.D., professor of genetics, University of Michigan; Ann Arbor, William B. Kannel, M.D., M.P.H., professor of medicine, Boston University School of Medicine, and C.R. Rao, Ph.D., holder of the Eberly Chair in the Department of Statistics at Pennsylvania State University.

The speakers addressed the frontiers and challenges facing researchers in biostatistics and genetic epidemiology.

Speaking about the role of genetic variation in coronary artery disease, Sing told his audience that the initiation, progression and severity of the disease are determined by anatomical, biochemical and physiological traits that are each likely to be influenced by several genetic and environmental causes. Yet most genetic research has concentrated solely on the metabolism of cholesterol, with the result that the true role genetic variation plays in predisposing to coronary artery disease is underestimated.

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**Cryer Named Editor**

Philip E. Cryer, M.D., director of the division of endocrinology, diabetes and metabolism, has been named editor of the leading diabetes research publication, *Diabetes*. He assumed duties January 1.

Cryer, professor of medicine, is on staff at Barnes Hospital, and is a consulting physician at Jewish and St. Louis Children's hospitals, all part of Washington University Medical Center.

Six other School of Medicine faculty members will serve as associate editors of the journal. They are: David D. Chaplin, M.D., Ph.D., associate professor of medicine and assistant professor of genetics and molecular microbiology; Michael L. McDaniel, Ph.D., associate professor of pathology; Mike M. Mueckler, Ph.D., associate professor of cell biology and physiology; M. Alan Permutt, M.D., professor of medicine; Julio V. Santiago, M.D., professor of pediatrics and associate professor of medicine, and Joseph R. Williamson, M.D., professor of pathology.

Published by the American Diabetes Association since 1952, *Diabetes* is the world's leading diabetes-related publication.
Implants Control Glucose Levels

Researchers at Washington University and CytoTherapeutics, Inc., have successfully controlled blood sugar (glucose) levels for extended periods in mice by using a small islet cell-containing membrane implanted under the skin. The research, reported recently in the journal Science, demonstrates the potential for treating insulin dependent diabetes by implanting encapsulated, insulin-producing cells beneath the skin.

"This research is an important step toward the development of islet cell implants to treat insulin dependent diabetes," says Paul E. Lacy, M.D., Ph.D., Robert L. Kroc Professor of Pathology and the lead author on the paper. "It is particularly encouraging that the implant functioned as well under the skin as when placed in the abdomen. A device placed under the skin is the most practical method for implanting islet cells because it can be inserted and retrieved easily. The findings also fulfill several other prerequisites for an islet encapsulation device for possible use in human diabetics, including biocompatibility and prevention of rejection."

"Encapsulation devices that isolate the implanted cells from the immune system, allowing them to survive and function without the need for immunosuppressive drugs, provide promise as a therapeutic approach to diabetes," says Lacy.

Islet cells are located in the pancreas, where they are responsible for producing and secreting insulin, a hormone critical for the breakdown of glucose. In insulin dependent diabetes, also known as diabetes mellitus, islet cells are destroyed. As a result, patients must receive daily insulin injections to control blood glucose levels.

According to the American Diabetes Association, diabetes mellitus affects more than 1 million individuals in the United States.

In their work, the researchers suspended rat islets in a gel and encapsulated them in hollow, semi-permeable plastic fibers. They placed the devices either under the skin (subcutaneously) or inside the abdomen (intraperitoneally) of diabetic mice. The mice implanted with the encapsulated rat islets did not receive immunosuppressive drugs. For 60 days, the implant maintained normal glucose levels in over 80 percent of the recipient animals at both the subcutaneous or intraperitoneal sites and with either 500 or 1,000 islets. When the implants were removed at the end of the 60-day period, the diabetic condition returned.

"The ability of the subcutaneous implant to function effectively in mice with as few as 500 rat islets provides encouraging support that a device of an acceptable size can be designed for human use," says Orion Hegre, Ph.D., CytoTherapeutics' director of endocrine science and a co-author of the study. "An implant suitable for human use is expected to require about 500,000 islets."

The scientists say that the next step in their collaboration is to design and test a device for use in larger animals. They hope to have a device ready for initial human testing in several years.

Aerobic Workout From A Chair

Some day, Cheryl Spessert may be to Broadway show tunes what Richard Simmons is to the oldies.

While Simmons and his overweight followers stay fit by groovin' to some of rock and roll's greatest hits, Spessert incorporates Broadway classics into an exercise routine she has developed for people physically limited by disease. Spessert, a pulmonary nurse clinician, is the impetus behind a new exercise and educational videotape called "Chairobics," which she says is the first of its kind.

The two-hour videotape demonstrates exercises performed in a chair and designed for people with moderate to severe chronic obstructive pulmonary disease. Spessert, who appears in the videotape, had the idea several years ago while directing cardiopulmonary rehabilitation at the Fitness and Health Institute in Tucson.

The fitness program is made fun, Spessert says, because the exercises are choreographed to familiar Broadway and classical hits including "If I Were A Rich Man," and "Hello, Dolly." "It makes an enormous difference to work out to music you know, and for this particular age group, these classics are some of their favorites," she says.
To the beat of pop classics, pulmonary nurse clinician Cheryl Spessert instructs people physically limited by disease in “Chairobics,” an exercise program that maintains fitness and provides pulmonary rehabilitation.

Spessert says the video provides instruction on breathing techniques and oxygen therapy and teaches stretching, weight training, a cardiovascular workout and relaxation techniques. Many of the exercises benefit the upper extremities because that’s where people with emphysema have difficulty maintaining strength.

Spessert authored the script with the assistance of Daniel M. Goodenberger, M.D., assistant professor of medicine. Other consultants were: Pam Becker Wollitz, pulmonary nurse specialist at Barnes Hospital; Jill Feldman Malen, pulmonary/thoracic nurse specialist at Barnes Hospital; and Cheri Carswell, exercise physiologist and co-director of pulmonary rehabilitation at the Fitness and Health Institute in Tucson.

Three Named To Study Sections

Three researchers at the School of Medicine have been asked to serve on separate study sections in the Division of Research Grants for the National Institutes of Health (NIH).

Stephen J. Giddings, M.D., Ph.D.
Institutes of Health (NIH).

Giddings, who will serve on the Physiological Sciences Study Section, researches the regulation of insulin gene expression. He is associate chief of staff for research and development at the St. Louis Veterans Administration Medical Center and is a member of the Endocrine Society and the American Society for Biochemists and Molecular Biologists.

Lee Ratner, M.D., Ph.D.

survey the status of research in their fields of science.

Ratner, who will serve on the AIDS and Related Research 3 Study Section, is researching the origin and development of human retrovirus infections. Ratner is co-director of the Washington University AIDS Clinical Trials Unit and oversees investigation of a variety of therapeutic interventions for HIV infection and related retroviruses.

Korsmeyer, asked to serve on the Pathology B Study Section, investigates chromosomal translocations that lead to various forms of leukemia and lymphoma. He is an associate investigator with the Howard Hughes Medical Institute at the School of Medicine and a member of the American Society for Clinical Investigation.

Study section members are selected on the basis of their demonstrated achievement in their scientific discipline as evidenced by the quality of research accomplishments, publications in scientific journals and other achievements and honors.

Stanley J. Korsmeyer, M.D.

expression.
Improving Heart Attack Treatment

Adding two drugs to the standard early treatment for heart attacks may help prevent blockages that often recur and inflict additional damage in the hours following an initial attack.

Using an animal preparation, scientists here have demonstrated that the drugs aspirin and recombinant hirudin can prevent the damaging blockage of heart vessels that sometimes occurs after the initial attack-inducing blockages are cleared away. Hirudin is a protein from the saliva of leeches produced by recombinant DNA technology.

Hirudin and aspirin prevent clots via two separate actions. Hirudin inhibits an enzyme that induces formation of the thread-like protein, fibrin. Fibrin entangles platelets in masses to form clots. Aspirin is an antiplatelet agent that prevents blood platelets from sticking together and contributing to clotting.

“Our results support the idea that an antithrombin agent alone is not sufficient, that one will have to give an antiplatelet agent as well,” to open arteries quickly and keep them open, says Dana Abendschein, Ph.D., one of the investigators.

The use of clot-dissolving drugs such as streptokinase and tissue-type plasminogen activator (t-PA) has been a major advancement in treating heart attacks, Abendschein says. Administered in the early hours after a heart attack, they break up clots that typically form obstructions. By restoring blood flow, they often can prevent substantial irreversible damage to the heart muscle.

But there are limitations to this treatment, explains Abendschein, a research associate professor of medicine. Blood flow is not restored in about one third of patients. And in about 20 percent of patients in whom flow is restored, blockages return within about 24 hours.

To avoid reblockage, clinicians sometimes give heart attack patients aspirin and heparin. But neither drug has been effective enough. “So the search is really on for new approaches that might be more effective than these conventional agents,” he says.

In the study, Abendschein and co-authors Nelson Prager, M.D., clinical fellow in medicine, Sheryl Torr, Ph.D., research instructor in medicine, and Burton Sobel, M.D., professor of medicine, induced blood clots in the arteries of dog hearts and mechanically narrowed the artery to mimic a site of atherosclerotic plaque. They found that hirudin — already shown in their lab to prevent reblockage without the presence of an artificial vessel narrowing — and aspirin, given separately with the clot-dissolving drug t-PA, did not prevent reblockage. But when both were given together with t-PA, the drugs prevented reblockage.

For heart attack victims, a combination of drugs is proving to be effective in preventing the blockage of heart vessels that sometimes recurs after the first blockage has been cleared away.

Tuition Increased, Frozen

The School of Medicine has restructured its tuition policy to freeze costs throughout the four years of medical school for students enrolling in the 1992-93 academic year, according to William A. Peck, M.D., vice chancellor for medical affairs and dean of the School of Medicine.

For new students entering the school in August 1992, annual tuition will be $19,800 and will be frozen at that amount for all four years of medical education. For currently enrolled students, tuition will be increased 5 percent, from $15,900 to $16,700.

The new tuition was approved by the University’s Board of Trustees upon the recommendation of the Executive Faculty, a medical school governing board composed of the 18 department heads.

“Tuition at Washington University School of Medicine has not and still will not cover the full costs of medical education, but the increase for incoming students addresses the fact that those costs have risen much faster than our tuition,” says W. Edwin Dodson, M.D., associate dean for admissions and financial aid. “At the same time, we wanted to change our tuition structure — to in effect freeze tuition — in order to stabilize our new students’ expenses and allow them to plan for all
four years of their medical education.”

The Executive Faculty has long held the line against sharp increases in an attempt to limit the debt load undertaken by medical students. Large educational debts have been associated with young physicians’ tendencies to select higher-paying specialties and to avoid careers in primary care and academic medicine, a trend the Executive Faculty would like to see reversed. The indebtedness of Washington University medical students is below the national average.

Medical school tuition at Washington University traditionally has been considerably lower than that charged by schools of comparable quality, such as Johns Hopkins, Stanford, Yale, Cornell, Columbia and Harvard. The School of Medicine’s tuition was reduced 5 percent in 1988-89, not increased at all in 1987-88 and increased only 3 percent in 1986-87. Increases in 1989-90, 1990-91, and 1991-92 were held in the 5- to 7-percent range. In recent years, Washington University’s medical school tuition has been well below the national average for private medical schools. In 1991-92, for example, tuition at Washington University ranked 46th out of 52 private medical schools.

Unlike most other medical schools, Washington University School of Medicine’s tuition is all-inclusive; no additional fees are assessed to cover student health or student activities, for example. And the school has an aggressive financial aid program that meets 100 percent of the documented financial needs of every student who applies for financial aid.

“The tuition increase will help ensure that we remain at the forefront of American medical education and that the total educational experience here is a rewarding one,” says Dodson.

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Researchers Track Down Writer’s Cramp

Dramatic new images of the brain show that writer’s cramp — once thought to be a psychiatric condition — can now be traced to abnormal brain function. “This is the first evidence of physiological changes in the brains of patients with this mysterious disorder,” says Lee W. Tempel, M.D., research instructor in neurology.

Tempel and Joel S. Perlmutter, M.D., assistant professor of neurology, explain that people with writer’s cramp suffer involuntary muscle cramps in the hand or forearm when performing specific activities such as writing or typing. In severe cases, the condition can impair use of the hand, forcing those affected to learn to write with their other hand. People with a less severe form of the disorder experience uncomfortable cramps while writing.

Because questions remained about the brain’s role in writer’s cramp, Tempel and Perlmutter used positron emission tomography (PET) to track blood flow in the brains of people suffering from the disorder. PET shows changes in brain blood flow, which doctors interpret as a signal of brain activity. Blood flow abnormalities tell doctors that there may be abnormal brain function even though the structure of the brain as seen with a CT or MRI scan is normal.

While in the PET scanner, six patients from 24 to 72 years of age with right-handed writer’s cramp and eight age-matched normal subjects had a vibrator touched to their hands. The group with writer’s cramp showed 30 percent less of an increase in blood flow to the area of the brain responsible for sensing and moving the hand (primary sensorimotor area) and the area that prepares for hand movement (supplementary motor area).

Responses were diminished on both sides of the brain, although only one side showed symptoms of writer’s cramp. “This was a surprise,” Tempel says. “It tells us that writer’s cramp involves more of the brain than we might otherwise have thought based on clinical observations. This may be reflected by the observation that about a quarter of the people with writer’s cramp in one hand will train themselves to use the other hand and will subsequently develop writer’s cramp in that hand.”

Despite these new findings that implicate the sensorimotor and supplementary motor areas of the brain in writer’s cramp, much remains to be learned about how the brain contributes to this condition. Though this study sheds new light on the disorder, it will not bring an immediate improvement in therapy, Tempel says. “But the better we understand what’s happening in the brain to produce writer’s cramp, the better our chances of eventually improving treatment.”
CIRCUIT of SADNESS

Charting A Pathway For Depression

By Robert Lowes

"I'm no good ... I can't do anything right ... I'm a burden to my family ... They'd be better off if I were dead..." Such thoughts breed unchecked in the minds of many depressed people. Proponents of pop psychology sometimes call these ruminations "negative tapes" — mental recordings from childhood of the voices of critical, unloving family members. All too often, they drive their listeners to self-hatred, sometimes even suicide.

The PET scanner works to reveal comparisons between normal brain function and brain function when things have gone awry.
Some negative tapes, however, have nothing to do with dysfunctional families or other traumatic circumstances. For these depressed people, misery is a matter of the brain's chemistry gone awry. Recovery depends largely on antidepressant drugs. But no one has understood the brain's precise function in this type of illness, nor how antidepressants exactly work. Many clues have led psychiatrists to hypothesize a neurological pathway for depression that includes brain structures responsible for memory and emotion.

This speculation is now giving way to proof. With the imaging power of positron emission tomography, or PET, a research team led by Wayne Drevets, M.D., has apparently mapped the route of the negative tapes. A type of physiologically based depression causes parts of the brain to "light up" in PET images.

"There's evidence of an entire anatomical circuit that seems to function abnormally during depression," says Drevets, an assistant professor of psychiatry. "A considerable amount of evidence suggests that this circuit must be involved. Ours are the first imaging data that corroborate this."

Understanding this depression circuit, says Drevets, may lead to better antidepressants. The goal is to silence the terrible negative tapes.

**Trait And State**

To study the anatomy of depression, Drevets focused on a variety of the disease that would yield the most meaningful PET data. First, Drevets examined not the sort of transient sadness associated with grief or hardship, but major depression. This illness, affecting 15 percent of the population at one time or another, can disturb a person's eating and sleeping patterns, destroy his ability to enjoy pleasure and haunt him with persistent thoughts of failure, loss, guilt and death.

Drevets had to choose between the two categories of major depression: bipolar and unipolar. Bipolar depressives experience episodes of mania as well as bouts of depression. Unipolar depres-
sives, who constitute roughly 90 percent of all depressed persons, do not have manic episodes.

While unipolar depression resembles the "blue" phase of its bipolar counterpart, says Drevets, the two illnesses are physiologically distinct. Structurally, the brains of unipolar depressives are no different from those of the non-depressed. Not so for the brains of bipolar depressives; their cerebral ventricles — the fluid-filled spaces in the center of the brain — are larger, for example. Because these physical differences would complicate PET comparisons between bipolar depressives and normal subjects, Drevets opted to study unipolar depression.

To further simplify his research, he selected unipolar subjects from a category called familial pure depressive disease (FPDD). These depressives had a depressed parent, sibling or offspring but no family history of alcoholism, antisocial personality or mania.

"This is the first PET experiment that's tried to subgroup patients to this extent," says Drevets. "I think that's why we were so successful. We obtained a relatively homogeneous group of people likely to have similar abnormalities."

In PET, radioactive tracers that emit positrons are injected into a person's bloodstream. The tracers gravitate to biologically active tissues by virtue of the compounds to which they are linked. Drevets' tracer was water with a radioactive oxygen atom. It tracks blood flow, a good mirror of neural synaptic activity.

The positrons collide with electrons in the tissues, producing gamma rays. These rays are recorded by the doughnut-shaped PET scanner that encircles the subject. A computer converts the data into a three-dimensional image.

The psychiatrist assembled three subject groups — 13 people with FPDD who were currently depressed, 10 people with FPDD who were in remission (that is, displaying no symptoms), and 33 control subjects with no personal or family history of psychiatric illness. Tom O. Videen, Ph.D., a research assistant professor of neurology, used a computer program to transform individual PET scans into a composite image for each group, despite differences in brain shape and head position inside the scanner.

This map shows precisely where the increased activity is centered. On the right (B and D), are line representations of the brain shape and (E) the level at which the two PET slices were recorded. On the left, two color images localize the increased brain activity of depressed patients.
Wayne C. Drevets, M.D.

"We bend and stretch and shape the images so they all line up," says fellow researcher Marcus E. Raichle, M.D., professor of radiology and of neurology. Videen also refined the data to minimize artificial differences between the composite images due to "statistical noise."

Comparing the brain images revealed simple but profound distinctions. In contrast to the control group, the subjects with active FPDD showed increased blood flow in two regions. One area of increase was the prefrontal cortex of the brain's left cerebral hemisphere. (The cerebrum, which gives us the word "cerebral," is the large, prominent brain mass that's fissured like a walnut. The cortex is the thin layer of wrinkled gray matter covering the cerebrum, literally the brain's thinking cap.) The frontal cortex governs decision-making, problem-solving and motivation. The prefrontal cortical area defined in the PET study may use a kind of short-term memory to guide behavior.

Previous PET studies of depression looked for irregularities in specific brain regions. Drevets, figuratively speaking, went in blind. He divided the 13 depressed subjects into two groups, each with a separate control group. For the first set of depressed and normal subjects, he produced composite PET images of the entire brain. After spotting the overactivity in the prefrontal cortex among the depressives, he focused his attention on just this particular region in the second set of subjects — and found the same quirk.

PET also detected increased blood flow among the depressed subjects in the left amygdala. The size and shape of an almond, the amygdala belongs to the limbic system, a group of structures underneath the cerebral hemispheres. The limbic system processes sensory input, adjusts bodily settings for temperature and blood pressure and generates emotional responses. Some neuroscientists theorize that the tiny amygdala's job is assigning emotional significance to external stimuli. You wake up at 2 a.m. and smell smoke. The amygdala tells the rest of your brain, "Be afraid!"

But when you wake up at 7 a.m. and smell frying bacon, the amygdala might trigger a neurochem-
tional chain reaction that ends with a smile.

Neuroscientists are honing in on this brainy “spin doctor” as a possible culprit in a variety of emotional disorders. Stimulating it with electricity can evoke fear and hallucinations. Monkeys whose amygdalas have been destroyed succumb to “psychic blindness.” They lose their fear of normally alarming stimuli, such as the sight of a snake.

Like subjects who were currently depressed, FPDD subjects in remission also had elevated blood flow in the amygdala. But remitted subjects demonstrated no such increase in their left prefrontal cortex, Drevets’ tentative conclusion? Heightened blood flow in the amygdala represents a “trait” marker of FPDD “that may predispose them to depressive episodes.” Heightened blood flow in the prefrontal cortex represents a “state” marker — when the patient is displaying symptoms.

A Lack of Inhibition

The provocative hypothesis of trait and state markers awaits more verification, but anatomical anomalies in depression raise more possibilities when examined in the context of neural circuits. The amygdala and prefrontal cortex form a circuit together with the mediodorsal region of the thalamus. In general, the thalamus is a processing station for all sensory information except smell. The mediodorsal thalamus fires off neurotransmitters to the prefrontal cortex, which in turn, rings up the amygdala. The amygdala completes the circuit by talking to the mediodorsal thalamus.

The same circuit also operates in reverse, except that no messages travel from the mediodorsal thalamus to the amygdala. Breaking the circuit dramatically alters behavior. Sever the amygdala from the prefrontal cortex, and you have performed an emotion-deadening lobotomy.

This three-part loop belongs to an even larger circuit that includes the ventromedial section of the caudate and the ventral section of the pallidum, both parts of the limbic system. Normally, the ventromedial caudate retards the firing rate of the ventral pallidum, which does the same to the mediodorsal thalamus. The larger circuit, therefore, tends to modulate the smaller circuit.

The PET study, says Drevets, appears to confirm what neuroscientists have long suspected: Disruptions in these two circuits play a key role in physiologically based depression. In FPDD, the amygdala, prefrontal cortex and mediodorsal thalamus may act “like a circuit running away with itself,” with the amygdala putting negative labels on all incoming sensory information, or failing to assign any positive labels. This hyperactive loop, he says, may thus explain the “negative tapes” that play in some depressed minds.

So what about the larger neural circuit that’s supposed to calm down the smaller circuit? PET scans suggest an apparent glitch in one of the larger circuit’s stops — the ventromedial caudate. The structure is one area of decreased blood flow in the brains of depressed subjects. Drevets says the blood-flow abnormality might be due to the ventromedial caudate not receiving enough of an inhibitory neurotransmitter called dopamine. An unrestrained ventromedial caudate, Drevets reasons, overinhibits the ventral pallidum. According to the curious laws of neurochemistry, that leaves the ventral pallidum unable to curb the mediodorsal thalamus. So the smaller circuit buzzes even more.

Other mental disorders share the quality of irrational mental fixation found in depression. Not surprisingly, Drevets and his colleagues are aiming PET at subjects suffering from panic disorders, simple phobias and obsessive-compulsive behavior. PET studies in depression will continue as well. One possible experiment involves treating depressed subjects with antidepressants and looking for sites of increased or decreased brain activity.

Such a study, Drevets says, may explain more precisely what the drugs do. These pharmaceuticals typically lift spirits by correcting imbalances of neurotransmitters like dopamine, serotonin and norepinephrine. Many people with unipolar depression simply don’t have enough of them. Interestingly enough, Drevets notes, most antidepressants “act as amygdala depressants.” He speculates that dopamine shortages in the amygdala as well as the ventromedial caudate could account for the runaway brain circuitry in depression.

Drevets doesn’t discount the importance of “talk therapy” as he seeks the physiological source of the illness. “If you break your leg, you need a cast so the bone will grow back together, but then you have to exercise your leg because your muscles have become weak. Antidepressants are the cast. Psychotherapy is the rehabilitation.”

The desire to formulate more effective antidepressants is a profound one for Drevets. “Our hope is that we’ll be able to tell what treatment will be best for a depressed patient based on PET scans. The way it is now, it’s trial and error. You try one antidepressant and see if it works. That may take six weeks. You then raise the dosage or add something to it. If that fails, you switch to a new one.”

While a psychiatrist searches for the right drug, the depressed patient continues to suffer the onslaught of the negative tapes: “I can’t do anything right. Nobody loves me. My life is worthless.” Drevets wishes he could have ended this morbid interior monologue for one of his depressed patients who participated in the PET study. She was a 50-year-old woman with a lot going for her — a loving family, a supportive church, a successful career. Neither drugs nor psychotherapy could dispel her gloom. Last summer, she took her life. “It’s people like her who motivate me to work hard on the research,” Drevets says.

Although PET images from his experiments look abstract and high-tech, Drevets remembers the faces of people who struggle with tormented thoughts. The science may be complicated, but the goal is basic medicine — alleviating another person’s suffering. And replacing negative tapes with positive ones.
Controversies have waxed and waned over the use of silicone gel breast implants during the 30 years since they were first introduced. From moral questions to accusations that the implants cause cancer, the subject has been bandied about repeatedly. Recently, feverish debate about possible effects on systemic health has been played out in the press. The February decision by an advisory committee of the FDA recommending limited use and further study of silicone implants did little to end the disagreement.

Oil- and silicone-filled implants can be made with similar tactile characteristics. Both of these — the smaller oil-filled prototype and the traditional silicone-filled implant — are encased in texturized silicone envelopes.
Alternative
On the left is a mammogram of a breast augmented with a silicone gel implant. On the right: the same breast augmented with an implant filled with organic oil. The mammographer’s view through the oil-filled implant clearly shows the simulated microcalcifications blocked by the radiopaque silicone.

"It’s unfortunate that the argument has become so emotionally charged," says plastic surgeon V. Leroy Young, M.D., professor of surgery. "The debate has left science behind and is running on rumor." Having performed more than 1,000 implant operations and cared for women with apprehensions about their implants, Young is familiar with the concerns. Unsubstantiated fears he works to calm. But real problems have prompted him and his colleagues in their research to develop an alternative to silicone implants.

"Women should be able to do what they want to with their bodies," says Judy M. Destouet, M.D., associate professor of radiology and one of the research team’s members. "They should have access to breast reconstruction without worry. If they want larger breasts, they should be able to have them. We want to provide an implant that has been thoroughly tested and is presented with its risks known."

**Biocompatibility**

The researchers’ new implant addresses concerns about silicone. Because the filler is a purely organic oil, such as peanut oil or safflower oil, Young says the body’s normal metabolism clears any that escapes or bleeds from its envelope, an occurrence that cannot be avoided completely.

Studies in which peanut oil was injected into and surgically implanted in laboratory animals showed no adverse effects. "We saw no difference in response to the peanut oil and to simple saline. The peanut oil is simply absorbed, much the way that the fat we eat every day is absorbed," Young says of the test results.

Further laboratory studies in which peanut oil molecules were tracked after labeling with radioactive tracers showed that the oil was redistributed to the animal’s body fat and assimilated. None of the animals in the study exhibited rashes, elevations in temperature or gave any other evidence that an immune response had been triggered, Young reports.

"When we began to investigate the possibility of using peanut oil as an implant filler, we discovered an enormous body of existing research to support its safety," Young says. Its use as a carrying agent for injectable time-release medicine is well-documented, and the oil is classified by the Food and Drug Administration (FDA) as "generally accepted as safe," the researchers report.

Even the question of whether those who are allergic to peanuts would be allergic to the implants has been addressed. Young says the protein fraction that initiates a reaction to peanuts is chemically removed from the oil, eliminating the potential for an allergic response on that score. To test whether the organic material might spoil, Young and his colleagues inoculated samples with bacteria and incubated them. But the colony counts dropped
off; the purified oil does not support bacterial growth. And all odor is removed from the oil.

Such documented biocompatibility goes to the heart of the recent furor over silicone. For several years, anecdotal evidence has been building concerning a variety of responses to silicone. Women and their physicians have reported scleroderma (a hardening and stiffening of the skin), arthritis-like joint problems, lupus erythematosus (a complex connective tissue disorder), shooting pains, rashes and other ailments that they believe to be attributable to silicone escaping from its envelope and migrating.

But Young says it has not been possible to 

Young says it has not been possible to show a causal relationship between these disorders and silicone: "There has never been substantiation for the charge that silicone implants cause cancer, and there's no real scientific proof that they are responsible for these other problems, either." He adds that neither is there proof that silicone is not responsible. Scientists have been unable to create a monoclonal antibody to silicone that would allow them to accurately demonstrate its allergenicity.

Still, case reports are becoming more common and convincing, witness the FDA's recent moratorium on implants to allow further study. And the identification of a human antibody to silicone by researchers at the University of Texas Medical Branch suggests that some people's immune systems respond to its presence.

The issue is complex. Young says science was "plodding along," trying to figure it out, when the heat was turned up. Is silicone absolutely inert or does it change over time? Might silicone form a complex with a protein or proteins that triggers a response? No one knows. With a well-tested peanut-oil filled implant, the risks that exist will be quantified.

Mammography

The concept for a peanut-oil filled implant was born from a search for an alternative that was radiolucent — one that allowed X-rays to pass unobstructed.

At the exposures used for mammography — the technique universally regarded as the best tool for detecting occult breast cancer — silicone is radiopaque; that is, it blocks the passage of X-rays. A physician looking at a film of breast tissue exposed through a silicone-filled envelope sees nothing but a white mass — no detail, no tissue, no calcifications, nothing.

The opacity is a function of silicone's atomic number, a measure of its relative atomic density. With an effective atomic number of 16, silicone is a poor match for average breast tissue's atomic number of 6.0. When John Eichling, Ph. D., associate professor of radiology and a member of the development team, tested peanut oil, he discovered that its atomic number was 5.9. X-rays pass through it slightly more easily than they do through breast tissue, making it radiolucent.

A study by Destouet and Barbara Monsees, M.D., associate professor of radiology, compared a number of fill materials in a silicone envelope and determined that implants filled with peanut oil or safflower oil allowed the greatest visu-
greater involvement of the lymph nodes. Says Destouet, an expert in mammography, only now, Destouet says, are large numbers reaching their 40s and 50s, ages at which screening mammography becomes essential. At the current rate, one in nine American women is expected to develop breast cancer in her lifetime.

At least one study has shown that women with silicone implants are diagnosed with breast cancer at later stages, with more invasive lesions and with greater involvement of the lymph nodes than those without implants. One reason: Silicone implants block the radiologist's view. That's especially true of the upper outer quadrant of the breast where more than 50 percent of breast cancers begin, says Destouet, an expert in mammography at the medical school's Mallinckrodt Institute of Radiology and director of the Breast Diagnostic Center.

Even in the best-case scenario, 10 percent of breast tissue is obscured by a silicone implant. That figure is for women with soft, compressible breasts and small implants who visit trained mammographers for the special views recommended. Some studies have shown that as much as 80 percent of the breast tissue can be graphically obscured by a silicone implant.

Destouet points out that implants also require more views of the breast to be made, with a subsequent increase in radiation. "At least four exposures, instead of two, are necessary," she says. The additional "modified compressed views" are an attempt to move breast tissue away from the implant in order to detect abnormalities that could indicate the presence of cancer. Beyond that, the radiodensity of implants often defeats a mammography machine's automatic exposure control, making additional test exposures necessary.

Contracture

A third issue that the new implant must address is that of capsular contracture — essentially scar tissue that the body often builds around an implant, turning it hard, noncompressible, more spherical and frequently painful. The problem occurs in perhaps 40 percent of all women who receive smooth silicone implants, Young says, although some studies put the number even higher.

Young explains that capsular contracture occurs when the body responds to a foreign object — in this case the implant — by depositing collagen. Common wisdom says that the envelope's smooth surface allows the collagen to build up in a highly symmetrical pattern. Fibroblasts in the collagen then contract and compress the implant uniformly, making it more spherical and forming a hard "shell."

A silicone-filled implant briefly available with a textured polyurethane foam coating reduced the incidence of contracture to about two to five percent, Young says. It is thought that the textured surface disorganized the collagen so that it was deposited in a bizarre array, with its forces vectored. "Plus," Young says, "the body likes textured surfaces. They're more self-

## Speaking Personally

Much of the controversy over silicone gel breast implants can be traced to the very different experiences women have had with them.

Barbara B., a 52-year-old small-town resident underwent a mastectomy nine years ago and chose to have a reconstruction using silicone implants. Within two years, she suffered chronic fatigue, experienced severe joint pains that made it difficult for her to get into her car and became allergic to house dust and mold that had never bothered her before. Worst, she reports developing an autoimmune disorder that was eventually diagnosed as chronic active hepatitis.

"I never put two and two together until last winter when my sister called to tell me about a report Connie Chung was doing on television. She described me exactly," Barbara says. After consultation, V. Leroy Young, M.D., performed surgery last spring to remove Barbara's silicone implants and replace them with a saline-filled version. He found the original implants ruptured, their gel filler extruded with many silicone granulomas, or small nodular aggregations.

"Within three weeks, my joint pain was gone and I had my energy back. Now, I'm much better," Barbara reports. She says she holds no hard feelings, certain that her first surgeon told her all that he knew at the time but sure that the silicone was the cause of her health problems. "I don't regret it, even though I suffered," she says.

Kim H. is 27 and has had her silicone-filled implants for seven years, since the birth of her first child left her unsatisfied with the appearance of her breasts. "I felt terrible about myself. I couldn't wear a swimsuit, and I didn't look good in my clothes," she says.

Delighted with the results of her augmentation, she says, "I've had no bad reactions whatsoever, not even any contracture. Immediately after the operation I felt better about myself. I still would recommend that a woman considering the operation go ahead."

A healthcare worker, Kim sees women with implants who are worried, and she comforts them. "I'm not scared. So much of this is paranoia. I'm not saying some women don't have problems, but some of what you hear is ridiculous," she says.

Kim had her first mammogram last year and says she was not told until recently that silicone implants might interfere with effective mammography. "If peanut oil implants become available, I'll probably change to them just to get better mammograms," she says. —S.K.
like than smooth surfaces." But the foam-covered implant was discontinued when it was determined that its polyurethane coating degraded into chemicals known to be carcinogens in animals.

The issue is confused by a Swedish study comparing implants filled with saline and silicone gel, all with smooth silicone envelopes. That research showed that 50 percent of the silicone-filled implants suffered contracture, but only 16 percent of the saline-filled implants were affected. The suggestion: It was not the texture of the implant's envelope that initiated capsular contracture but rather silicone bleeding from the implants.

In any event, Destouet says the oil-filled implant will not have a silicone envelope: "Silicone is out. The capsular contracture of smooth silicone envelopes means that the breast cannot be compressed effectively for mammography. And textured silicone that might solve the capsular contracture problem appears like a fine mesh on a mammogram. That mesh could easily obscure small tumors."

Development

From Desotoet and Young's early interest in the potential for an alternative breast implant has evolved a complex effort to serve women. Now under development by a plastic surgery firm, peanut-oil-filled implants still face a long trial and approval process.

According to Brian Clevinger, Ph.D., who manages the further development of the project and whose efforts secured a patent on radiolucent implants for the university, the issues are:

1) The implant must be filled with a biocompatible, radiolucent substance that presents no threat, even upon release into the system. It must also provide a natural feel and shape. Triglycerides like peanut oil already meet most of these criteria, and techniques under development by organic chemists promise to provide the necessary consistency.

2) The implant envelope must not invite capsular contracture, must in no way interfere with mammography and must maintain its integrity. Clevinger says these requirements probably dictate an entirely new material for the envelope after extensive testing of candidates. New materials that maintain long-term integrity and do not degrade into hazardous substances hold great promise, he says. Texturization of the surface is likely.

3) All of these issues must be dealt with in the context of the pre-market approval required by the FDA. Because breast implants now are listed as Class III devices by the FDA, Clevinger expects full federal scrutiny to be brought to bear. "We don't know what the FDA will require. We may meet all published requirements only to be told that we have to provide 10 years of clinical trial results," he says. "It is a bold step into a very big abyss to try to do something about this."

The only guarantee the research team can offer is that when the alternative implant becomes available, it will have been thoroughly tested. The risks associated with it will be known.
Some people tie string around a finger to remember their purpose. David Gottlieb, Ph.D., keeps a black and white photograph on the bulletin board in his office to remind him why he’s a neuroscience researcher.

Two dark bands of raw data from an old experiment are all that’s visible in the image. The picture forces Gottlieb, a professor of anatomy and neurobiology, to concentrate on what he calls the “development question:” How do genes operate to decide the fate of growing brain cells? Gottlieb relies on the photograph because recently he and his colleagues at the medical school have been thrust unexpectedly into the world of diabetes research, a strange place to find neuroscientists interested in the fate of nerve cells.

By Jim Keeley
David Gottlieb, Ph.D., at the microscope in his office.
The research team was pursuing a better way to track down a particular brain protein, Gottlieb recalls. But in one of the detours that sometimes affect basic research, the group unknowingly fashioned a tool that captured a major culprit in juvenile diabetes.

More appropriately called insulin-dependent diabetes, that disease has a peak age of onset of 12 years but can strike those into their 40s as well. It renders patients dependent on external sources of insulin to sustain their lives. The National Institute of Disease Control estimates that 14 million Americans live with diabetes, though how many are insulin-dependent is difficult to assess because the disease often progresses into insulin dependency.

Neurons in the cerebellum stained with the monoclonal antibody to GAD obtained by David Gottlieb, Ph.D., and his colleagues. Only neurons containing GAD are stained. Sera from patients with stiff-man syndrome show a similar staining pattern., Gottlieb says. The photomicrograph is by Thomas A. Woolsey, M.D.

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The Origins

Six years ago, Gottlieb chose to look for genes that influence the destiny of immature nerve cells. A topic of increasing interest at the time, the field was wide open. It was an exciting period, Gottlieb recalls, because even a modest increase in knowledge would represent a dramatic improvement over the then-current understanding.

Gottlieb chose to study neurons that make GABA, a chemical that applies the brakes to nerve impulses. He reasoned that because about one out of every four nerve cells in the brain produces this chemical, it must be important to neural functioning. Gottlieb explains that just as some brain chemicals initiate impulses, others must limit them. Moreover, effective and widely prescribed drugs such as Valium are aimed at the GABA receptor, where they slightly increase the activity of the so-called inhibitory neurons. The result is that feelings of tranquility are enhanced.

Actually, GABA wasn't the real prey. Gottlieb began by stalking GAD, or glutamic acid decarboxylase, at that time a poorly characterized enzyme that scientists knew descriptively as a molecule that cleaved a carbon off glutamic acid, thereby producing the functional neurotransmitter GABA. "We thought GAD would prove to be very important because you can't find a cubic millimeter of gray matter that doesn't have neurons that produce it," Gottlieb says. "And without GAD, a neuron will never make GABA."

Before Gottlieb could determine the answers to his first major questions — where and when GAD appeared in nerve cells — there was an issue to clear up: He had to find out exactly what GAD was. "At that time, we had to step back from our developmental questions because people didn't really know what GAD was. GAD had been partially purified, but it was still impossible to say which proteins were really GAD," Gottlieb says.

In a twist of fate, Gottlieb and post-doctoral fellows Yen Chung Chang and Jim Schwob decided to attack the problem by obtaining a GAD-specific monoclonal antibody, a protein designed to
reach into the crowd of proteins normally found in brain tissue and grab only GAD. Using their monoclonal antibody, named GAD 6, as a probe, they were surprised when they discovered two GAD proteins.

The two proteins — named GAD 1 and GAD 2 — differed in weight but were about 70 percent similar in composition. Finding two GAD proteins was a surprise, and several groups are still trying to figure out the functional difference between the two.

At about that time, scientists led by Pietro Camilli, M.D., at Yale University were studying patients with stiff-man syndrome — a rare, paralyzing neurological disorder. They contacted Gottlieb when their work showed that stiff-man syndrome somehow caused patients to manufacture antibodies that attacked their own supply of GAD. This immune system revolt, it was later learned, contributed greatly to the progression of the disease. “This was a completely fortuitous finding,” Gottlieb notes. “Researchers also found that the disease results in death from an attack on inhibitory neurons in the brain.”

Investigators then learned that a number of patients with stiff-man syndrome were also stricken with insulin-dependent diabetes. As fate would have it, a group of scientists led by Steinunn Baekkeskov, Ph.D., at the University of California San Francisco (UCSF) Medical Center happened to be tracking an antibody in the blood of juvenile diabetes patients. The antibody attacks a protein with the approximate molecular weight of GAD.

“The GAD 6 monoclonal antibody that we developed proved to be crucial in establishing the identity of the antigen,” Gottlieb says.

Just as brain cells do, insulin-producing cells in the pancreas synthesize GABA, although medical scientists don’t yet know why. Because GABA is present in the pancreas, so is GAD. One theory holds that when an immune system goes awry by producing an antibody that attacks GAD, the body’s insulin production is interrupted. The result is insulin-dependent diabetes. Another theory is that GAD is an innocent bystander to the injury to the insulin-producing islet cells, and the culprit lies elsewhere. “Either way, GAD is diagnostically important,” Gottlieb says.

Today, laboratories around the world use the GAD 6 monoclonal antibody for diabetes research and to develop clinical tests. The antibody is distributed freely; if a scientist needs it for research, all he or she must do is pick up the phone and call the NIH-sponsored hybridoma bank that stores it or call Gottlieb directly. Researchers in at least 60 labs are using the antibody, Gottlieb says, and the number may be considerably higher.

The presence of the antibody to GAD in the blood is one of the earliest known signs of insulin-dependent diabetes. Now that physicians have the tools for detecting anti-GAD antibodies in the bloodstream, they can screen patients at risk to see if their bodies are attacking GAD.

The potential clinical impact of a screening test for diabetes is enormous, because patients often have lost 90 percent of their islet cells before they reach their doctor’s office. To diagnose patients earlier might mean saving many of those cells and their function.

Staying At The Bench

Having answered the question of what GAD is at the molecular level, Gottlieb and his colleagues — post-doctoral fellows Gerard Bain and Michael Morales, technologist Min Yao and student Ben Abella — are returning to basic questions in developmental neurobiology. In particular, they want to uncover the mechanisms by which inhibitory neurons decide to express the GAD genes.

Plans have been made to develop transgenic mice as a means of taking a closer look at how nerve cell development is influenced by GAD. The mice will have their gene for GAD deleted, and the consequences of that deletion will be assessed. There’s also excitement about in vitro cell lines that will permit the study of GAD expression outside the living brain. “At the moment, we have a good timetable showing when these cells express the GAD genes, but we’re completely in the dark about the signals that determine neural cell fate,” Gottlieb says.

Before moving on to address that issue, he comments about the detour in his developmental neurobiology research:

“We always hoped the basic work would result in a clinical tie-in, and we were very gratified when it did. This is one of many instances in which the assumption that support for basic research will eventually produce clinically important results was validated.”

After making a major contribution to clinical investigations into diabetes, the Gottlieb lab has returned to the pursuit of basic science.
A Needed Addition  

The Program for Women in Science and Medicine

By Marion Hunt

When Aphrodite Jannopoulo entered Washington University School of Medicine in 1918 as one of the first two women admitted to the full four-year course of study, she confided to her diary: "At last my dreams are realized ... Carol Skinner Cole and I are the only women in the class, so we will have to brave the storm alone." Her pride in realizing one of her life's ambitions was tempered by the knowledge that being among the first women students would present special challenges.

Now that women are routinely accepted as medical students and physicians, what Aphrodite Jannopoulo meant by "the storm" may be hard to understand. However, until recent years, women who wanted to enter science or medicine faced serious opposition.

Until recent years, women who wanted to enter science or medicine faced serious opposition.

Patricia L. Cole, M.D., associate dean of student affairs, and medical student Nancy MacDonald.
situation. Their ability and commitment often were doubted, and the doubts were used as an excuse to restrict admission and training opportunities for women.

Since the 1960s, women have become an increasingly significant presence in science and medicine. However, even now they must meet particular challenges during their careers that their male classmates and colleagues seldom encounter. Men combine career and family as a matter of course; for women, having successful careers and fulfilling family lives requires superb planning and tactical skills.

A new Program for Women in Science and Medicine has been in operation here for just over a year to assist women. Dean William A. Peck, M.D., says the program was established because “Washington University School of Medicine is absolutely committed to promoting the academic growth and careers of women.” Headed by Patricia L. Cole, M.D., associate dean of student affairs, the program provides a network of faculty advisors for different career choices and a forum for formal and informal discussions about topics of particular concern to women physicians and scientists. In addition, Cole’s office serves as a liaison between the American Medical Women’s Association, the Women’s Section of the AMA and the medical school’s Academic Women’s Network, a women’s faculty organization. Another of the program’s goals is to enhance the quality and quantity of women applicants.

Trained as an invasive cardiologist, Cole decided to head the program because of her strong belief that it could make a significant improvement in women’s professional lives during their student years and beyond. Though new, the program is already having positive effects. First-year medical student Nancy MacDonald says that “it was a definite factor” in her decision to come here. Of 10 medical schools she contacted during the admissions process, only Washington University gave her information about a special program for women. “That showed an interest and sensitivity that immediately attracted me,” she says.

MacDonald’s parents are pediatricians who practice out of their home, so Nancy literally grew up with medicine. The youngest of six children, with five older brothers, Nancy gained confidence from her mother’s ability to combine medical practice with a large family. Even so, she feels the program has helped make her feel more at home in medical school. During orientation week, she attended a brunch Cole organized for women students and faculty. The opportunity to meet women scientists and physicians on an informal basis gave Nancy an immediate sense of the professional choices awaiting her upon graduation.

The Program for Women in Science and Medicine already goes well beyond giving new women medical students a warm welcome. Noon luncheon talks on aspects of women’s lives and work in science and medicine have been well attended — with a significant number of interested men in the audience. All events are open to the entire medical school community, and men are encouraged to attend. Last October, Professor Darlene Clark Hine of Michigan State University opened a distinguished speakers’ series with a lecture on the history of African-American physicians, co-sponsored with the Office of Minority Affairs. In March, the program sponsored a half-day genetics symposium at which outstanding women scientists from this school and other institutions discussed their research. Next fall, Congresswoman Patricia Schroeder (well-known for her work to improve research on women’s health) will give the annual keynote address.

“Pat Cole has provided outstanding leadership in developing this unique new program,” says Peck. The leadership she provides is as much by example as by conviction. Married to F. Sessions Cole, professor of pediatrics and of cell biology, and the mother of two young daughters, she carries both clinical and administrative responsibilities. Encouraged by the achievements of the program’s first year, Cole notes, “The immediate response suggests it’s a needed addition that enhances the educational environment not only for women students and faculty but for the entire medical school community.”
While on maneuvers with the U.S. Army in Texas in 1942, lying on his back and looking up at the stars, Richard A. Sutter, M.D. '35, decided that he would not go into private practice as his father had. A year of working with his uncle in a St. Louis medical practice and many years of watching his father provide care without sending bills to his patients set Sutter on a path to establish an organization that would be paid for the services it provided and would also do good for the community and especially for the working man.

That decision was a fateful one, illustrative of the idea that every choice and every action affects a huge range of people and events downstream. Sutter went on to pioneer the practice of occupational medicine in St. Louis, serving 1,500 St. Louis businesses with health care for employees and eventually bringing Barnes Hospital into the practice of occupational medicine.

When he left the service, Sutter returned to University City — more than just a hometown to him, the original area including what is now University City having been founded as Sutter, MO, by Richard's great-great grandfather, a pioneer 1830 dairyman who began what later became the St. Louis Dairy Co. The post office for Sutter, MO, was located on what is now Olive Street Road. Sutter set out to investigate health practices in the factories of the day. During 1936, a year spent practicing with his uncle, Otto, Sutter says he had recognized that most workmen lacked access to good health care. Despite the earlier Workmen's Compensation Act that protected a man's job and benefits if he was injured in an accident, there was still much to do. Many diseases born of exposure to industrial agents were not recognized, and caps were placed on the reimbursements an injured worker could expect. Sutter believed that "the working man is entitled to the best care" and opened the Sutter Clinic to provide it.

Through his efforts, many St. Louis companies came to realize that they could save money by instituting safety programs to protect their workers. Sutter also fostered the revolutionary concept of physical examinations paid for by employers, and he was instrumental in getting occupational medicine recognized as a legitimate specialty, complete with its own regulatory board. Sutter and others established the Medical-Dental Service Bureau, forerunner to Blue Cross and Blue Shield.

When federal officials working on the Occupational Safety and Health Act (OSHA) sought an independent, unbi-
ased physician to advise them, they ultimately chose Sutter. For two terms, he served on the National Advisory Committee on Safety and Health as the only physician. Sutter contributed to OSHA’s modern approach of assisting industry with safety measures and training, helping to steer the agency away from just handing down fines to violators of the act.

Closer to home, Sutter advised commissioners of occupational health in Missouri and was influential in bringing forth state laws to protect workers from lead poisoning, silicosis, the inhalation of hazardous gases and chemicals and other conditions. His dedication to the field came at a time when the definition of occupational medicine was changing from including only work-related accidents to cover the many other types of disability that result from workplace exposure.

Timing was instrumental in the success of the Sutter Clinic, too. “Everybody else was standing still, so we pretty much developed the practice of occupational medicine in St. Louis,” Sutter says. He remembers the occasion on which he was called on a Saturday by the manager of the then famous Forum Cafeteria in downtown St. Louis, near his offices. An employee had deeply cut four fingers in an automatic slaw cutter. Sutter and his nurse responded, spending many hours repositioning the severed bones and tendons so the unfortunate patient might regain use of the injured hand. The insurance company’s agent on the case was so impressed with the degree of the patient’s recovery that Sutter’s “name went to the top of the list.” He remained the principal surgeon for that major insurer.

Employees were sold to Barnes Hospital in 1984, changing its name to Barnes/Sutter Healthcare, a subsidiary of the hospital. The Sutters — a closely knit team — were married four days after Richard’s graduation from medical school, the three days between commencement and the nuptials having been devoted to state board examinations.

As a priority, Sutter maintained his clinic’s independence. It was never dependent upon referrals and, in its 38-year history, accepted no contracts, choosing instead to be paid for work performed. Sutter believes he was the first Missouri physician to incorporate and, on that score as well as many others, always enlisted the wise counsel of his wife, Betty Henby Sutter. The clinic that employed 10 physicians and 35 ancillary employees was sold to Barnes Hospital in 1984, changing its name to Barnes/Sutter Healthcare, a subsidiary of the hospital.

Today, the Sutters enjoy homes in Longboat Key, FL, and in St. Louis. Successful children and grandchildren and interests in golf, fishing and travel keep them busy. Sutter, who is mentioned prominently in Who’s Who In America, currently advises the directors of St. Mary’s Hospital in East St. Louis, IL, on matters involving occupational medicine, a new direction for that hospital. The couple continue to travel the world and work for the betterment of the community.

In fact, Sutter seems clearly to have attained the two life goals he set for himself: to achieve a position that allows his family to be free from worry about the future and to do something of measurable value for the community and especially the working man.
When fifth-graders put on surgical gloves to explore firsthand the lungs of smokers and the livers of alcoholics, the impact is powerful and unforgettable. At least that's the hope of medical students who deliver the gross specimens to the grade-schoolers.

In fact, in their effort at drug education, the first- and second-year medical students do more than bring a startling object lesson to the children. They run a complete education program for the nine- and 10-year-olds that they hope will steer the youngsters away from substance abuse throughout their impressionable years. They build the self-esteem that translates into resistance to peer pressure. And they reach the elementary school children at a cost per child of less than one dollar.

Now in its second year, the Washington University School of Medicine Drug Education Program is one of a growing number of ways in which programs funded by the Alumni Association at Washington University School of Medicine reach out to the community. Headed up by second-year students Ashley Hill, Ray Lee and Steven Wei, the effort was born as a collaboration between students and St. Louis' Maritz Corporation, which provided logistical support during the program's first year of 1991.

Since its inception, the students have set the program's direction. Armed with data that say an estimated 70 percent of Missouri high school seniors use alcohol, a team of three medical students per classroom (about 12 per event, since most elementary schools average four fifth- or sixth-grade classrooms) visits the youngsters for two consecutive days. Each session lasts an hour and 45 minutes.

On day one, the medical students discuss with the children the effects of various drugs including marijuana, cocaine, nicotine and alcohol. Normal gross specimens and those from drug users are available for the children to compare. No one misses the point, Ashley Hill says. On day two, time is spent in games and exercises focusing on self-esteem, decision-making skills, risk and consequence analysis and learning to say "no."

Hill, who brought experience with developmental psychology to the effort, says the medical students base their approach on the philosophy that kids turn to drugs for any or all of five reasons: 1) They have no information about the effects of drugs. 2) They are poor decision makers. 3) They succumb to peer pressure. 4) They can't deal with their own moods and seek an escape from stress. 5) They are adrift without substantial goals. The program works to address all of those possibilities.

During its first year, the education program reached 500 children in St. Louis schools. This year, the hope is to expand the effort to reach as many as 1,700 more children in both city and Parkway school districts. Toward that end, the medical students approached the executive...
Hungry For More

Paul Hodges, M.D. '18, is both fortunate and fulfilled. Ninety-nine years of good health have been his blessing. And, in nearly a century packed full of living, he has maintained the spirit to pursue experience and wisdom at every turn.

Born just about the time the School of Medicine was being founded (when he celebrates his personal centennial on January 6, 1993, he will miss the school's by just a year and a few days), Hodges left for a young man's adventure in China after graduating from the University of Wisconsin. In Shanghai, he taught physiology and planned his career as a physiologist. But Simon Flexner, Rockefeller Institute director, personally convinced Hodges to attend Washington University in pursuit of a medical degree.

While studying here, Hodges says he "always had to have a job," and recalls that he was fortunate enough to land a position as a student assistant in the laboratory of Joseph Erlanger, M.D. There, he was party to groundbreaking work being done on the replacement of fluids in shock.

The job paid additional dividends. Part of Hodges' assignment was to instruct nursing students in physiology, and in one of those classes he met Merle Johnston, who later became his wife. Together, the couple raised five children, two of whom survive.

Upon graduation from medical school, Hodges went back to China to work for the China Medical Board of the Rockefeller Foundation at Peking Union Medical College. He stayed until 1927, when he returned to this country to become chief of radiology at the University of Chicago. He served on the faculty there for 31 years.

For many years, both he and his brother, Fred J. Hodges, II, chaired major radiology departments. Today, Paul's nephew, Fred J. Hodges, III, M.D., is a member of the faculty at the medical school's Mallinckrodt Institute of Radiology.

After Merle passed away, retirement took Hodges to Taiwan, where he remained for three years until the University of Florida called from...
halfway around the world in March of 1964. Hodges signed on there for what he thought would be a few months, undertaking an assignment to re-establish the department of radiology that had collapsed at the death of its chairman. He elected to serve as visiting professor and ended up staying 17 years. After 14 years of single life, he remarried when Janet Reid, a talented Florida watercolorist, agreed to become his wife. The couple lived in Florida for 20 years, until Janet passed away in 1988.

Today, Hodges lives in a retirement home in Green Bay, WI, where his twin sister also resides. Thought to be the senior alumnus of the School of Medicine, he remains a full professor emeritus of two universities, a highly regarded man of medicine, a teacher, a world traveler and a father — nearly a century of experiences clear in his memory.

His biggest frustration is that declining hearing and sight have made it difficult for him to get access to books — the source of much of his long life's joy. Lately, though, new technology has provided a video screen on which printed words are enlarged 60 times, once again making reading possible. His only complaint about the machine: "Too slow." That's just the sort of comment a man might make whose first 99 years of life have brought him fulfillment but also have keenly sharpened his appetite for more.

Edwin G. Krebs, M.D.
'43 (December), a pioneer in biochemistry, has been awarded the prestigious Robert A. Welch Award in Chemistry, recognizing his outstanding contributions to the field. Krebs is senior investigator emeritus for the Howard Hughes Medical Institute and professor in the Department of Pharmacology at the University of Washington at Seattle. He shared the annual award, given by the Texas-based Welch Foundation, with Earl Reece Stadtman, M.D., of the National Institutes of Health.

James C. Folsom, M.D.
'46, reports that he retired on August 9, 1991, and now resides in Cedar Key, FL. He is presently training to do Medicare evaluations of psychiatric facilities, a project he will undertake on a part-time basis.

Russell D. Shelden, M.D.
'49, was honored with the Distinguished Service Award by the University of Missouri - Columbia Alumni Association on September 27, 1991.

In mid-October, Robert C. Drews, M.D. '55, was elected president of the Pan American Association of Ophthalmology. With more than 9,000 members in the western hemisphere and several hundred affiliated members in the rest of the world, it is by far the world's largest international organization in ophthalmology.

Glendall King, M.D. '55, reports that his wife, Lila, passed away on August 22, 1991, and writes that, "She was one of three wives who started out with the medical school class of 1955."

Philip Weinstein, Jr., M.D. '56, and his wife, Nancy, retired in 1991 and now spend time travelling to visit their children and grandchild. He writes that they look forward to tennis, hobbies, more travels and, perhaps, golf.

Jerome F. Levy, M.D.
'58, has published a book for the general public titled, Your Breasts (Farrar, Straus and Giroux, Inc.).

Dick D. Briggs, Jr., M.D.
'60, holds the Eminent Scholar Chair of Respiratory Disease at the University of Alabama School of Medicine, where he also serves as chairman of the Department of Medicine. He is completing his third year as president of the University of Alabama Health Services Foundation and has served as CEO during development and building of the $125 million, I.M. Pei-designed Kinklin Clinic in the University of Alabama Medical Center.

John H. Stone, III, M.D.
'62, has co-edited (with Richard Reynolds, M.D.) On Doctoring, published by Simon and Schuster. The book is an anthology of literature concerning the practice of medicine. The Robert Wood Johnson Foundation will give a copy to every freshman entering medical school in the U.S. The gift
books will go out annually for four years—a total of 72,000 copies. The paperback edition of Stone’s fourth book, *In The Country Of Hearts*, was released in February 1992.

**Jeanie Kinzie, M.D. ’65**, writes that she married Johnson Wachira in Nairobi, Kenya on October 7, 1991. She hopes to work as a physician in East Africa and, in the company of her husband, climb the great mountains of the world. Both are accomplished mountaineers.

**Michael R. Treister, M.D. ’67.**

Michael Roy Treister, M.D. ’67, was recently elected president of Chicago’s Jewish Vocational Service. Treister now heads the public service agency that last year helped 15,000 residents of metropolitan Chicago, including many Russian immigrants, to find jobs, train in new skills and learn to live independently in the community.

**Bruce D. Fisher, M.D. ’70,** has been promoted to clinical professor of medicine and dentistry at Robert Wood Johnson Medical School of the University of Medicine and Dentistry of New Jersey in New Brunswick/Piscataway, NJ.

**John Eisenberg, M.D. ’72,** reports his move to Washington, DC, where he has been appointed to the post of chairman of the Department of Medicine at Georgetown University Medical Center.

**Donald R. Graham, M.D. ’74,** serves as chief of infectious diseases at the Springfield Clinic in Springfield, IL. He and his wife celebrated the birth of their sixth child, Edith, in 1990.

**Pamela Gallin, M.D. ’78,** was among the doctors named in the November 11 cover story of *New York* magazine titled “The Best Doctors in New York.” An ophthalmologist affiliated with Columbia-Presbyterian Medical Center in Manhattan, Gallin was honored for her work with strabismus. Nominations totaling 11,000 were narrowed to 1,085 doctors on the final list.

**Robert D. Rosenberg, M.D. ’79,** has been promoted to the position of associate professor of radiology and recently celebrated the birth of his second child, Leah.

**80s**

**Henry F. Sadovsky, M.D. ’81,** has joined the Department of Internal Medicine/Cardiology at Group Health, Inc.’s Riverside Medical Center in Minneapolis.

**Jeffrey Stein, M.D. ’82,** practices vascular surgery at Mount Sinai Medical Center in New York and began a private practice in July 1990.

**Daryl L. Jacobs, M.D. ’83,** F.A.C.C., has been elected to fellowship in the American College of Cardiology. Jacobs is in the private practice of cardiology with Cardiology Consultants, Ltd., in St. Louis.

**Jonathan W. Jantz, M.D. ’84,** reports that he was married to the former Sue Ann Goossen—an attorney in Newton, KS—on June 8, 1991.

**David Lubarsky, M.D. ’84,** the first graduate of the Washington University School of Medicine’s Scholars’ Program in Medicine, is currently an assistant professor of anesthesiology at Duke University and was promoted in July to the position of chief of the section of vascular and thoracic anesthesiology. Together with Chris Gallagher, M.D. ’84, he wrote the book, *Preparing for the Anesthesia Oral—Board Stiff*, that has become a favorite in the field of anesthesiology. On a more personal note, he reports that he was married in June of 1990 and that he and his wife, Cindi, celebrated the birth of their son, Isaac Daniel, on September 6, 1991.

**Dianne H. Levisohn, M.D. ’86,** lives in Portland, OR and works as a pediatrician for Kaiser Permanente Group. Her husband, Marshall, is also employed by Kaiser as a pediatric dentist. The couple have a “wonderful” daughter, Julia Rose, born in October of 1990.

**Eric E. Stevens, M.D. ’86,** is currently a second-year fellow in pulmonary-critical care medicine at the University of Colorado Health Science Center in Denver.

**William L. Becker, M.D. ’87,** was married on June 2, 1990. He completed his training and joined the St. Louis Eye Clinic in July 1991.

**Former House Staff Notes**

Robert Maltz, M.D., F.H.S., in otolaryngology, has been elected to the Board of Governors of the University of Cincinnati Alumni Association and appointed to the Executive Council of the University of Cincinnati College of Medicine.

**John D. Halverson, M.D., F.H.S. in surgery,** has been appointed professor of surgery, vice chairman of the Department of Surgery and chief of the division of general surgery at SUNY, Syracuse.
Mary A. Alexander, NU '48, Ed.D., plans to retire from the faculty of the Arizona College of Nursing in June 1992. She has worked recently in China as a consultant for the World Health Organization. In 1989, she received the Nurse of the Year Award from the Arizona Nurses' Association and in 1991 received the Award of Distinction for Excellence in Nursing Education from Sigma Theta Tau International Nursing Society.

Joanne Parrott, NU '50, has been appointed to the Board of Directors of the Auxiliary to the American Dental Association. She assumes the chair of the Dental Health Education Committee on which she served last year.

Geneva F. Newman, NU '69, has retired and now volunteers with the literacy council in her home state of Arkansas.

Robert R. Kulesher, HA '77

Robert R. Kulesher, HA '77, has been appointed to the post of administrator of the St. Francis Country House in Darby, PA, a 273-bed facility established in 1913. Kulesher is on the faculty at Penn State University's School of Health and Human Development and at Saint Joseph's University's graduate school, Department of Education and Health Services.

Linda Birkinbine, O.T. '90, writes that she enjoys "being an O. T. in the eastern part of North Carolina. I work with patients with spinal cord injuries and would love to hear from my classmates who graduated in '90." Phone (919) 355-3705.

IN MEMORIAM

Max Deutch, M.D. '26, recently honored for his 50 years of service to St. Louis Children's Hospital, died January 1, 1992, following a brief illness. Deutch retired from private practice in 1965 but continued to work part time as a pediatrician in St. Louis' well-baby clinics, county school districts, at the Missouri School for the Blind and at city and county health departments.


Robert S. Weinhaus, M.D. '45, succumbed to complications from a liver transplant on December 31, 1991, at Presbyterian University Hospital in Pittsburgh, PA. Weinhaus practiced internal medicine until a back injury curtailed his work; he then completed a psychiatry residency and became a board-certified psychiatrist.

Roy O. Kelly, Jr., M.D. '53, died October 22, 1991, in Shawnee, OK.

Leonard J. Tolmach, Ph.D., professor emeritus of radiation biology, died Tuesday, November 26, 1991, at the age of 68. He succumbed to cancer. Tolmach worked for more than 30 years at the medical school's Mallinckrodt Institute of Radiology, where he investigated the mechanism by which radiation kills cancer cells. An inventor and a highly regarded contributor to the field of radiation research, Tolmach often claimed to be "just an average, hard-working scientist. There are thousands of them; every university's full of them." In fact, he was "anything but average," according to Ronald G. Evans, M.D., director of Mallinckrodt Institute, who says, "Professor Tolmach received not only some of the nation's highest honors in radiation research but also the admiration of his colleagues and peers."

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The alumni association has funded a drug education program designed and operated by second-year medical students. Fifth- and sixth-graders in two area school districts encounter the direct effects of drug use and abuse when medical students like Ashley Hill bring gross specimens into the elementary school classroom. For more on the program, see page 28 of this issue.