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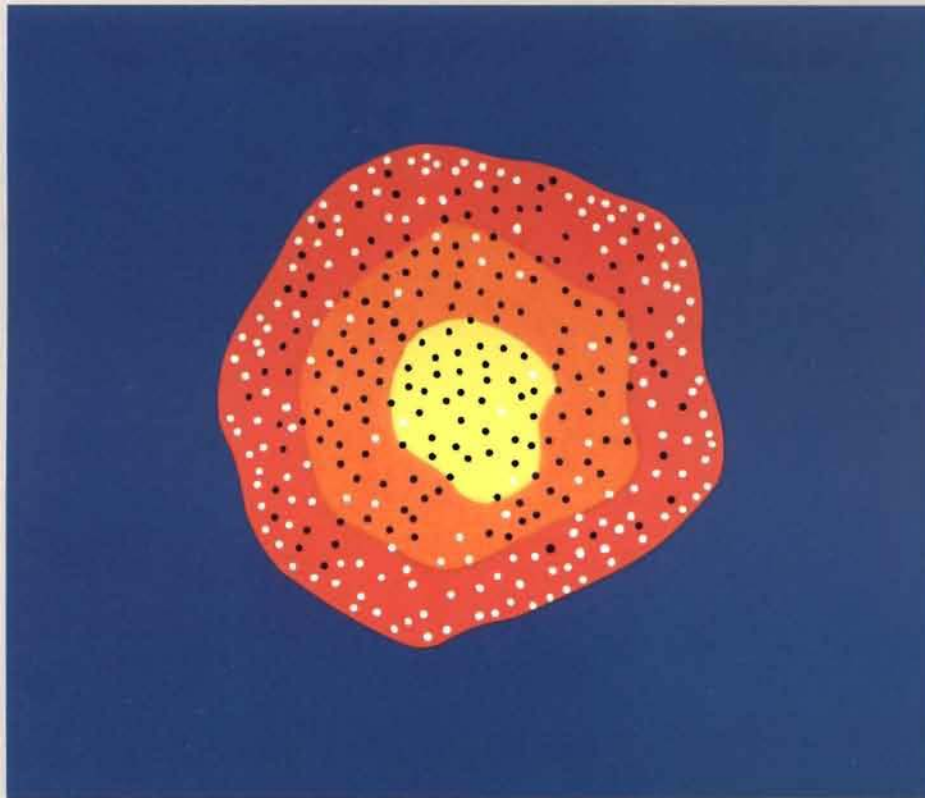
OUTLOOK

MAGAZINE Indexed y.23n1, 1986

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From Disasters to Daily Stress:
Assessing Psychological Impact

NO
TRESPASSING



On cross section, most sizable tumors reveal three regions that differ in their blood supply and therefore their oxygen content. At the tumor's core, the tissue is essentially dead because of a lack of oxygen, which is shown above as the light-colored dots. The dark dots represent accumulations of a radiosensitizing drug that accumulates even in low-oxygen regions of tumors, making the cells more vulnerable to killing by radiation therapy. See "The Cells We're After," page 22.

OUTLOOK

Volume XXIII, Number 1 Spring 1986

Director, Medical Public Relations

Glenda King Wiman

Executive Editor

Don Clayton

Editor

Suzanne Hagan

Design

Suzanne Oberholtzer

Circulation

Barbara Hebrank

On The Cover:

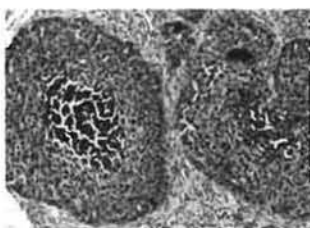
Families uprooted by floods or other disasters become persons who may need mental health services. Thanks to a diagnostic survey developed in part by W.U. researchers, "psychiatric triage" can be performed by trained laypersons.

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Leading Questions

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Catastrophic occurrences add to the burden on mental health services, as do high-risk members of populations. Diagnosing and assessing prevalence of mental illness is now easier, thanks to a psychiatric interview that can be administered by trained laypersons.

Kinesin: A New Cellular Motor

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This newly discovered "motor" protein enables cells to rapidly transport substances from one place to another. A researcher in the Department of Cell Biology and Physiology uses an enhanced video system that demonstrates this movement along the cell's microkeleton.

Transplanting Life

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Liver, heart and long-bone transplants join the well-established kidney transplant program at the medical center. In the offing are heart-lung transplants, and a revival of human heart valve transplants is underway.

Behind the Ether Screen

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Like all surgical procedures, organ transplants would be impossible if not for the skill of the anesthesiologist. Some "internists of the operating room" describe the special problems that they surmount to make these major surgical endeavors successful.

The Cells We're After

22

An older drug's newer analog can help improve radiation therapy's ability to destroy cancer cells. Washington University is one of the North American medical centers where the drug SR-2508 will undergo Phase III testing.

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NEWSBRIEFS

Alzheimer's Research Center Dedicated

US. Sen. Thomas F. Eagleton, D-Mo., delivered a keynote speech at ceremonies designating Washington University in St. Louis as an Alzheimer's Disease Research Center (ADRC). Washington University is one of ten institutions that have received five-year funding from the National Institute on Aging (NIA) to study Alzheimer's Disease.

Eagleton was instrumental in establishing the National Institute on Aging and has worked to obtain federal funding for health care research, particularly through the National Institutes of Health.

The center will receive more than \$3.7 million in NIA funding over the next five years. A neurological disorder with no known cause or cure, Alzheimer's Disease affects an estimated two million Americans and is the most common cause of intellectual impairment and institutionalization among the elderly.

The Washington University ADRC will take an interdisciplinary approach to research on Alzheimer's disease and related disorders. Established investigators will conduct a wide range of studies, examining behavioral as well as biomedical aspects of the disease. Researchers will compare the healthy aging process with

that of Alzheimer's-induced dementia; search for neurobiological factors that could be associated with the disease; explore changes in the aging brain that may contribute to Alzheimer's disease; and investigate the disease's impact on the family and the community.

The ADRC also will train scientists and health care professionals, and provide the public with information on research advances.

The center's director, Leonard Berg, M.D., is professor of clinical neurology at the School of Medicine. He is program director of the medical school's Memory and Aging Project, a long-term study of intellectual function in people aged 65 and older, and a physician at Barnes, Children's and Jewish hospitals.

For further information about the new center, call ADRC coordinator Sandy Venegoni at 362-2881.

Cowan Appointed Provost

WMaxwell Cowan, vice president of The Salk Institute for Biological Studies in La Jolla, Calif., has been appointed provost and executive vice chancellor effective August 1986, Chancellor William H. Danforth has announced.

Cowan returns to Washington University where he previously served as head of the Department of Anatomy and



W. Maxwell Cowan

Neurobiology from 1968 to 1980 and director of the university's Division of Biology and Biomedical Sciences from 1975 to 1980.

A co-founder of the Division of Biology and Biomedical Sciences, Cowan led a pioneering effort to bridge the gap between the faculties of arts and sciences and of medicine, especially in the graduate training of young biological scientists. The division involves several of the university's scientific departments — biology, anatomy and neurobiology, biological chemistry, cell biology and physiology, genetics, microbiology and immunology, pathology, and pharmacology. The program enables young scientists in training to move freely among the disciplines in areas as varied as population biology, ecology, plant biology, molecular and cellular biology, and neural sciences.

Cowan's association with the university began in 1965 when, on sabbatical from Oxford University, he was a visiting associate professor of anatomy in the School of Medicine.

After spending two years at the University of Wisconsin, he returned in 1968 as professor and head of the Department of Anatomy. He also held a joint position in biomedical engineering in the Department of Electrical Engineering and, in 1978, was appointed Edison Professor of Neurobiology.

In 1978, Cowan was asked to serve as a non-resident fellow of The Salk Institute for Biological Studies and, in 1980, moved to La Jolla as a research professor at the Institute and as a senior investigator of the Clayton Foundation for Research. In 1982, he was named vice president of the Institute and director of the Weingart Laboratory for Developmental Neurobiology. He also has served as an adjunct professor in the departments of biology and neurosciences at the University of California—San Diego.

A native of Johannesburg, South Africa, Cowan received his undergraduate degree from Witwatersrand University, Johannesburg, and his graduate degrees from Oxford University, England, on whose faculty he served from 1953 to 1966.

Cowan, who also is the author of many scientific publications, currently serves as editor-in-chief of the *Journal of Neuroscience* and editor of the *Annual Reviews of Neuroscience*. For 11 years, he was managing editor of the *Journal of Comparative Neurology*. He also serves in an editorial capacity with two other scientific publications.

He has served on the Board of Scientific Counselors at the National Eye Institute, chaired the Scientific Advisory Committee of the Neurosciences Research Institute, served on

the Advisory Council of the National Institute for Neurological and Communicative Diseases and Stroke and on the Medical Advisory Board of the Howard Hughes Medical Institute.

His honors include fellowship in the Royal Society, and he is foreign associate of the U.S. National Academy of Sciences (1981) and member of the American Academy of Arts and Sciences, Alpha Omega Alpha, and Institute of Medicine. In 1984, he was awarded the Karl Spencer Lashley Prize for Neurobiology by the American Philosophical Society.

He is an associate of the Neurosciences Research Program and a member of the International Brain Research Organization, the Society for Neuroscience (president 1977-78), the American Association for the Advancement of Science, Sigma Xi, the Anatomical Society of Great Britain and Ireland, the Royal Microscopical Society, the American Association of Anatomists, and past president of the St. Louis Society of Neurological Sciences. ■

Two Researchers Receive Javits Award

Two faculty members will conduct research for the next seven years with almost \$1.5 million in funding from Javits Neuroscience Investigator Awards.

Recipients of the most recent Javits Awards include Harold Burton, Ph.D., professor of neurobiology and associate professor of physiology and biophysics; and David I. Gottlieb, Ph.D., associate professor of neurobiology and biochemistry.

Washington University faculty members have received eight of the 125 Javits Neuroscience Investigator Awards presented since October 1983, when the highly competitive awards program began. Award recipients are selected three times a year.

The U.S. Congress gives the awards in honor of Sen. Jacob K. Javits of New York, on recommendation of the National Advisory Neurological and Communicative Disorders and Stroke Council of the National Institutes of Health. Javits suffers from amyotrophic lateral sclerosis (ALS) more commonly known as Lou Gehrig's disease. ALS is a degenerative neuromuscular disorder, affecting the nerve cells that control muscles.

The awards, given to investigators who have submitted regular research grant applications for competitive review, encourage research and training in communicative and neurological disorders. The prestigious grants provide a seven-year commitment of support to the researchers who receive them.

Burton's research is designed to learn more about neural codes associated with the sense of touch. His studies should illuminate the role that specific areas of the cerebral cortex play in texture perception and the way in which neuronal activity relates to sen-

sory discrimination behavior. These experiments may facilitate understanding of how the cerebral cortex operates in learning to recognize touched objects, such as braille symbols and tactile graphics for the visually impaired.

Gottlieb's research goal is to understand the mechanisms that control the expression of important neuronal properties during the development of the mammalian central nervous system. He plans to use monoclonal antibodies that recognize subsets of neurons to determine when cell-specific antigens — substances that cause antibodies to form — are first developed. He also hopes to find out if the formation of appropriate neural connections is necessary to the development of cell-specific antigens. ■

Volunteers Needed for Three Studies

Several research projects at the School of Medicine need volunteers to make them a success.

The Lipid Research Center is conducting several studies on the effect of diet and medication on blood cholesterol. Among the projects is a diet study funded under a three-year, \$110,000 grant from the NIH. According to the center's director, Gustav Schonfeld, M.D., an inherited protein defect that affects 25 percent of Americans is believed to make them more susceptible to cholesterol

and thus at a higher risk of cardiovascular disease.

This is the first study of its kind to examine the effect of diet on cholesterol levels in persons with that trait. Researchers will screen volunteers aged 21-60 to select those who have the trait, as well as a group of controls who do not have the defective protein.

Two other studies will test new cholesterol-lowering drugs, one in liquid form and the other in capsule form. Researchers will use volunteers aged 21-70 to test for optimum dosage and long-term clearance.

More information about any of the cholesterol studies is available from 1-4 p.m. weekdays at the Lipid Research Center, 314-362-3500.

The Memory and Aging Project (MAP), begun at the School of Medicine in 1979 to conduct long-term research on intellectual function in persons aged 65 and older, seeks volunteers to participate in studies comparing healthy aging with Alzheimer's disease.

The project needs volunteers aged 65-85 who are experiencing some form of memory loss and/or dementia without obvious cause. They should not have other serious disease, including stroke, heart failure, lung failure or cancer. For further information, contact MAP at 314-362-2683.

The Diabetes Control and Complications Trial (DCCT) needs persons with insulin-dependent diabetes to participate in one of the largest and most important studies of the disease ever performed. The DCCT is a seven-year study that will include 1,100-1,200 participants at 21 medical centers, including Washington

University, across the country.

The study, funded by the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases, seeks to answer one of the most important remaining questions about diabetes: how effective are some of the newer forms of diabetes therapy at preventing, delaying or reversing the presence of diabetic complications? These complications may affect the eyes, kidney, nerves, heart and blood vessels.

Participants in the DCCT must be between the ages of 13 and 39 and have had type 1 diabetes for 1-15 years. They cannot be taking more than two insulin injections per day, be using an insulin pump, or have any severe complications from diabetes. Volunteers will receive free medical care for the next seven years. To volunteer, contact Julio Santiago, M.D., at 314-454-6051. ■

Seeing the Light

For King Fetsch, failing the vision test for her driver's license was a real eye-opener.

Fetsch's low score revealed something she had not even suspected — that her eyes were succumbing to complications of diabetes. Her poor performance would lead her to become, literally, an eyewitness to the unfolding legacy of the laser.

Mrs. Fetsch is one of 92 patients in a landmark study proving that the laser can reverse the leading cause of vision loss in diabetics, a pre-



R. Joseph Olk's recent study proves that the leading cause of blindness among diabetics, macular edema, can be reversed through laser therapy.

viously untreatable condition known as diffuse diabetic macular edema. That success has catapulted the laser, already widely used to repair retinas and cut away cataracts, into still another ophthalmologic spotlight.

The latest focus on laser's ability to aid lapsing vision could benefit many people, says the study's principal investigator, because the condition is much more widespread than its rather obscure reputation would indicate.

"Macular edema is the major cause of visual impairment in all diabetics," says R. Joseph Olk, M.D., who conducted the research at Washington University. "It doesn't cause people to go blind, but it interferes with their ability to read, drive, maintain a job or do close work. In other words, the necessary tasks of life."

Macular edema, Olk explains, is a vision-blurring buildup of fluid inside the eye. The condition is less damaging to eyesight, but much more

prevalent than the other vision problem common among diabetics, proliferative diabetic retinopathy. Proliferative retinopathy, a condition in which the eye's tiny blood vessels hemorrhage and the retina sometimes detaches, can cause legal blindness if untreated.

Of the nearly 6 million diagnosed diabetics in the United States (and the American Diabetes Association estimates there are 4-5 million undiagnosed cases), nearly 1 in 5 report some vision impairment. Retinopathy, which includes both macular edema and proliferative retinopathy, is considered one of the disease's major complications. It is tied to duration of the disease: 1 in 2 diabetics will develop retinopathy after ten years with the disease, and 9 in 10 will after 20 years.

Olk, an assistant professor of ophthalmology, presented the first research results proving that laser therapy can almost always eliminate macular edema at the annual meeting

of the American Academy of Ophthalmology in October. Previous studies have suggested some benefits from laser treatments, but none have shown such clear results.

A subsequent report from the Early Treatment of Diabetic Retinopathy Study, published in the December 1985 Archives of Ophthalmology, confirmed the results found in Olk's study. That study also demonstrated a positive treatment benefit from argon laser in people who have "clinically significant" macular edema, though it used a different treatment technique than Olk's.

His new technique, called "modified grid," reduces fluid in the macula, a tiny part of the retina that is most responsible for sharpness of vision (acuity). Further, Olk reported that laser therapy preserves — and in many cases improves — vision already impaired by the condition.

Research results published in 1976 proved that another laser technique, panretinal photocoagulation, can reduce by more than 50 percent the vision loss caused by proliferative retinopathy. Since then, laser has become routine treatment for those patients.

As Olk points out, though, those findings did not even address macular edema, leaving a much larger group of patients in an ocular lurch.

"Most ophthalmologists have told their diabetic patients that nothing can be done about macular edema," Olk says. "They have not considered any form of laser therapy because research results have not been very promising. Until now, there was no statistical evidence

that treatment is better than no treatment. So the majority has not been treated. Their vision either has stayed the same, or slowly deteriorated.

"Now, ophthalmologists can use our results to recommend, without question, that their patients with diabetic macular edema should undergo this treatment to reduce severe vision loss."

Olk's findings are based on a three-year clinical trial of modified grid photocoagulation. The study was conducted at the School of Medicine and Barnes Hospital.

For King Fetsch, the modified grid laser has meant a liberation of sorts. The 56-year-old widow, who received three treatments in her left eye as part of Olk's study, has seen such an improvement in vision that her glasses need less correction for that eye.

"When I first saw Dr. Olk, he told me that there was no chance of improving my vision and only a 40 percent chance of saving my existing vision," she recalls. "He not only saved it, but he improved it, too." She has not experienced the side effects reported by most other patients.

The eye that was treated is now the one she depends on. Vision in her right eye, a control during the two-year study, has deteriorated. She has just had a third laser treatment in that eye and will learn in the coming months if she'll need further therapy.

While Mrs. Fetsch waits, she's optimistic and does what any good eyewitness would do: she gives enthusiastic testimony to the effectiveness of modified grid laser.

"I recommend it," she says. "I know a diabetic with the same condition I have. His doctor said nothing could be done. I referred him to Dr. Olk, and he's had two laser treatments since July. Your vision is definitely worth a second opinion."

Gift Endows Medical Research Lab

The C.V. Mosby Company and the Times Mirror Foundation have announced a \$100,000 gift to endow a pathology laboratory at the School of Medicine. The gift is presented as part of the ALLIANCE FOR WASHINGTON UNIVERSITY, a \$300 million program to provide support for the institution.

The funding will endow a pathology laboratory in the Clinical Sciences Research Building and will support the research of department head Emil R. Unanue, M.D. Unanue is Edward Mallinckrodt Professor of Pathology at the School of Medicine and pathologist-in-chief at Barnes, Children's and Jewish hospitals.

An immunopathologist, Unanue has investigated interactions among immune system cells. He has been instrumental in showing the critical role played by macrophages, cells which activate the body's immune response to foreign invaders. Macrophage interactions with other immune system cells are important in

organ transplants and in the body's response to many disease states, especially infection and cancer.

The Times Mirror Foundation is the corporate foundation of Los Angeles-based Times Mirror, parent company of C.V. Mosby as well as television station KTVI, Channel 2, and The Sporting News Publishing Company, all in the St. Louis area. Times Mirror publishes the *Los Angeles Times* and seven additional newspapers, and has other extensive media holdings.

The C.V. Mosby Company publishes medical and health care books for students and professionals, and produces such electronic publications as educational software and test/review materials.

FURTHERMORE

The 1986 Medical Center Alumni Reunion will be held May 1-3. Classes specially honored at the reunion this year include those who graduated in 1931 and every five years thereafter, including 1976. For more information, contact the Alumni Office at 314-362-8278.

Timothy L. Ratliff, Ph.D., research associate professor and director of urologic research, division of urologic surgery, has been awarded a World Health Organization Travel-Study Fellowship and a Burroughs-Wellcome Travel Research Grant to conduct research at the Middlesex Hospital in London, May-June 1986.

Ratliff is currently funded by the National Cancer Institute and the American Cancer

Society for his research on BCG therapy for superficial bladder cancer. The fellowship and grant permit him to investigate the immune response induced by mycobacterial antigens (the active components of BCG vaccine) in the laboratory of Graham Rook, a noted researcher in the field.

George E. Murphy, M.D., professor of psychiatry and director of the psychiatry outpatient clinic, has been awarded a \$316,000 grant by the NIMH. The grant will support an investigation of cognitive therapy as a specific treatment for depression. In a previous study, Murphy demonstrated that cognitive therapy is at least as effective as medication in the treatment of depressed outpatients. The present study seeks to find any specific aspect of cognitive therapy that would explain its usefulness in treating this disorder.

Thomas F. Deuel, M.D., professor of biological chemistry and medicine and director of the Fixman Cancer Center at Jewish Hospital, has been awarded the 1985 Dameshek Prize at the annual meeting of the American Society of Hematology.

The 1985 Awards Luncheon, presided over by Dean Herweg, was held December 11. At this annual event, first-through third-year students are honored for their academic prowess during 1984-85. The prizes, and recipients, are: *The George F. Gill Prize in Anatomy*, and *The Kehar S. Chouke Prize in Anatomy*, awarded to

Kenneth M. Carnes, Robert G. Kaniecki, and Robinna G. Lorenz.

The Edmund V. Cowdry Prize in Histology, awarded to Robert J. Optican.

The Dr. James L. O'Leary Neuroscience Prize, awarded to Russell E. Hillsley.

The Carl F. and Gerty T. Cori Prizes in Biochemistry, awarded to Richard C. Bell and Paula J. Chor.

The Antoinette Frances Dames Prize in Physiology and Biophysics, awarded to Robert J. Optican and Kenneth M. Zabel.

The Howard A. McCordock Book Prize in Pathology, awarded to Jesse S. Little, Jr.

The Dr. Margaret G. Smith Award, given to Laura A. Rokusek.

The Medical Center Alumni Scholarship Fund Prize, awarded to James A. Schiro.

The Academic Achievement Award, given to Albert B. Ross.

Oliver H. Lowry Prize in Pharmacology, awarded to Peter L. Smith.

The McGraw-Hill Book Prizes, awarded to Kenneth M. Zabel and Russell E. Hillsley.

The Richard S. Brookings Medical School Prizes, awarded to Brian A. Armstrong, Jesse S. Little, Jr., and Eric E. Stevens.

The Dr. Robert Carter Medical School Prizes, awarded to Jeffrey L. Elliott, Robert M. Forstot, and Harris S. Chrysikopoulos.

Morris J. Karnovsky, M.B., Ch.B., D.Sc., delivered the 32nd annual Robert J. Terry Lecture. Karnovsky is a cell biologist and experimental pathologist who developed a

widely used technique to visualize microscopic images. He is Shattuck Professor of Pathological Anatomy and chairman of the Program in Cell and Developmental Biology at the Harvard School of Medicine.

The Department of Anatomy and Neurobiology sponsors the Terry Lectureship, which was established by alumni and friends to honor Terry, who was department head from 1900-41.

Yasutomi Nishizuka was the featured speaker at the 28th Shaffer Lecture, part of a mini-symposium sponsored by the Department of Biological Chemistry and The Howard Hughes Medical Institute. Nishizuka, of Kobe University in Japan, is an expert on phospholipids (fats), some of which are involved in the activation of protein kinase C. The latter transforms normal cells into tumorous ones and may be an important regulatory aspect of the process.

Philip W. Majerus, M.D. '61, professor of biological chemistry and medicine, was another of the symposium speakers. He described his work on specific phospholipids that encode information in their structure. These compounds are "second messengers" and are part of a system analogous to adenylate cyclase / cyclic AMP. The lipids Majerus investigates show a particular structural shape in cells stimulated to form tumors.

H. Gobind Khorana presented the first Carl and Gerty Cori Lecture. Khorana, now in the departments of biology and chemistry at Massachusetts Institute of Technology, worked

at Washington University when Arthur Kornberg was here. Khorana was awarded the Nobel Prize in 1968 for his work on the genetic code. His presentation for the Cori Lecture described bacteriorhodopsin, a bacterial protein that is a light-driven proton pump.

J. Michael Bishop, M.D., was the thirteenth Carl Vernon Moore lecturer. Bishop, professor of microbiology and immunology, is director of The Hooper Research Foundation at the University of California, San Francisco. His topic was "Oncogenes: Trouble in our DNA." Oncogenes are activated when cells form tumors.

U.S. Sen. Thomas F. Eagleton, D-Mo., delivered the third annual Edward Massie Lecture in Cardiovascular Disease. His talk, titled "Health Care's Third Revolution — Sowing Seeds for the Fourth?", honored Edward Massie, M.D. '35, professor emeritus of clinical medicine.

Eagleton, a U.S. senator since 1969, has been very involved in funding health care research, particularly through the National Institutes of Health. He was instrumental in establishing the National Institute on Aging, and in the mid-1970s played a key role in passage of the Health Manpower Act.

Frederick Sweet, Ph.D., professor of reproductive biology, has received more than \$900,000 to continue studying the role of enzymes in producing steroid hormones. The four-year grant renews a previous award to Sweet from the National Institute of Child Health and Human Develop-

ment. Sweet hopes his research eventually will lead to improved management of fetal development during pregnancy and to a better understanding of how hormones are produced in the body.

In previous animal studies, Sweet and another investigator isolated and described an enzyme that they believe forms part of a unique hormonal communication system between the fetus and mother. They think similar communication systems function throughout human pregnancies.

Sweet's research is in conjunction with three separately funded laboratories, including one headed by James C. Warren, M.D., Ph.D., professor and head of obstetrics and gynecology. The other laboratories are in Australia and Massachusetts. The investigators are collaborating on two other projects that examine the role of enzyme systems important in the production and regulation of hormones.

The WU School of Medicine chapter of the Alpha Omega Alpha medical fraternity initiated fourteen newly elected senior medical students at its annual banquet.

The new members are Trevor C. Axford, Nancy L. Bartlett, Charalabos Harris Chrysikopoulos, Bradley A. Evanoff, Fredric J. Gross, Rachel F. Haft, Daniel H. Hechtman, David A. Johnson, Jean P. Molleston, Michael E. Presti, James A. Schiro, Eric E. Stevens, O. Clark West, and Judith L. Zier. ■

LEADING QUESTIONS

BY LINDA SAGE

The Diagnostic Interview Schedule (DIS), a tool for diagnosing specific mental disorders, was born at Washington University. Now fully matured, it's traveling the world. From Iceland to mainland China, from Portugal to Puerto Rico, researchers are using the DIS and its 22 translations in clinical and epidemiological studies.

Only a few years have elapsed between the DIS's conception and this spate of globe-trotting. The need for such a tool became evident in 1978 when the President's Commission on Mental Health, asking how the mentally ill are served, concluded that information about the prevalence of mental disorders ought to be linked to data on the use of mental health facilities. But at that time, there was no comprehensive information on either topic.

Epidemiologic studies of mental illness in the U.S. began in 1855, when physician Edward Jarvis tried to determine the frequency of the two major diagnoses of that era, insanity and idiocy. Later, other disorders — such as depression and anxiety — were defined and surveyed. But after World War II, most American epidemiologists either rejected the tenet of multiple disorders or decided that psychiatrists were unreliable diagnosticians. So subsequent studies measured blanket mental illness instead of different disorders. Result: Some questionable conclusions about the mental health of Americans. For example, the Midtown Manhattan Study, published in 1962, concluded that 82 percent of its sample had psychiatric problems.

During the 1960s and 70s, opinion swung once again to favor specific diagnoses such as schizophrenia, mania and depression. And during that time, psychiatrists developed tools to define the different disorders, eliminating the greatest source of error in diagnosis: variation in diagnostic criteria from one psychiatrist to another.



A psychiatric diagnostic interview written by Lee N. Robins, left, attracted sponsorship from NIMH because it effectively unmasked low-prevalence disorders in very large population studies. Elizabeth M. Smith is examining the mental health of persons exposed to floods, dioxin and radioactive well water.

One such tool, the Research Diagnostic Criteria (RDC), grew out of ten years' research on diagnosis, much of it under the direction of Eli Robins, M.D., then head of psychiatry at Washington University and now Renard Professor of Psychiatry. Today, the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), which evolved from the RDC, is the official diagnostic system in the U.S. and is widely used elsewhere.

The DSM-III was in preparation when the President's Commission announced its findings in 1978. So when NIMH took up the Commission's challenge and decided to conduct a nationwide survey of mental health, it wanted to use DSM-III criteria. It also had to find a survey method.

Early surveys assessed mental disorder by inspecting official records and asking leaders about severely disturbed people in their communities. So they missed all but the obvious cases. Later, psychiatrists began to do personal interviews but refrained from asking "embarrassing" questions about sexual behavior, violence and drink-

ing. More recently, they discovered that people are willing to admit to "deviant" behavior, and their interviews have become more comprehensive.

Assessing the written interviews available in 1978, NIMH concluded that one developed by Lee N. Robins, Ph.D., professor of sociology in psychiatry, and her colleagues at Washington University, was closest to its requirement. "It formed the best base from which to begin," says Darrel A. Regier, M.D., M.P.H., then head of the Division of Biometry and Epidemiology at NIMH, now director of NIMH's Clinical Research Division. "We needed an interview that could be administered to a very large population in order to assess disorders that are found at very low prevalence. In order to conduct such a large-scale survey, we knew that we would have to use lay interviewers, which meant that the interview had to be highly structured. It had to replicate as much as possible the clinical diagnostic process."

NIMH scientists sponsored and coordinated the development of a new diagnostic

interview. Working with John E. Helzer, M.D., professor of psychiatry, and Jack L. Croughan, M.D., clinical associate professor of psychiatry, and scientists Robert Spitzer and Janet Williams from the New York Psychiatry Institute, Lee Robins converted the interview into the DIS by incorporating DSM-III criteria, adding questions about the recency of symptoms and making it scorable by computer. Then in 1981, the DIS took to the field in the five areas of NIMH's survey, which was called the Epidemiological Catchment Area (ECA) study.

DIS IN THE FIELD

The study assessed the prevalence (lifetime occurrence) of specific mental disorders in and around five American cities. Between the two study phases, a telephone survey asked about the use of mental health facilities. The same people were interviewed on all three occasions.

The ECA study is the largest psychiatric epidemiologic study to date, each site being nearly as big as the combined total of all previous North American studies. With 3,000 household residents and 500 institutionalized residents at each site, the study surveyed nearly 20,000 people age 18 and older. Regions of inner cities were also included because of their known high rates of psychopathology.

The interviewers — mostly market researchers and census data collectors — trained for eight days, where they learned how to ask the DIS questions and code the answers. They needed no prior knowledge of psychiatry because the questions are read exactly as written and because the computer makes the final diagnoses. The only tricky part was learning to use the probe flow chart, the interview's "road map." The chart directs the interviewer to a subsequent question on the basis of the previous question's answer.

After training, the interviewers took their expertise into homes and institutions, where they conducted the interviews. The results were then collected, cleaned and analyzed, giving the first assessment of the prevalence of 15 mental disorders. Incidence figures are not yet available.



Felton J. Earls is using the Diagnostic Interview Schedule, DIS, developed at Washington University in his assessments of mental illness among adolescent populations. He says the DIS overshadows all the other existing interviews.

MENTAL HEALTH IN AMERICA

The study found that about one-third of the sample had experienced at least one psychiatric disorder sometime during their lives. The most prevalent diagnoses were alcohol abuse, phobias, major depression, antisocial personality (chronic amoral and impulsive behavior), and drug abuse.

There was no difference at any site between the total prevalence of disorders in men and women. This contrasts with earlier surveys, which consistently found that women have more psychiatric illness. "It appears that the reason for this repeated earlier finding," conclude the researchers, "was that symptoms of the male-predominant diagnoses such as alcoholism, drug dependence and antisocial personality were little inquired about."

Researchers also uncovered a surprising relationship between age and incidence of mental disorders. They expected to find higher rates in older persons, who have been at risk for longer periods. But alcohol abuse, major depression, mania and panic disorder were least prevalent among those over age 65. Drug abuse was highest among 18- to 24-year-olds. The drug abuse results are understandable, the researchers say, because the drug epidemic began in the late 1960s.

But the other findings have no ready explanation.

Unlike the age-related findings, the effect of urbanization on mental health was predictable. Inner cities had higher rates of drug abuse, antisocial behavior, schizophrenia and cognitive impairment. Only panic disorder was higher in the rural and small-town areas.

The study also showed that fewer than one-fifth of persons with recent symptoms had visited either a general physician or mental health specialist to discuss psychiatric problems in the previous six months. And though about one in two schizophrenics and one in three people with affective disorders (mania, depression) had sought help, the ratio was only one in ten for persons with alcohol-related problems.

"It was suspected before our study that there was a lack of treatment for substance abuse, but no one could put a number on it," says Lee Robins. "And what was most interesting to me was not the numbers so much as the barriers to treatment. Things that are easy to remedy — such as cost, opening hours of clinics, or not knowing where to get help — are not very frequent. People with alcohol problems think that they should be able to stop drinking on their own, that it's not a proper thing to talk to a doctor about, or that it's a bad habit that

How to Write Leading Questions

they will overcome. So they don't think it's a reason to seek care. I think that's a very important finding. It means that the problem is not just to improve facilities but also to educate the public."

NEW STUDIES SPAWNED

Since the completion of the ECA study, Washington University has continued to work with the DIS. Helzer and Robins are among collaborators developing a computer-based DIS that can be either self-administered or given by an interviewer. And a computer-based screening interview will help general physicians distinguish patients with psychiatric disorders from those with physical illness. Next year, the researchers hope to computerize an interview called CIDI (Composite International Diagnostic Instrument), a combination of a British interview and the DIS.

Other studies using the DIS as a diagnostic tool include the Health Effects of Environmental Hazards, in which Lee Robins and Elizabeth M. Smith, Ph.D., research assistant professor of social work in psychiatry, are looking at the mental health of persons exposed to floods, radioactive well water and dioxin, and the Health in Teens Study headed by Felton J. Earls, M.D., Blanche F. Ittleson Professor of Child Psychiatry.

The Health in Teens Study (HITS) compares adolescents (ages 10-13) treated in traditional public health clinics with those cared for by consolidated clinics that provide a network of comprehensive services. An adolescent with multiple problems could visit a clinic for, say, pregnancy but not receive treatment for her depression or drug abuse. In 1980, the Robert Wood Johnson Foundation supported establishment of 20 consolidated clinics, each a network of services providing comprehensive treatment. HITS evaluates the performances of seven of these compared with three traditional clinics in ten different cities.

Fieldwork began in 1984, when HITS interviewed 3,000 adolescents who visited one of the clinics for any medical purpose. Using parts of the DIS plus the related Diagnostic Interview for Children and Adolescents, it diagnosed the disorders that were present in the sample. Then in No-

"Writing an interview is really more an art than a science," says Lee Robins. "There's little in the literature about it except for rules about not leading the respondent with biased questions and not combining two ideas in a single question."

Compiling the 259 sets of a main question plus subquestions in the DIS began with a list of psychiatric symptoms compiled from DSM-III. For example, psychiatric researchers need to know about a client's possible heavy alcohol intake, recklessness, violence and job loss — symptoms of alcohol abuse. So they had to write understandable questions that would uncover any of these symptoms. "That's the hard part," says Robins. "A question has to be perfectly clear, short and mean exactly what you think it means."

The questions also had to be non-judgmental and inoffensive. "Do you have trouble getting along with people?" would probably provoke most persons to respond, "No." So a series of more tactful questions was needed: "How many times have you been divorced? Other than when you separated just before a divorce, have you and your husband ever separated for a few days or longer because of not getting along? Did you separate more than once?"

The Interview was tested on small groups of people, and any ambiguous or offensive questions were rewritten and tried out again. After about 50 such pre-

tests, the DIS was ready for the field.

The probe-flow chart grew out of the psychiatry department's conventional way of asking questions. Like other physicians, psychiatrists probe patients to assess the significance and physical basis of symptoms, but they don't usually work from a script. The chart provides lay interviewers with written instructions for routine and efficient questioning. Following these, an interviewer asks a patient who admits to frequent headaches, "Did you tell a doctor about your headaches?" A "Yes" elicits, "When you told your doctor, what was the diagnosis?," whereas a "No" prompts, "Did you tell any other professional about your headaches?" Each subsequent answer likewise leads to one of two or more questions or tells the interviewer to enter a code for later diagnosis.

The Interview was evaluated during the largest national survey of mental illness ever made in the U.S. — the Epidemiological Catchment Area study. During the ECA, lay interviewers' results were compared with diagnoses made by psychiatrists using several diagnostic methods including the DIS. Since there was good agreement on many items between the different methods, researchers feel optimistic about the DIS's validity for clinical and epidemiologic studies. However, the real test will come in learning how well it predicts the respondent's future problems and his or her success in seeking care. ■

ember 1985, HITS re-interviewed the same adolescents and also reviewed medical records. After this wave is completed in May 1986, it should reveal any differences in the effects of the two types of health care on the lives of adolescents.

Earls says this study would be impossible without the DIS because of the tremendous cost of using psychiatrists for diagnosis. "Other questionnaires for lay interviewers do exist," he says, "but whereas they may have been partially tested for reliability, the DIS has been exhaustively tested for precision and accuracy. So the DIS overshadows all the other existing interviews."

In May 1986, data from DIS-based studies in Asia, Europe and North America will be compared at a meeting of the Amer-

ican Psychiatric Association in Washington, D.C. Moreover, the World Health Organization is presently testing the CIDI prior to a large epidemiological study in nine countries.

Thus, CIDI — an outgrowth of DIS — and the DIS itself must surely make statesmen envious. These psychiatric tools enable cross-cultural differences to be neutralized and diagnostic disputes settled, paving the way for progress in psychiatric diagnosis. Perhaps leaders in the arena of world politics would do well to emulate the vision and creativity of researchers at Washington University. ■



Illustration by Greg Michaels



KINESIN

A NEW CELLULAR MOTOR

BY SUZANNE HAGAN

Zippering along microtubule "tracks," organelles create a flurry of traffic in cells. Kinesin, a unique cellular protein, piggybacks the organelles across the cell's vast inner spaces. But how to view this hidden world in the laboratory? Washington University researcher Michael Sheetz has coated tiny glass beads with kinesin. Using videotape and a microscope, Sheetz monitors the movement of these kinesin-coated beads, enabling him to analyze the properties of this newest member of the family of motile proteins.

Miniature railroad enthusiasts know — but probably couldn't explain — the fascination that this hobby holds. Even a casual observer can't help but be mesmerized by the sight of a locomotive, with a shrill whistle and puffs of smoke, chugging ceaselessly around the railroad track. Through tunnels and train stations, over hills and trestles, the locomotive continues its journey.

There is a risk of being mesmerized by a different sort of transport system when you visit the laboratory of Michael P. Sheetz, Ph.D., professor of cell biology and physiology. A video screen in Sheetz's lab bears an enhanced microscopic view of certain cellular contents, hair-like fibers called microtubules. While the viewer watches, these microtubules seem to take on a life of their own. They become mini-railroad tracks, with barely visible "locomotives" zipping along on their surfaces — sometimes in only one direction, other times in the opposite direction. And some locomotives careen toward each other as if bent on a head-on collision: They don't stop or slow down, yet they don't collide. As if directed by some unseen engineer, the mini-locomotives streak past each other, continuing unimpeded.

"On video tape," says Sheetz, "we see dramatic examples of multiple tracks on single microtubules, with organelles passing each other going opposite directions." Viewing microtubules with an electron microscope provides the explanation. These hair-like fibers are each made up of 13 or 14 tinier fibers called protofilaments. Each protofilament is a separate track, enabling organelles — the tiny "locomotives" that zip along the microtubules' surface in cells — to avoid collision. Sheetz and co-workers have discovered that this movement along microtubules is powered by a unique cellular protein, kinesin.

Kinesin is the most recently discovered protein that powers movement. Kinesin, along with another motile protein called cytoplasmic dynein, propels the smallest of organelles from one part of the cell to another.

ON THE MOVE

The most well-known of the cell's motile proteins is myosin. Its sliding action along actin filaments, worked out by Hugh and Andrew Huxley in 1954, is the basis for muscle movement. For many years after the Huxleys' classic studies, researchers searched for the proteins that power the movement of substances inside cells. Dynein was the next motile protein to be uncovered. It propels cilia and flagella of some single-celled organisms through a fluid medium.

All cells need to move the smaller organelles within their cytoplasm, like the membrane-encased droplets that form at the cell's surface when it takes in substances. And a nerve cell needs to quickly move organelles and substances from the cell body — the neuron's "headquarters" — to the tip of its axon, a distance of up to a meter or more. But no one knew how this was accomplished. Many scientists thought that dynein, or a dynein-like protein, was responsible.

In August 1985, Sheetz and his collaborators at Woods Hole and Stanford published the news of their discovery of kinesin. "In essence," muses Sheetz, "kinesin and dynein provide a pair of motors that move objects in two directions along microtubules. A microtubule — which is larger than a single actin filament, with a lot more structural stability — can support two directions of movement." And because of the protofilaments on each microtubule, bidirectional movement can be accomplished without collision.

TWO DIRECTIONS

Microtubules form a fine mesh, a micro-skeleton within cells. "There is one major microtubule-organizing center in the cell," explains Sheetz, "and that's the centriole or centrosome. From that emanates all the cell's microtubules. Recent studies suggest that this organizational structure gives the cell a directional polarity. It's very easy with a motor like kinesin, which moves substances from the centriole to the periphery, to set up a traffic pattern going from the centrosome to the cell membrane."

Sheetz and co-workers think that a cytoplasmic dynein, or a protein similar to

dynein, moves substances in the opposite direction — from the cell membrane toward the cell's center. ATP provides the energy that drives both of these motor proteins.

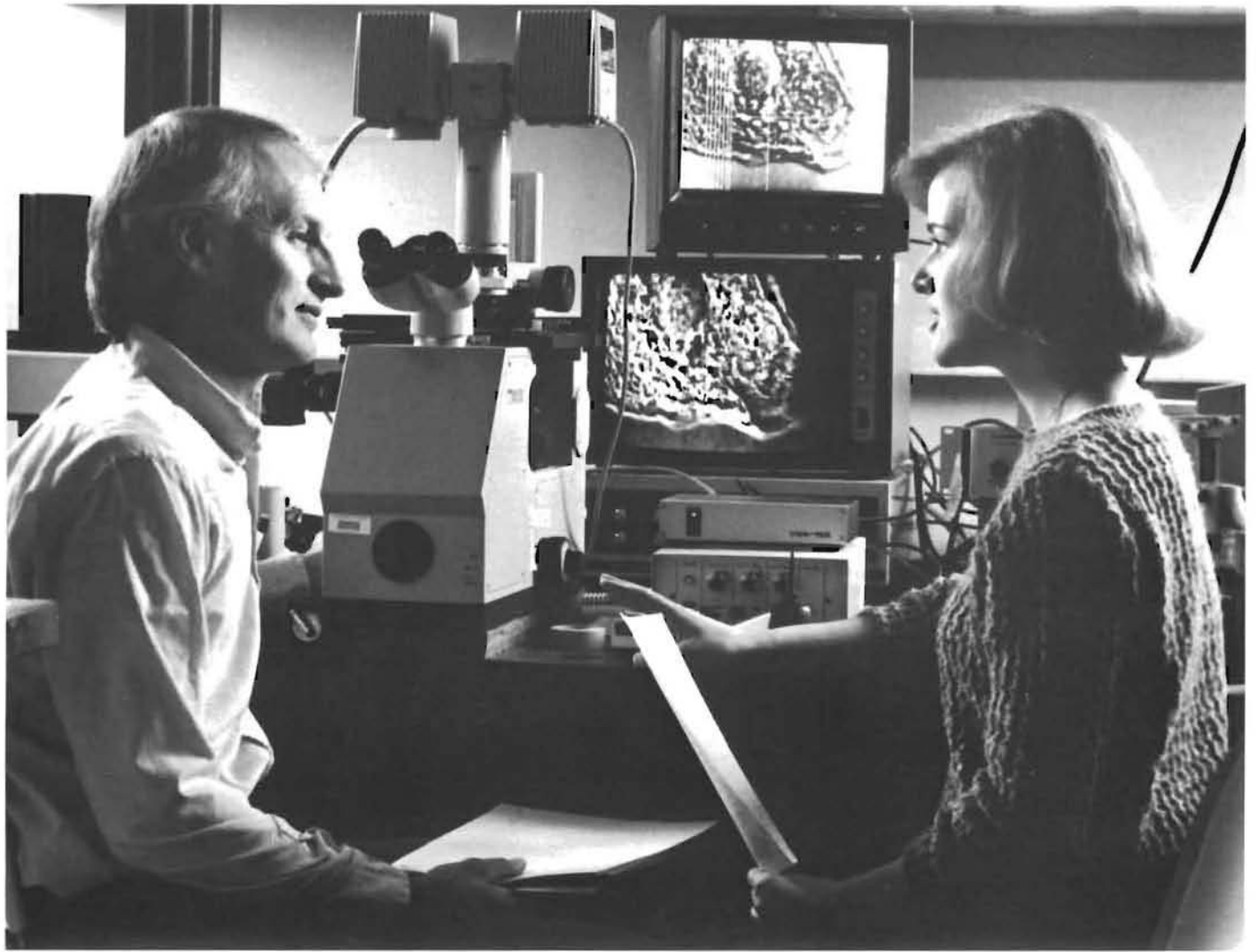
The assay system Sheetz uses is simple. It consists of microtubules stabilized by attachment to glass. To that is added the motor (kinesin), a source of energy (ATP), and something to move. A good substitute for fragile organelles are small latex beads, and these are the barely visible locomotives that can be observed zipping along the microtubules. Kinesin has an affinity for both the beads and the microtubules, "walking" along the latter in a movement that Sheetz describes as "... hand over hand. Perhaps the best analogy for all motile proteins is that they move somewhat like a centipede. There are probably at least ten 'heads' or 'arms' reaching out from the protein and interacting with the appropriate filament. In the case of kinesin or dynein, that's a microtubule; in the case of myosin, it's actin." As these motile proteins "walk" along their filament, they don't let go; one arm is always attached.

Sheetz has performed similar experiments with myosin-coated beads: "I always joke when I go to seminars that I've thought about forming a company that would make myosin-coated shoes," he says with a laugh. "But not many people would want shoes that would require an actin 'roadway' and only let them move at five micrometers per second."

ALL CELLS HAVE IT

Sheetz is buoyed by the fact that kinesin seems to be ubiquitous among species: "We've found kinesin everywhere we've looked." Recently, his group has developed an antibody to kinesin, enabling them to spot the protein no matter where its biological home.

In collaboration with Ursula Goodenough, Ph.D., professor of biology, kinesin's possible role in the movement of a single-celled organism will be explored. "Everywhere we've looked," says Sheetz, "from vertebrates to invertebrates, from cows' cells to sea urchins, we've found kinesin. And in all those systems, we've



gotten movement to occur and found that the polarity of kinesin movement along microtubules is the same.”

And in all these systems, kinesin powers the movement of organelles at approximately the same rate, but that’s no surprise to Sheetz: “All our experiments are in the test tube, outside of the cell, so there’s no inhibition of movement by surrounding cytoplasm. When you go into cytoplasm, however, there’s a dramatic three-dimensional network — a latticework or cytoskeleton — in which there are pores of varying sizes. The organelles that are moving along microtubules are roughly the same size as these pores or gaps in the cytoskeleton. Consequently, they’re constantly bumping into it. To the extent they adhere, they slow down. So it’s thought that the cytoskeleton acts as a molecular sieve, and that it’s inhibiting the movement of the large organelles more than it’s inhibiting the movement of smaller ones.”

For unusually shaped cells like neurons, in which a long projection — the axon — extends away from the cell body, “we be-

Michael Sheetz shows his video system that demonstrates kinesin-powered movement to second-year student Emily Dohe.

lieve that kinesin is the motor which drives objects from the cell body to the synapse,” says Sheetz. “We believe that the motor driving things from the synapse back to the cell body is the dynein-like protein we’re trying to isolate.”

This work will continue at Washington University in collaboration with Mark B. Willard, Ph.D., professor of neurobiology and biological chemistry. Sheetz is also working with Robert H. Waterston, M.D., Ph.D., associate professor of genetics and anatomy and neurobiology, on different types of myosin from mutant worms. They want to know how *in vitro* movements of myosin-coated beads correlate with the unusual movements that can be seen in worms that have these mutations in muscle myosin. Together with Elliott L. Elson, Ph.D., professor of biological chemistry, Sheetz will study movement of intact cells on cover-

slips, to see what relative roles kinesin and myosin play in this type of cell movement.

Sheetz continues collaboration with his long-time Woods Hole colleague. They are cloning the gene for kinesin to investigate the “nuts and bolts” of which amino acids are linked together to form the protein.

“With the tools we have now,” says Sheetz, “the video systems, the gene cloning, the antibody production techniques — it’s possible to take a phenomenon, such as axonal transport, and go quickly from the phenomenon to a protein — cloning the gene — in two years.

“We know what kinesin is, but there are many unresolved questions,” he continues. “How is kinesin controlled? What tells an organelle to move? There are some questions that are harder to crack than others. But now the technology is in hand to address a number of problems that were out of reach before.”

TRANSPLANTING LIFE

BY KAREN BURNS

The immune system is both ally and adversary to the human body. Its warriors, so adept at fending off ominous foreign microorganisms, have also stubbornly resisted entry of the good guys — healthy organs needed to replace those that are diseased and dying.

This battle is truly one of life or death. But thanks to the persistence of the medical community, organ transplantation is enjoying its greatest success ever. Immunosuppressive therapy, surgical acumen and other advances such as monoclonal antibodies and cryogenics are improving the odds favoring organ transplantation; now it is possible for seriously ill patients to be restored to near-normal. Although the cost of a transplant remains high, many insurance companies that once viewed the operations as experimental (and therefore refused coverage) are beginning to pick up the tab.

At Washington University School of Medicine, success is most evident in the ever-growing list of organs transplanted: Liver, heart, cornea, pancreatic cell, and long-bone transplants — called allografts, or homografts, because they are from one patient to another — are joining the well-established kidney transplant program (600 done to date). Revival of an old idea is underway in the transplantation of aortic and pulmonary homograft heart valves, and the tiny incus and stapes of the middle ear have joined the list, too. Preparations are also being made for clinical heart-lung transplantation, and small bowel transplants are being studied in the lab.

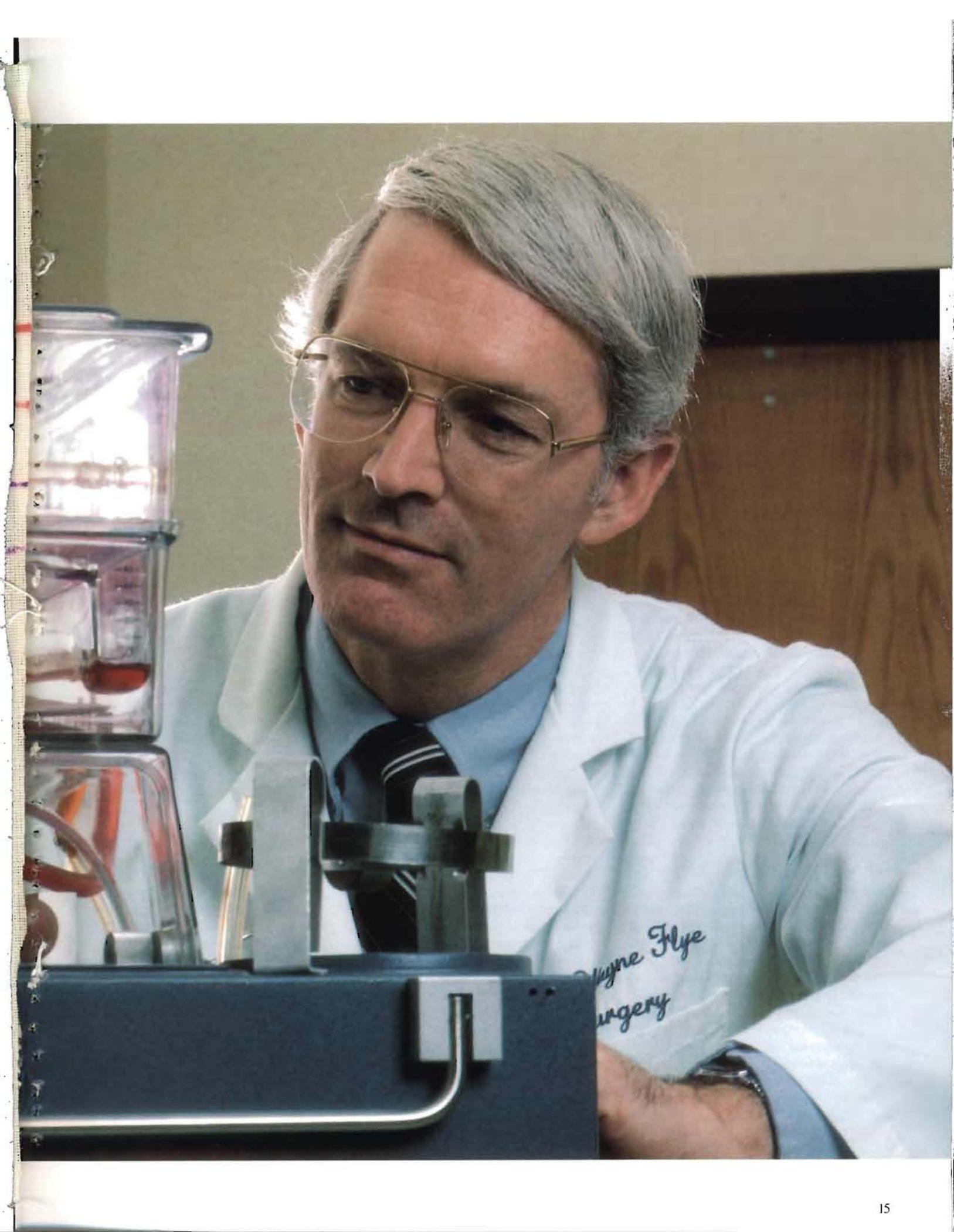
Autotransplantation — the process of transplanting an organ in the same body — continues to be viable therapy in plastic surgery, where distant components of the body are used to reconstruct faulty areas; skin is being transplanted in burn patients; and bone marrow autografts are helping people survive the treatment for certain types of cancer.

But even with these advances in organ transplantation, we've won only half the battle. According to the *Journal of the American Medical Association (JAMA)*, almost 20,000 people will suffer brain death from trauma this year, yet only 15 percent will become organ donors. And there are at least 100,000 potential recipients nationwide, more than 100 in St. Louis alone. *JAMA* says the organ shortage is exacerbated by several factors: people fail to will their organs before they die; family members refuse to donate the organs of the dead; hospital personnel neglect to ask for organ donations; available organs cannot be matched with recipients; and organs are allocated improperly. A bright spot is that multiple-organ donors are increasing, sometimes allowing as many as ten recipients to benefit from the organs from one donor.

Some states are considering — and others have passed — required request laws. *JAMA* states that as a result of those laws,

M. Wayne Flye is director of the organ transplantation program at Washington University.





physicians will be required to notify the nearest organ procurement agency when brain death occurs in patients who have willed their organs. Upon brain death in a person whose wishes regarding the fate of their organs are unknown, physicians will be required to request that the family consider organ donation.

According to M. Wayne Flye, M.D., Ph.D., professor of general surgery and director of the organ transplantation program at Washington University, the best way to donate an organ is to make the decision "out of the stress" of the catastrophic event. "It is really up to each individual," says Flye, "to make a decision to donate organs before death, and to make this wish known to family members so they can carry it out."

Flye says that physicians should also examine their feelings about organ transplantation so they are prepared when a donor is available. Because of increased public awareness of organ donation, more and more families initiate donation when death of a loved one is near. (A January 1983 Gallup Poll showed that 93 percent of those polled were aware of organ transplantation and of those, 72 percent said they would give permission to donate kidneys or other vital organs; 80 percent said they were aware of organ donor cards.) Flye adds that physicians themselves often donate the organs of their deceased family members: "We're seeing more and more of that," he says. "And it's just as difficult a decision for them."

TRANSPLANT SUCCESS SHARED

Flye came to Washington University last year to perform the center's first liver transplants at Barnes Hospital, and he is pleased with the results. Overall, Washington University's transplant success rates are comparable to those at other major transplant centers: kidney transplants here have an 80-85 percent success rate; livers, a 65-75 percent success rate; hearts, 80-85 percent; and corneas and long bones, almost 100 percent.

As quickly as he quotes success rates and extols the merits of transplants for the recipients, Flye just as quickly — almost in the same breath — remembers the donors with deep gratitude. "Transplantation of these

living tissues is only possible because of the generosity of anonymous donors and their families," stresses Flye, attending surgeon at Barnes, Children's and Jewish hospitals.

Heart transplant surgeon R. Morton Bolman III, M.D., assistant professor of cardiothoracic surgery who came to Washington University last year, agrees and adds: "It is incumbent upon us as physicians and healthcare personnel to be aware of the need for donated organs so others can be given a chance to live."

Washington University is among the growing number of select medical centers that have a multi-organ transplant program. The university's transplant team, which includes six nurse coordinators, is on call 24 hours a day. In addition, the university is affiliated with the Mid-America Transplant Association and is plugged into the national computer lines that record available organs.

The transplant team also has a jet on 24-hour standby that flies them on "lifeguard" status. The status gives them top-priority air space for optimum travel time. The jet and other up-to-date procurement techniques make it possible for them to retrieve and use any organ from almost any distance. "The transplant surgeons here have a personal commitment to making this a fine, active transplant program," says coordinator Judy Dickens, R.N. "They spend a good part of their time and effort not only directing it, but also going out and implementing it." (Heart transplants have been performed at both Barnes and Children's hospitals.)

Much of the success of organ transplantation, here and elsewhere, has been due to immunosuppression by cyclosporine, either alone or in combination with other drugs. Washington University was one of the first to use a regimen of cyclosporine combined with Imuran and prednisone; heart transplant surgeon Bolman says the combination relieves blood pressure and kidney complications created when cyclosporine is given alone.

Another reason for the success is that doctors are more selective of their recipients, who should be free of other disease and have good overall function of other organs.

The oldest and best-established compo-

nent of the university program involves kidney transplants, which are the only transplants other than bone marrow that involve a living donor. The program began in 1963 and has been actively promoted and directed by Charles B. Anderson, M.D., since 1973.

"Kidney transplantation is now the preferred method of treating most patients with end-stage renal disease, especially those younger than 55," says Anderson, head of general surgery. "But even though it's a routine operation, it's still an evolving field. We have a lot to learn."

Anderson and his colleagues want to learn why some kidney transplants work and others don't.

Kidney transplants have long been a viable alternative to dialysis, partly because of Medicare's early decision to be responsible for providing treatment for permanent end-stage renal failure. At Washington University, the living/related transplant's success is primarily due to donor-specific blood transfusions, a method that was developed here in 1971. The protocol involves transfusing the kidney donor's blood to the recipient three times over the six weeks before the transplant is performed. At the same time, the recipient is given immunosuppressive drug therapy. The process "tricks" the body into accepting foreign tissue and has resulted in an 85-90 percent success rate, says Anderson, general surgeon-in-chief at Barnes Hospital.

Anderson's transplant group is also studying immunosuppression with azathioprine, as well as trying to identify methods of decreasing rejection by altering prostaglandin production. Another area of research is the donor-recipient relationship between husbands and wives; those transplants so far have been successful.

A major advance in fighting renal allograft rejection is in the area of monoclonal antibodies. Flye and his colleagues recently published the results of a study of OKT3 — a murine monoclonal antibody that reacts with, and blocks the function of, the T3 antigen on human T cells. In a study of 129 patients, rejection was reversed in 71 percent, with 61 percent of the grafts functioning after 12 months. The study showed that OKT3 is an effective treatment for acute renal allograft rejection that is uncontrol-



Charles B. Anderson has directed the kidney transplant program since 1973.

lable by present conventional treatments.

"With the addition of heart and liver transplants, this has become one of the premiere centers in the world for transplantation — both clinically and experimentally," says Anderson, attending surgeon at Children's and Jewish hospitals.

OLD IDEA REBORN

One of the newest areas of organ transplantation at Washington University involves aortic and pulmonary valve allografts. The operation was first done in 1962 in England and New Zealand but didn't become popular in the U.S.: Techniques for

sterilizing, storing and preserving the valves resulted in shortened graft function. Xenografts and mechanical valves were the mainstays, despite side effects like thromboembolism and infection, and difficulties with anticoagulation and hydraulic function. All these problems cause significant morbidity and mortality and are especially troublesome in younger adults and children. This group has had a five-year complication-free survival rate as low as 50 percent.

New preservation methods have changed all that, according to Richard A. Hopkins, M.D., assistant professor of cardiothoracic surgery, who performs valve transplant op-

erations. The technique — using antibiotic sterilization and DMSO-liquid nitrogen freezing (a technique similar to that used for preserving sperm) — has made human valves a viable alternative. Some of the advantages include nature's better engineering design, resulting in optimal function, and freedom from thromboembolism and hemolysis. Also, larger valves can be fitted into smaller patients (for better performance) and the patient doesn't need to be anticoagulated, as is needed with mechanical valves. Since the procedure is often done in small, active children, not needing to give anticoagulants is significant, says Hopkins.

Another significant difference between heart valves and other transplanted organs is that the patient doesn't need immunosuppressant therapy, though the reasons aren't yet clear why valve leaflets resist rejection, says Hopkins, attending surgeon at Barnes Hospital. Excellent valve function has persisted in some patients for up to 15 years.

"This [valve transplants] will eventually take place in all medical centers doing state-of-the-art surgery because the performance of these valves is so much better," says Hopkins, who trained in London at The Great Ormond Street Hospital for Sick Children, where 50 such operations are performed a year. "I tell my patients that the engineer on this valve is a lot better than any of our engineers — the valves are really better than anything we could make."

Donated valves come from hearts that are not transplantable. The procedure to donate the valves is the same as any organ — if a donor is available, a transplant center or agency should be called. And, like skin, corneas and long bones, the valves can be removed for up to 12 hours after the donor has died, and can be stored almost indefinitely. This differs from the vital organs — kidney, liver, heart and heart-lung — that must be removed from the brain-dead patient before the heart stops.

Heart valves, like all transplantable organs, are life-saving. Unfortunately, physicians can't save every patient from death. However, through transplantation, they can grasp back from death something that is good: life. ■

BEHIND THE ETHER SCREEN

BY SUZANNE HAGAN

Newsweek calls them the “doctors you can’t see.” They’re the anesthesiologists and anesthetists — physicians and nurses — hidden behind the ether screen. They staff the intensive care units, snatch the dying from death’s grasp, and give the gift of relief to patients suffering chronic pain. They’re the untouted “internists of the operating room,” who help in the surgical miracles that happen every day.

Giving anesthesia to any patient, says William D. Owens, M.D., Mallinckrodt Professor and head of anesthesiology, is very much like conducting an orchestra: “In anesthesiology, many potent drugs that allay consciousness and pain must be titrated — carefully administered in measured doses — for an individual patient. A poor titration is much like what you hear as a symphony orchestra is warming up; sounds come from every which way and none of it is harmonious. When anesthesia is titrated properly, though, it’s like an orchestra playing beautiful music.

“In one sense, anesthesia’s safety hasn’t really changed much in the last 35 years,” reflects Owens. “The mortality related to anesthesia in healthy young people is about one in 10,000. That’s about the same as it was in the late 1940s. But on the other hand, we’re taking sicker and sicker people to the operating room and doing more extensive, prolonged surgery on them. So even though the numbers are about the same, we must be improving on safety or those other patients would have raised the mortality and morbidity.”

Anesthesia has progressed remarkably

since the days of ether, which posed a considerable explosive hazard and made patients extremely nauseous. “We can sedate people without totally removing them from their conscious state,” says Owens. “It’s not the same as the ‘twilight state,’ which formerly was used during labor and delivery and took advantage of anesthetics we don’t use today. But the end result is much the same.”

GOING UNDER

The anesthesiologist must make allowances for the weakened physiological state of the patient about to undergo surgery. Another important consideration is the type of medication the patient may be taking. “Someone with rheumatoid arthritis may take a great deal of aspirin, which increases bleeding time — such patients’ blood doesn’t clot as well,” points out Owens. “Consequently, blood loss is higher, and there’s a greater chance of needing a transfusion in these patients. There are interactions between many of the heart medications and anesthetics, and between many of the tranquilizers and sedatives — the sleeping pills people take at home, even the over-the-counter medications. It’s very important that the anesthesiologist know what medications a patient is taking. We can work around them in most cases; there are only a few that we need to have them taken off.”

Carey I. Weiss, M.D., instructor of anesthesiology and director of anesthesiology for organ transplants at Barnes Hospital, has been involved in every liver transplant that’s been done at the medical center. Weiss, also



acting director of cardiac anesthesiology, is pleased with the progress of the organ transplant program. But he points out that popular perceptions of anesthesiologists’ duties are rife with misconceptions: “As anesthesiologists, we need to provide the patient a comfortable and anxiety-free perioperative period and provide for the goals of anesthesia — amnesia and analgesia. But a lot of times, that’s not the hardest part of our job.

“We must achieve analgesia and amnesia in a way that causes no harm to come to the patient and in many cases, enhances the patient’s condition, and that’s very difficult,” he continues. “The other part of our goal, in addition to patient comfort, stability and preservation of homeostasis, is to provide an adequate — if not ideal — working environment for the surgeon.

“If only pentothal was as perfect as people think it is,” muses Weiss. “We simply don’t have in our armamentarium the



Carey I. Weiss directs anesthesia for organ transplants at Barnes Hospital.

with the possibilities of gastrointestinal hemorrhages and varices — just a legion of problems from one perturbation. Most transplant patients with liver problems have low blood albumin and poor nutritional status. That changes the way you need to induce anesthesia.

“An impaired liver can’t produce proteins that clot the blood. There will be a cascade of interrelated problems that need to be handled. If we’re doing a good job for the surgeon and the patient, all the surgeon has to worry about is the procedure. Our job is to take care of the patient in such a way that homeostasis is preserved. That means that as blood or fluid is lost, we replace it, or as any other changes occur, we work to keep the patient on an even keel.”

Several liver transplants have been performed on children, the youngest only six months old, entailing special considerations for this group of patients. “They’re not just small adults,” points out Weiss. “Their physiology is different.”

Weiss collaborates with pediatric anesthesiologists to select just the right drug, or assortment of drugs, to enable the surgery to proceed smoothly. But medical problems are only one facet of the problems faced by anesthesiologists. Patients about to undergo surgery may be overwhelmed by anxiety. “If their health dictates that they need to have some operation,” says Owens, “we can tailor some kind of anesthetic for almost anyone, and do a good job of helping them pull through the operation and take care of them post-operatively.

“The fear of the unknown is by far the biggest fear,” he concludes. “Patients would do themselves a big favor if they would just open up with their anesthesiologist before surgery and let the questions come out, because we can answer them. No one should put off having anesthesia and surgery today because they think it’s too risky.” ■

anesthetic drug that will accomplish all these goals. What we need to do, for most patients, is pick out a balance of imperfect drugs. In cardiac anesthesia, many drugs can provide anesthesia, but they all have different liabilities for the heart or lungs. Our job is to know the patient’s pathophysiology well enough, and our pharmacology well enough, so we can pick the right drug combination without pushing things to the toxic level.”

Anesthesiology is really a meld of pharmacology and physiology, says Weiss; neither is more important than the other.

Cardiac anesthesia may be made up of perhaps a dozen drugs. “Benzodiazepines will be used to produce part of the amnesic state, as well as scopolamine,” Weiss says. “For profound analgesia, high doses of potent opioids are commonly used. That still doesn’t help us provide the immobile field — muscle relaxation — required by the surgeon, so we’ll use a muscle relaxant. All of

those we’ll try to blend because they also interact with the cardiovascular and pulmonary systems in ways other than producing anesthesia. Some will raise heart rate, some will lower heart rate, some will depress the heart’s ability to work, some will increase the heart’s ability to work. All of them we try to blend to provide a smooth and stable course for the patient.”

Liver and heart transplants involve fundamentally different considerations, says Weiss. Although in both, the overwhelming problem is the major defective organ, patients who need a liver transplant have healthy hearts, with good cardiac reserve. Their problems are determined by the specific type of liver pathology affecting them.

“If the pathology is an impedence of portal blood flow,” says Weiss, “then we’ll get into all the problems of portal hypertension and enlarged collateral venous tracts, and all the bleeding that will create, together

STUDENT STAGE

Medical Scientist Training Program: Academic Researchers for the Future

Some people take the direct route to get where they're going in life; others meander around a bit. Scott Selleck, a fifth-year student in the Medical Scientist Training Program (MSTP), is a meanderer. "I moved around a lot when I was growing up," reports Selleck, a native of Saskatoon, Canada. "I lived in Brussels from when I was six years old until I was about 11." Another move to Ithaca, NY, allowed Selleck to finish high school and enroll in a marine biology program, spending 1976-77 at a field station in Grenada. After transferring to McGill University for a year, he moved to the U. of Washington in Seattle, where he finished his studies in marine biology.

After graduating with a B.A. in zoology, he couldn't find a job in marine biology, partly because as a Canadian, he couldn't work for any U.S. national oceanographic concerns. To make ends meet, he hired on as a cashier in a bus depot for eight weeks. Finally, he got a job as a hospital technician in Seattle, spending two years researching drugs that produce defects in embryos, to see what role maternal metabolism exerted in either causing the defect or protecting the embryo. It was this job that kindled his interest in returning to school and the M.S.T.P. (medical scientist training program, whose graduates earn an M.D. and Ph.D.) at Washington University.

"I'd actually not thought about going into medicine but was interested only in research at that point," remembers Selleck. But he elected to work for a while as a volunteer at the hospital, to get an idea of what clinical medicine was like. And that was another turning point in his life. He met many patients who were in desperate emotional straits. Some had no families; others were dying or suffering from chronic illnesses: "You get a perspective on what you're doing in the lab by working with patients," he reflects. "It emphasizes how research is much more than simply an intellectual game."

Today, as a student who's completed one year towards his M.D. and is enmeshed in research towards his Ph.D., Selleck doesn't stray much outside the environs of the laboratory of John E. Majors, Ph.D., assistant



Scott Selleck is "Big Brother" to Sean Sedach. Selleck was honored in September for his longterm participation in the Big Brother/Big Sister Program sponsored by the Jewish Community Centers Association. (photo by David Henschel)

professor of biological chemistry. There, using yeast DNA, he looks for "footprints" that demarcate the chromosomal points where the production of m-RNA — the "messenger" that directs protein synthesis — first begins.

Yet his busy research career doesn't eat up all his time. He participates in the JCCA's Big Brother program. His two years as a Big Brother have been as rewarding for him as for his Little Brother, Sean Sedach.

"I like the questions that Sean asks me, things that maybe he wouldn't ask his mother. And it gets me out, doing the things I like to do but wouldn't have made time for."

As far as Sean is concerned, having a Big Brother is the perfect complement for the "grueling" life of an 11-year-old fifth grader: "We do lots of things together," says Sean, "like go to [St. Louis Soccer] Steamers games, or to the museum, or bowling or

golfing. We'll usually go out to eat, too." They see each other once a week or every other week, says Sean, and between milkshakes and movies, there's plenty of time for talking: "We talk about lots of things," says Sean, "like my problems, or anything going on with me."

In appreciation for Selleck's participation, the JCCA honored him last September as "Big Brother of the Month." Taking advantage of opportunities like the Big Brother program isn't unusual for someone like Selleck, whose future isn't confined to a university research setting.

One of the appealing things about the MSTP is that it increases his options for the future, says Selleck: "Graduates can go into pure science, or clinical work, or even a government job setting health policy. The education we receive trains us for an amazingly wide variety of positions in research and health care."

Currently, Selleck is one of 92 students enrolled in MSTP, a program begun 16 years ago thanks to a then-new National Institutes of Health program channeled through the National Institute of General Medical Science. In 1969-70, ten students enrolled in the Washington University program initiated by Roy Vageles, M.D., Ph.D., then chairman of the Department of Biological Chemistry and now president of Merck and Company, Inc. The program concept was vigorously supported by Luis Glaser, Ph.D., Carl Frieden, Ph.D., and Barbara Fox. Today, these same three persons (Glaser and Frieden are co-directors, and Fox is assistant director) still steward a training program that is, according to Lee Van Lenten, M.D., the national program administrator at NIH, "one of the top programs in the country. It's very successful — our peer review group just returned from a site visit there, and they were very favorably impressed."

In 1964, when the NIH first provided funding for medical scientist training programs, only three schools participated. Today, reports Van Lenten, 25 schools across the nation — with 683 students — receive funding from the NIH for their pro-

gram, supported by grants totalling \$12.6 million.

The NIH's MSTP grant provides about half the support needed for the WU program, says Fox, with the university providing the remainder. "Without the university's support, we couldn't enroll the number of students we do," reports Frieden. Several schools, he says, have only NIH support and can accept only a small number of students.

"Thus far," says Frieden, "we've graduated about 90 students. About half have completed their residencies, and almost all are in research settings today. Our success rate in training academic scientists, skilled in clinical and basic research, is even better than the NIH envisioned."

Frieden heads the MSTP admissions committee, which has representatives from all the preclinical departments at the School of Medicine as well as the Department of Medicine. "The faculty is very committed to, and enthusiastic about, the MSTP," says Frieden. "These students represent a really top-notch group, and they're fun to have around. At any given time, they represent about a fourth of our graduate students, and they contribute enormously to that group. They enhance both graduate and medical education."

"The MSTP was the first inter-departmental educational program we ever had," says Glaser. "It set the stage for the formation of the Division of Biomedical Science. The MSTP and our graduate program benefit from each other since they each attract a unique flavor of student."

The NIH is keenly aware of this advantage and has boosted support for this program through the years, says Van Lenten. "In 1979, the NIH spent about \$77 million to support 666 students," he reports. "Today, we fund about the same number of students — 683 — but it costs much more, \$12.6 million. The monetary increase has been primarily in tuition increases, although we have increased the amount of the stipend." Currently, Washington University provides each MSTP student with a stipend of \$7,250.

One of the program's strengths, says Frieden, is the fact that it only accepts students who have done some research.

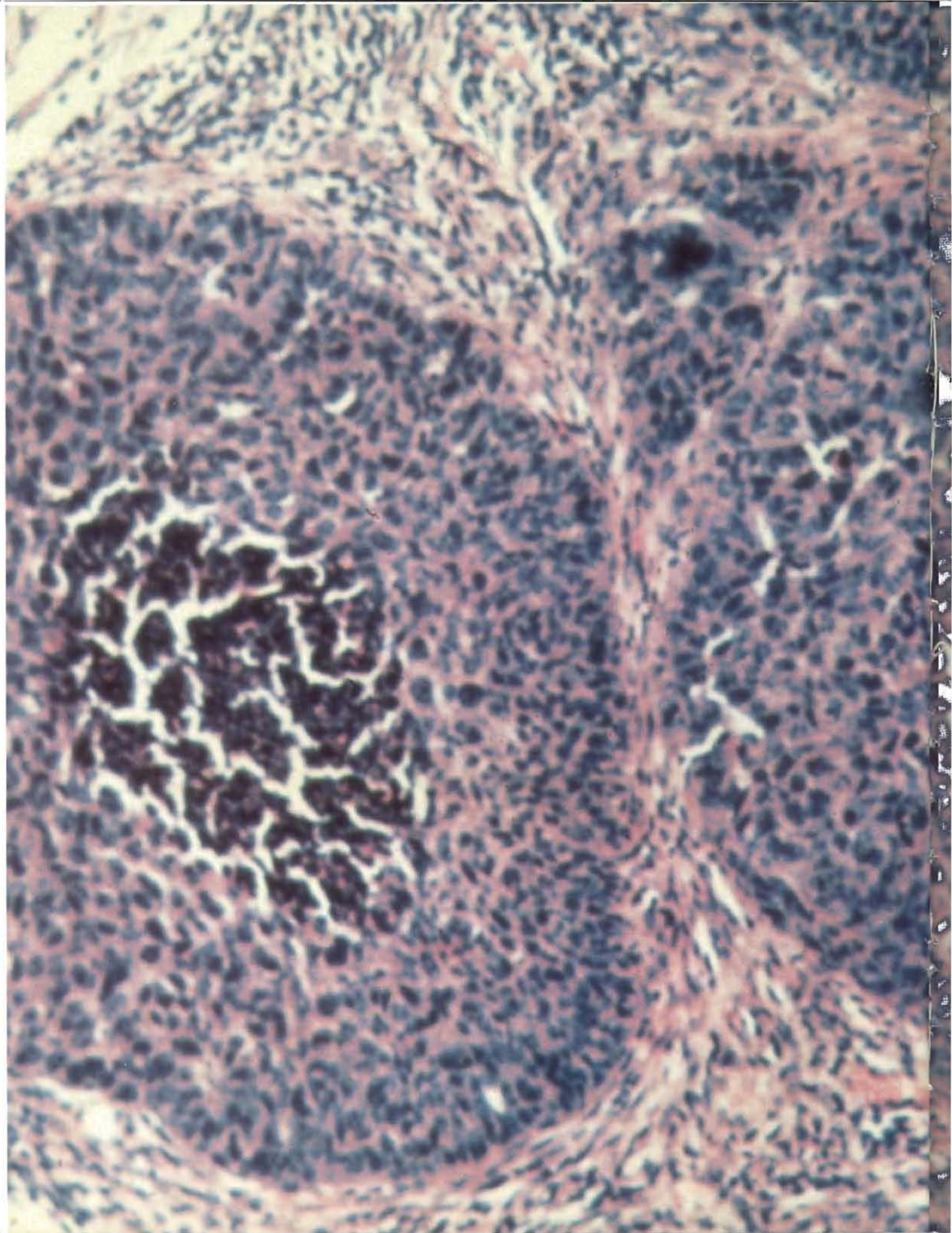
Another, pointed out by Van Lenten, is the strong recruiting program: "They have gone out even to the smaller schools and made themselves known," he points out. "Not every university does this."

So what kinds of students does the program attract? Very good ones, like Scott Selleck, with strong academic records and proven ability as researchers. "In many ways, Scott is typical of the student who comes through the program," muses Frieden, "but he's perhaps had a more diverse range of experiences. Overall, this is a group of students who can simultaneously do a number of things well."

"Our students are perhaps our greatest challenge," says Fox with a laugh. "Carl Frieden and Luis Glaser are really open to student input when it comes to program policy and procedure. Student suggestions are implemented whenever feasible, and they have greatly influenced the direction this program has taken. Scott is one of our most active students, and he really keeps us on our toes."

EDITOR'S NOTE

The hard-working and enthusiastic admissions committee for the MSTP currently consists of the following members in addition to Glaser and Frieden: Irving Boime, Ph.D., professor of pharmacology and obstetrics/gynecology; Thomas J. Braciale, M.D., Ph.D., associate professor of pathology; Jonathan B. Cohen, Ph.D., professor of neurobiology and biological chemistry; Paul J. DeWeer, M.D., Ph.D., professor of cell biology and physiology; Elliot L. Elson, Ph.D., professor of biological chemistry; Ted H. Hansen, Ph.D., associate professor of genetics; David I. Gottlieb, Ph.D., associate professor of anatomy and neurobiology and biological chemistry; David Schlessinger, Ph.D., professor of microbiology and immunology and medicine; John L. Schultz (ex officio), assistant dean and registrar, School of Medicine; Douglas Tollefsen, M.D., Ph.D. '77, assistant professor of biological chemistry and associate professor of medicine.





The Cells We're After

BY DON CLAYTON

After several years "back at the drawing board," researchers at Washington University and elsewhere are now ready to begin major clinical trials of a drug thought capable of increasing up to two-fold the effectiveness of anti-cancer radiation therapy.

The drug SR-2508, when present in a tumor, helps ensure that the damage caused by radiation treatments will be irreparable and lethal to cancer cells, says Todd Wasserman, M.D., radiation therapist at Washington University and chairman of the group that will test the drug on cancer patients.

Hopes are high for SR-2508 because lab tests and an initial clinical trial indicate the drug enhances radiation and penetrates tumors more uniformly than previously tested drugs. In addition, SR-2508 does not exhibit the major side effects that have forced physicians to hold the dose of other "radiosensitizers" to less-than-effective levels.

Results of the Phase I clinical trial and plans for wide-scale Phase III testing at 15 to 20 U.S. and Canadian medical

centers were announced during the Conference on Chemical Modifiers of Cancer Treatments, held recently in Clearwater, FL. Wasserman, involved in radiosensitizer research for eight years, chaired the session in which the SR-2508 report was presented. The report reflects data from trials at Washington University, Stanford, University of California-San Francisco, and University of Alberta in Canada.

"The safety of SR-2508," says Wasserman, "enables us to give doses three times higher than we could with other radiosensitizers. Because of the way SR-2508 is administered and the way the body handles the drug, it can be given to patients on a schedule compatible with the five-times-a-week schedule preferred for radiation treatments."

Phase III clinical trials of SR-2508 will be conducted by the Radiation Therapy Oncology Group (RTOG), funded by the National Cancer Institute. Twenty-one medical institutions are currently full members of the RTOG, although each does not necessarily participate in every study.

The SR-2508 trials, scheduled to be underway by mid-1986, will involve a variety of tumors including advanced bladder, prostate, and head and neck cancers. Wasserman, chairman of the RTOG committee coordinating the trials, says that Washington University researchers will use the drug on selected patients with each of these types of cancer.

Cross section through two lobes of a solid tumor. Researchers are using "sensitizing" agents to make cells between the tumor's core and periphery more susceptible to radiation therapy.



"These trials will include hundreds of patients, and should take from three to five years," Wasserman says. SR-2508 will be given intravenously three times weekly throughout a standard course of radiation therapy, five to six weeks. Patients who receive the drug and radiation will be compared to similar patients who receive radiation but no SR-2508. As in the past, Washington University patients will be admitted to the General Clinical Research Center during the administration of their therapy.

EARLY FAILURES

The sensitizer that oncologists have the most experience with is misonidazole, or "miso," a precursor to SR-2508. By the late 1970s, several institutions had begun clinical trials with miso. While some of miso's properties made it appealing, others soon led to problems. Administered in pill form, miso caused nausea and vomiting. It could cross the blood-brain barrier and cause nervous system side effects.

"In the time that I was involved in miso therapy here at Washington University, I can't remember encountering any patients who remained on the medication long

enough to develop central nervous system toxicities," recalls Faye Jennings, a supervisory nurse in radiation oncology. "However, other centers did report such effects."

Wasserman, with James S. Nelson, M.D., a Washington U. pathologist, confirmed that miso could cause observable physical damage to the myelin sheath around peripheral nerves.

"The neuropathy reported was always temporary, but sometimes severe," says Wasserman. "There were reports of the same type of peripheral neuropathy we still have with SR-2508, but there were also reports of patients who had exhibited a state of confusion during their course of therapy. On top of that, even when we thought that ample doses of miso penetrated the tumor, the cancers didn't respond as well as predicted. The severity of the side effects discouraged researchers from further increasing the dose of miso administered."

"Considering all the factors pointing toward success, miso's failure made it incumbent on us to find out what the problem was," recalls Wasserman. "The whole area of research fell into a slump while we retrenched."

The National Cancer Institute asked

several teams of chemists and biologists to develop misonidazole analogs, hoping that some might be even more potent radiosensitizers but lack miso's side effects. Stanford Research Institute developed SR-2508. "Our initial clinical trial was crucial because it would have indicated whether SR-2508's toxicities were similar to miso's. Administered intravenously and at dose levels three to four times greater than miso, we saw some side effects. But none was severe enough to abandon SR-2508 as the best alternative to miso," says Wasserman. "No toxicities from such a drug would be best, but at least SR-2508's side effects are predictable, reversible and don't overlap with any of the side effects from radiation therapy or the cancer itself."

According to reports at the Florida meeting, only 25 percent of the 103 patients tested to date have complained of nervous-system side effects related to SR-2508 therapy. "Those complaints," adds Jennings, "have been peripheral neuropathy, expressed as a numbness or tingling sensation in the extremities. Most patients describe the sensation as a feeling of 'pins and needles' or of having the limb 'fall asleep.' To ensure the earliest detection of these side

Todd Wasserman chairs the group that will test the radiation-enhancing drug SR-2508 on cancer patients.

effects, the nurses and physicians regularly ask patients if they are experiencing such feelings. The neuropathy always disappears when the treatments are halted. The tingling sensations subside gradually. Within a two-month period, most patients can report some improvement."

SUSPENDED ANIMATION

The radiation-enhancing, or radiosensitizing, properties of drugs like miso and SR-2508 are based on the cellular characteristics of solid tumors. On cross section, most tumors larger than a walnut reveal three regions that are distinguishable by their proximity to blood supply and, therefore, by the amount of oxygen they receive. The tumor's core, most removed from the capillaries, is so oxygen poor that the tissue is essentially dead and poses minimal threats to the patient. The outer ring of the tumor is closest to the blood supply. These peripheral cells siphon enough nutrients and oxygen from the blood to fuel the tumor's rapid, invasive expansion. The mid-region of the tumor, between the core and the outer ring, contains cells that are dormant, a state some liken to a "metabolic suspended animation." They lack sufficient oxygen for rapid growth but can revitalize if the surface of the tumor is stripped away, providing better contact with the blood supply.

The oxygen-rich cells on the tumor's surface respond to chemotherapy and standard radiation therapy because these interventions kill cells that are metabolically active and dividing. The oxygen-poor cells in the mid-region are protected from current therapies by their suspended animation. During a tolerable course of therapy, the treatments wipe out the peripheral cells. But after therapy is suspended, blood-borne oxygen revitalizes the remaining cells, and a relapse can occur as the tumor begins again to increase in size.

The oxygen-poor, or hypoxic, region of tumors was documented 30 years ago: William Powers, M.D., and Leonard Tolmach, Ph.D., both of Washington U., were among the first to confirm the pres-

ence of the hypoxic region. When scientists realized that the hypoxic cells had a natural defense against radiation and chemotherapy, they set out to find ways of increasing the oxygen content of a tumor's hypoxic area.

One of the earliest methods for raising the oxygen content of these cells was what Wasserman calls the "sledgehammer approach." Patients were placed in a high-pressure oxygen chamber in the hope that the high pressure would drive so much oxygen into the blood that some of it would diffuse to the tumor's central regions.

Hyperbaric oxygen therapy was abandoned in the late 1960s for several reasons. The treatment was expensive, uncomfortable and difficult to administer safely.

In the mid-1970s, misonidazole came along. Laboratory tests with tumor cells, and later animal trials indicated that misonidazole could, like oxygen, help increase the cancer cells' DNA damage caused by radiation therapy.

"The intriguing thing about miso is that it offered us the opportunity to have a simple, orally administered sensitizer that could be given right before radiation treatments," says Wasserman.

Miso and its safer derivative, SR-2508, mimic the biochemical properties of oxygen. "Radiation damages DNA in the cells it enters," explains Michael Welch, Ph.D., a Washington U. radiation chemist who has conducted considerable research on miso and miso derivatives and has collaborated with Wasserman. "If an oxygen molecule or any other molecules with certain properties of oxygen are present in the tumor cell, that cell's DNA is more likely to sustain a double-strand rather than a single-strand break. The cell has mechanisms for repairing single-strand damage, but a double break is usually lethal."

FOOL'S GOLD

"The body's cells treat SR-2508 like fool's gold," explains Wasserman. "Each cell passes the drug along. Eventually, SR-2508 accumulates selectively in hypoxic cells, making it an ideal radiosensitizing agent. It has a specificity for just the group of cancer cells we are after."

"This selective accumulation of miso and SR-2508 was something that was observed

before it was predicted," adds Welch.

"While we still don't understand why miso and its derivatives are deposited preferentially in hypoxic tissue, we can nonetheless imagine many ways that such drugs could be used. They have great potential. Hypoxic tissue is either the cause or the result of a wide variety of diseases, including stroke and myocardial infarction as well as cancer. Because of this great potential, we have been working to prepare and manipulate miso analogs as radioactive drugs."

Welch, along with a former Washington University researcher now working at the University of Washington, Kenneth A. Krohn, Ph.D., has demonstrated that a miso analog tagged with radioactive fluorine can be used as a positron tomography scanning agent. "In our animal studies, we've confirmed drug accumulation in tumors, and mapped damaged brain tissue," continues Welch. "Our guess is that it will be equally effective at outlining heart damage caused by myocardial infarct, and that it will be able to penetrate almost any other tissue we're interested in examining."

In the immediate future, labeled SR-2508 could well be used to help study how the radiosensitizer penetrates a tumor, resulting in information that could help optimize dose schedules and dose levels. Labeled SR-2508 or other miso derivatives might also become useful diagnostic tools for the oncologist, revealing the presence and growth stages of secondary tumors, and perhaps even help screen high-risk patients for cancer.

Clinicians will investigate several additional possibilities as clinical trials proceed, Wasserman predicts. While intravenous injection seems a reasonable way to administer SR-2508, several researchers wonder if the drug could be injected directly into the tumor.

Although SR-2508 looks promising, several other sensitizing agents are on the horizon. Each of these will be tested on its own. "Also," says Wasserman, "we'll examine whether these different agents can be combined to increase their therapeutic effects."

Death in Peace or in Pieces

Voltaire had reached the ripe old age of 81 when he wrote this, a remarkable age for his generation. He could not have written it two centuries later, in 1986, because the otolaryngologist would have restored his hearing, the ophthalmologist would have removed his cataracts, and the orthopedist would have given him two total hip replacements. Furthermore, his heart disease would have been alleviated with a coronary artery bypass, and he would have received a kidney transplant to restore his renal function. However, it is obvious that Voltaire's cerebral functions were active, and that was his good fortune, because even with our technological achievements today, we could not have restored the "failing soul."

Today, the medical profession, the legal profession, sociologists and ethicists are in a quandary. Technological advances in medicine and biomedical innovations can maintain respiration, circulation, metabolism and excretion into old age. But sooner or later, the brain deteriorates; what do we do then? Let us consider the following patient:

An 87-year-old woman, mentally incompetent, fell as she was trying to get out of bed in the nursing home where she had been for four years. She was brought to hospital, where it was found she had several fractures of the left thigh. She had a history of cardiac failure. She was not oriented to time, place or person, was obviously dehydrated and anemic, weighing 85 pounds, with two bedsores. She was not in severe pain. Because of a total hip replacement that had been performed ten years previously, and the nature of the present fractures, the surgical opinion was that the only feasible operation was a total amputation of the left leg, a so-called hindquarter amputation.

Should this patient with chronic brain syndrome have her leg amputated? If she survives, she will return — still with cognitive brain function lost — to permanent disability in the nursing home. Or should she be made as comfortable as possible in her present condition? Obviously, the patient has a right to govern any intrusion of her body, but this patient's chronic brain syndrome made such decisions impossible. Failing that, her relatives should be con-

It is true that I am rather deaf, rather blind and rather crippled and that all this is capped by three or more atrocious infirmities; but nothing deprives me of hope.

Voltaire, 1775

sulted; but in this instance, there were none. Therefore, the ultimate decision rested with the attending physician, who may be uneasy with the concept that a certain patient may need less intervention, not more.

Society and physicians face such dilemmas more frequently as the proportion of our aged population grows. Now 29 million or 12 percent of the population, it will double by the turn of the century. There are currently no official guidelines, and hopefully there never will be — every situation involving the terminally ill presents a unique set of circumstances. Yet the enormous and increasing cost of Medicare sets the federal bureaucracy rumbling with the dilemma, how to contain costs? Inevitably, concepts about death will have to adapt to circumstances. In the last 20 years, medical technologies have mushroomed. They preserve life at all costs — hence the growth of intensive care units. As Landau and Gustafson have stated, a "crusading mentality" has come into being, and almost any means are justified to delay the enemy, death. But "the real enemies are disease, discomfort, disability, fear and anxiety."

Individual groups attempt to solve these dilemmas. In 1984, under the auspices of the Society for the Right to Die, a group of physicians published "The Physician's Responsibility Toward Hopelessly Ill Patients." It indicates that any mechanical or surgical intervention should be discouraged if it does not make the patient comfortable. Moreover, they believe that "severely and irreversibly demented patients need only care to make them comfortable. Sense-

less perpetuation of the status quo is decision by default."

In Canada, a Law and Reform Commission, composed of leading lawyers, has established a "Protection of Life Project." After pointing out that committing euthanasia and aiding suicide are criminal acts, they discussed factors culminating in the decision to end medical treatment, thus leading to death. They indicate that the value of life should be considered, not only from a "quantitative" perspective but also from a "qualitative" viewpoint. Incompetent patients should have the right to die in peace and dignity, assisted by palliative care.

Practically speaking, what can be offered to assist the patient who wants to end life in peace and dignity?

In 16 states today, including Missouri, a "living will" law permits a person to prepare a written statement of the care preferred in the event of a terminal illness. Such a statement is useful to the attending physicians and spares relatives from making heart-rending decisions.

Recently, an independent state-wide body, Oregon Health Decision, undertook a project to address and resolve problems relating to: 1) the rationing of health care, exacerbated by the push to contain costs; 2) technological advances that outrace the ability to pay for, or even understand, them; and 3) the protection of the "autonomy and dignity of dying patients from the tyranny of treating for treatment's sake" (*JAMA* 254: 3213-6, December 1985). Among other things, this project has heightened the public's awareness of the dilemmas and their solutions.

We all face problems created by care of the failing older patient. The primary aim of medical professionals has become preservation of life at any cost. Perhaps, death in a peaceful and humane fashion may provide more "salvation for the soul." ■

*C. Ron Stephen, M.D., C.M.
Clinical professor of anesthesiology*

Making a Baby

In his spare time, second-year student John Constantino is making a baby . . . a MacBaby, to be precise.

MacBaby shows, in step-by-step fashion, the developmental events that transform the human egg into a fetus. Constantino's extracurricular tinkering with the MacIntosh computer is supported by the Medical Alumni Association via its Teacher of the Year award. Four-time winner Roy R. Peterson, Ph.D., professor of anatomy, used the funds from this award to purchase the computer and software and to pay Constantino to develop the animated drawings.

MacBaby portrays, in three dimensions, an overview of human development. The computer "movie" grew out of Constantino's frustration that surfaced several times over the course of his pre-medical career — his inability to mentally picture the three-dimensional events that occur in biological phenomena.

"Embryology always interested me," says Constantino. "When I started my first-year studies, I took anatomy, which included an embryology section in the course and an elective. In one of those classes, they flashed up a slide — a picture of a bilaminar germ disk. It looked to me like a swimming pool. When I saw it, suddenly everything I'd been struggling with just clicked.

"A few months later, I was studying for a final in histology. We were studying the placenta, but I never had really understood the anatomical relationship between the placenta and the embryo. I thought, 'There's got to be a better way to understand how they relate.' Then, I remembered the swimming



Roy R. Peterson (left) and John Constantino have created a computer "movie" that charts the course of development from egg to embryo.

pool picture. And I got so excited thinking about how it all fit together that I blew off studying for my histology test, and just spent the rest of the night making sketches."

Soon after, Constantino showed his sketches to Peterson and Jane Phillips-Conroy, Ph.D., his anatomy and embryology instructors, respectively; he wanted to write a book: "I was prepared for them to laugh me right out of their offices, but they didn't. They were very encouraging."

It was Peterson, though, who came up with the idea of creating a computer movie rather than a book. Constantino, no hacker, wasn't enthusiastic; he'd had no experience with computers. But a few weeks of learning to manipulate the MacIntosh mouse through MacPaint (an easy-to-use software package), then

mastering VideoWorks (the animation program), won him over. Since he had already thoroughly researched the embryological events he wanted to portray, the only time-consuming part was creating the individual drawings necessary for animation.

"The program makes it easy to move images from place to place on the screen," explains Constantino. "But in order to make the shape of an image change — which most of embryology really is — you have to draw separate pictures for each change, just like a cartoon. In ordinary two-dimensional drawings, it's impossible to see the twisting and folding that are the important embryological events. And that's the important thing to understand — how this ball of cells can twist into layer upon layer, and invaginate upon it-

self. Once you understand that, the rest you can get out of a textbook."

MacBaby portrays the formation of the basic body plan, including the three germ layers and the "tube within a tube" design of the body.

"I think the program has gone about as far as it can because the more complicated, further developments require more attention to detail," says Constantino. "But I would like to get in two more systems — the uro-genital system, and the formation of the circulatory system — how the heart develops, and the switch from placental to mature circulation."

Peterson's role included meticulous checking of the scientific events Constantino drew and the narrative text describing these events. "I made lots of mistakes on the science," says Constantino, "but Dr.

Peterson never made one change without telling me first and asking me what I thought. He tells me, 'This is your story — you tell it your way, I don't want to interfere, because I like the way you say things.' "

Constantino explains that this is Peterson's natural style, one that he displays in his role as anatomy instructor for all first-year students: "He never forces his way on anybody — he wants people to learn on their own. He knew that because I had just learned all this myself, I could teach others to go through the learning process. He knows that each student must go through the learning process on his own, in his own way. Dr. Peterson's just the ultimate teacher."

Peterson traveled to San Francisco in January, at the invitation of MacIntosh, to participate in a three-day demonstration of computer applications. His was one of 24 university exhibits showing either software or teaching programs that had been developed for the MacIntosh by academic institutions. Repeatedly, says Peterson, the \$15-a-head visitors expressed admiration for Constantino's work.

Once back from the conference, Peterson phoned the software company, who had already heard of Constantino's work: "The person who answered the phone said, 'Oh, yes, MacBaby. Your disks caused us to rewrite our program,' " remembers Peterson. He explains that the original version of VideoWorks called for text to be entered as a graphic, which takes more memory. The revised version of the software will allow MacBaby to be compressed to one or one-and-a-half disks from

its present three-disk version.

Eventually, says Peterson, they may market MacBaby after Constantino finishes the uro-genital and circulatory systems. "The student evaluations of John's work have been very positive," reports Peterson, who asked first-year students to give them feedback on the movie. "We plan to use it as a supplement to the textbook-only phase of the course. And people who stopped by our exhibit at the conference — physicians, lawyers, and non-scientists — all said the same thing: 'I wish I'd had that when I took embryology.' "

"The things I like are simple," muses Constantino, whose goal is to go into family practice or general surgery. "I want to find a niche where somebody needs me; I don't want to compete with anybody, even though I'm a very competitive person, because that misses the point."

His goal in creating MacBaby, he says, "derived from my frustration as a student, sitting in lecture and wondering, 'Where did that come from?' I thought, if nothing else, I wanted to leave nothing out in describing how to get from an egg to an embryo. Dr. Peterson knew I felt that way and that it would take time to use such an approach. Yet, he still said, 'Do it one step at a time — don't compromise your view because of time, do it right.' And that's what we did."

CLASS NOTES

'30s and '40s

Edward W. Cannady, M.D. '31, and **Robert W. Elliott, M.D. '36**, are chairing the reunions of their respective classes at the 1986 Medical Alumni Reunion.

Kenneth A. Koerner, M.D. '41, is hosting his class at this year's reunion.

Virgil Loeb, M.D. '44, clinical professor of medicine at Washington University School of Medicine, has been elected vice-president and president-elect of the American Cancer Society. Loeb is a medical oncologist at Barnes Hospital.

Willard B. Walker, M.D. '46, invites his former classmates to the festivities at this year's reunion.

James W. Owen, M.D. '46, and **Everett R. Lerwick, M.D. '48**, are medical director and owner, respectively, of the Lerwick Clinic, newly opened in downtown St. Louis. The \$7 million facility will eventually have 30 full-time physicians who supervise diagnosis, outpatient surgery, and preventive medicine.

J. Neal Middelkamp, M.D. '48, professor of pediatrics at Washington University School of Medicine, has been elected secretary-treasurer of the American Board of Pediatrics. He is a member of the board's residency review committee.

Elizabeth Happel, M.D. '49, has been honored by the New Milford Hospital board for her role in the Connecticut

hospital's building campaign and her 29-year practice there. Happel, who has delivered more than 5,500 babies, will discontinue practicing obstetrics but provide gynecology services. She plans to train in microsurgery so that she can specialize in treating infertility, which includes performing reverse sterilizations.

Happel has contributed to many professional committees, including the medical education committee of the Maternal and Child Care Division, which she headed. She also served as medical staff representative to the hospital's board.

Happel completed residencies at Bellevue Hospital and French Hospital in New York. Before moving to Connecticut, she taught at several New York hospitals. Recently recertified by the American Board of Obstetrics, Happel was recognized by the AMA for her continuing medical education.

'50s

Walter A. German, M.D. '51, contributed an editorial on tort reform as a legislative priority to the Missouri State Medical Society Magazine, *Missouri Medicine*. German is president of that organization.

Marvin E. Levin, M.D. '51, welcomes his former classmates to the 1985 Alumni Reunion. In addition, he has led the Medical Eliot Society to a new milestone: In only two years, he and his committee have secured the endowment for the second Alumni Endowed Professorship by enlisting 145 new members. What's more, the committee has led

the medical school halfway toward the endowment needed to fund the third AEP. "I think we can do it by July," says Levin.

The goal is to eventually endow one AEP in each of the School of Medicine's 18 clinical and preclinical departments. "When you're in a great place like Washington University Medical Center," remarks Levin, "it generates good feelings; helping the institution is only a reflex. It stimulates you to want to do something for those yet to come, to leave a heritage — excellent teachers. I owe this place something."

Robert E. Hermann, M.D. '54, heads the board of the American College of Surgeons. Hermann, chairman of the Department of General Surgery at Cleveland Clinic Foundation, was elected last fall to represent the 220 governors on the association's Board of Regents. He joined CCF in 1962 after completing internship and residency in surgery at University Hospitals of Cleveland.



Robert E. Hermann

Richard W. Hudgens, M.D. '56, is hosting his class reunion this spring.

Samuel S. Kurohara, M.D. '57, has been named a fellow of the American College of Radiology. A native of Hawaii, Kurohara is on the medical staffs at several hospitals, including the Beverly Hospital in Montebello, CA, and the LAC/USC Medical Center in Los Angeles.

Morris Reichlin, M.D. '59, is professor of medicine and chief of immunology at the University of Oklahoma. He was a participant in a rheumatology symposium held in Birmingham, AL, last fall.

60s

Floyd E. Bloom, M.D. '60, has been elected to the board of the American Association for the Advancement of Science. His four-year term begins May 31, 1986. Bloom, director of the division of preclinical neuroscience and endocrinology at the Scripps Clinic and Research Foundation in La Jolla, CA, was the subject of the "Silhouette" in the winter 1985 issue of *Outlook*.

Nicholas T. Kouchoukos, M.D. '61, and **Harold S. Zarkowsky, M.D. '61**, are co-hosts of their class reunion.

Richard Marchick, M.D. '61, is serving a three-year term as vice-chairman of the California Bay Area Section of The American College of Obstetricians and Gynecologists. In private practice in Berkeley, Marchick is on staff at Alta Bates Hospital, where he chaired obstetrics/gynecology and served on the medical executive board, and at Herrick Hospital. He is associate clini-

cal professor of obstetrics and gynecology at UCSF School of Medicine. Formerly, he was president of the East Bay Gynecological Society and is a member of several professional organizations.

Ronald E. Rosenthal, M.D. '61, is chief of the trauma service in the Department of Orthopaedic Surgery at the Long Island Jewish Medical Center in New Hyde Park, New York. Rosenthal also heads orthopedics at the Queens Hospital Center and is associate professor of clinical orthopedics at the State University of New York Health Sciences Center at Stony Brook.

Rosenthal, who formerly lived in Nashville, writes that he is looking forward to his 25th class reunion in May.

John Stone, M.D. '62, has prepared a third book of poems, *Renaming the Streets*, published by Louisiana State University Press (Baton Rouge, LA 70893). The book is described as "... a work that speaks to the future but remains mindful of the endless intersection of the past and the present. Stone writes about the human experience in all its seasons: if there is suffering, pain, loneliness, there is also love, mercy, humor, and, always a sense of wonder ..."

Stone, associate dean at Emory University School of Medicine, was profiled in the summer 1984 issue of *Outlook*.

Roger L. Mell, M.D. '65, heads the council of the Southern Medical Associations. An orthopedic surgeon practicing in St. Louis County, MO, Mell trained in general surgery at Barnes and St. Luke's hospitals in St. Louis and in orthopedic

surgery at Barnes and allied hospitals. Before entering medicine, he was a pilot in the U.S. Air Force.

Ronald K. Grady, M.D. '66, and **Jay L. Liss, M.D. '66**, are co-chairing their class reunion this spring.

Johnny Bliznak, M.D. '67, is a fellow of the American College of Radiology. A native of Texas, Bliznak is on staff at the Hendrick Medical Center and the Humana Hospital—Abilene (TX).

Lynn M. Taussig, M.D. '68, is professor and head of pediatrics at the University of Arizona College of Medicine. He had been acting head of that department since last July and associate head since 1979.

Taussig, a specialist in pediatric pulmonary disease, is the principal investigator of a five-year, \$1 million grant to study children's risk factors for acute and chronic lung diseases. His special interest is cystic fibrosis.

He serves on the pulmonary diseases advisory committee of the National Heart, Lung and Blood Institute. He is also on



Lynn M. Taussig

the editorial boards of two professional publications. Formerly the vice-chairman of the medical advisory council of the National Cystic Fibrosis Foundation, Taussig assisted in the development of a pediatric pulmonary examination for the American Board of Pediatrics.

A 1964 *cum laude* graduate of Harvard, Taussig earned his medical degree at Washington University. Then, he went for further training to the University of Colorado, the National Institutes of Health, and The Montreal Children's Hospital. Taussig returned to Tucson in 1974 after completing a clinical fellowship from the National Cystic Fibrosis Research Foundation.

'70s

Robert G. Harmon, M.D. '70, is the director of the newly-created Missouri Department of Health. Formerly, he served as director of public health and was health officer for Maricopa County (AZ).

As director of the MDOH, Harmon oversees seven district offices. Its programs are in environmental health and epidemiology, health resources, personal health services, and local health and institutional services.

After graduating from Washington University School of Medicine, Harmon earned an M.P.H. from Johns Hopkins University in 1977. Board-certified in preventive medicine, he completed a residency in internal medicine. He is a fellow and board member of

the American College of Preventive Medicine. He has been a consultant for several overseas health projects and organizations.

Dixie J. Aronberg, M.D. '71, is heading her class reunion this spring.

Lary A. Robinson, M.D. '72, is a fellow of the American College of Cardiology. Currently, he is staff cardiothoracic surgeon at the University of Nebraska Medical Center, Omaha.

Wishwa N. Kapoor, M.D. '75, has been elected a fellow of the American College of Physicians. Kapoor, an internist, is on staff at Presbyterian-University Hospital, Pittsburgh.

Patricia Newton, M.D. '75, psychiatrist-in-chief of Provident Hospital, Baltimore, was honored by *Essence* Magazine for her contributions in health and medicine. In 1983, Newton was cited by *Baltimore Magazine* as one of the city's 100 most influential women.

In 1985, she chaired the First Baltimore International Congress of Transcultural Psychiatry, co-sponsored by the NIMH. Newton is assistant professor of psychiatry at Johns Hopkins and president of Newton-Thoth, Inc., an international behavioral science management consultant corporation. A member of the American Psychiatric Association and the Black Psychiatrists of America, she is a frequent media spokesperson on health-related matters.

After completing her undergraduate work at University of Arkansas (Pine Bluff), she earned a master's degree from Vanderbilt University—

Peabody College. She completed a residency in psychiatry at Washington University following graduation from medical school there. She earned an MPH in Mental Health Administration from Johns Hopkins School of Public Health and Hygiene. Board-certified in psychiatry, she is a diplomate of the American Board of Psychiatry and Neurology. Newton also has certification in administrative psychiatry from the American Psychiatric Association.

Kenneth S. Rotskoff, D.D.S., M.D. '75, moderated the Symposium on Nutrition for the Oral and Maxillofacial Surgeon at a meeting in Washington, D.C., last fall. He also presented abstracts of his work on surgical orthodontic patients.

Robert L. Lamberg, M.D. '76, has been selected to serve on the Executive Council of the Medical Center Alumni Association. A St. Louis ophthalmologist, Lamberg is clinical instructor of ophthalmology at the School of Medicine. He also chairs the Medical Century Club, an organization of medical alumni who are university donors. Lamberg also serves as reunion chairman for his class.

Keith H. Bridwell, M.D. '77, assistant professor of orthopedic surgery at Washington University School of Medicine, chose "Surgical Treatment of Spine Burst Fractures" as the subject of an audiotape he made for a national organization for continuing medical education. He also has completed a book chapter on the upper thoracic spine and has

co-authored a paper on complications of spinal instrumentation. His work was featured in the winter 1985 issue of *Outlook*.

Pamela Freeman, M.D. '77, FHS, is a rheumatologist in practice in Orlando, FL.

Charles O. Hershey, M.D. '77, is a fellow of the American College of Physicians. An internist, Hershey is on staff at Cleveland Metropolitan General Hospital.

Cecil J. Holliman, M.D. '79, has been accepted as a member of the Berks County Medical Society (PA). He practices emergency medicine at Community General Hospital.

Carol Mitchell Simmons, M.D. '79, has begun a residency in family medicine at the Mayo Graduate School of Medicine, Rochester, MN.

FORMER HOUSE STAFF NOTES

David A. McLain, FHS '75-9 and former faculty '79-81, is chief of rheumatology at Brookwood Medical Center in Birmingham, AL. He was course director for the third annual Brookwood Rheumatology Symposium. Speakers included C. Conrad Johnston, FHS '56-7, director of the division of endocrinology and metabolism, Indiana University Medical Center. Thomas Traylor, FHS '75-8, was on the program committee; he is a Birmingham rheumatologist.

Harry Burack, FHS in gastroenterology, recently opened a private practice in St. Peters, MO.

Keith LaFerriere, FHS, has been named clinical assistant professor, Department of Surgery, division of otolaryngology, at University of Missouri School of Medicine (Columbia). A member of Head and Neck Surgical Associates of Springfield Ltd., LaFerriere previously served as research associate at Kresge Hearing Research Institute and instructor of otolaryngology at Washington University School of Medicine. A fellow of the American College of Surgeons and the American Academy of Facial Plastic and Reconstructive Surgery, he is president of the Missouri Society of Otolaryngology — Head and Neck Surgery.



Keith LaFerriere

Ramon Iglesias, FHS, practices obstetrics and gynecology in Coral Gables, FL. An article about him in the *Miami Herald* describes his advocacy of sports, especially for women.

Harold H. Sandstead, FHS, is professor and chairman of the Department of Preventive Medicine and Com-

munity Health at the University of Texas Medical Branch, Galveston. A noted researcher in human nutrition, Sandstead previously served as professor of nutrition at Tufts University and senior scientist and director of the USDA agricultural research service. He received the M.D. from Vanderbilt in 1959, then completed residency in internal medicine at Barnes Hospital and at Vanderbilt University Hospital. His worldwide scientific reputation is in the field of trace mineral metabolism, particularly zinc.

H A P P E N I N G S

Lawrence E. Acker is administrator of the MEDICAL Rehabilitation Center of St. Louis, a comprehensive outpatient rehabilitation facility. A 1979 graduate of HAP, he formerly was associate administrator at St. Louis County Hospital.

Jeffrey M. Fried has been named vice president of operations at Lancaster General Services Corp., PA. Formerly, he was assistant vice president of Sinai Hospital, Baltimore.

Dana S. Hensley is assistant vice president at Baptist Medical Center, Montclar, AL. Hensley is a Ph.D. candidate in religion at Vanderbilt University.

Mark S. Wiener joined Research Medical Center (Kansas City, MO) as vice president of clinical services. Previously, he was assistant hospital director at University of Nebraska Hospital and Clinic in Omaha.



Mark S. Wiener

Ned Wilford was interviewed in the November 1985 issue of *Referee*. Wilford, who earned the master's degree in HAP in 1966 and is president of Holmes Regional Medical Center in Florida, is also a Southeastern Conference football official.

His interest in sports dates back to his high school days: He played on a team ranked number one in his home state, Arkansas, when he was a senior.

I N M E M O R I A M

1923
Quince B. Coray, M.D.
October 18, 1985

1926
Clinton K. Higgins, M.D.
February 3, 1986

1927
Charles H. Leslie, M.D.
June 18, 1985

1931
Delevan Calkins, M.D.
July 28, 1985

1932
Orville R. Clark, M.D.
October 7, 1985

1934
Howard R. Little, M.D.
July 21, 1985

1935
Harry Agress, M.D.
January 15, 1986

1936
Lawrence Breslow, M.D.
January 1986

1940
William M. Tomlinson, M.D.
February 3, 1986

1943
Jean M. Modert, M.D.
August 31, 1985
Nathaniel D. Ewing, M.D.
1985

FORMER HOUSE STAFF
Charles D. Phelps, M.D., FHS,
September 13, 1985
Harry Wilkins, M.D., FHS,
February 14, 1985

Medical Center Alumni Association
Box 8049
660 S. Euclid
St. Louis, MO 63110

Nicholas T. Kouchoukos, M.D. '61
President

Jack Siefkas, Director
Medical Alumni and Development Programs

Kellie Semler, Director
Medical Alumni Programs

Ruth Moenster
Secretary

SILHOUETTE

Thomas Frist *Empire Builder*

Insurance charts have no category for physicians who fly jet airplanes. But Thomas F. Frist, Jr., M.D. '65, is an experienced jet pilot who has flown on business all around the country. And conventional wisdom has it that medicine and business don't mix. But Frist, chairman and C.E.O. of the Hospital Corporation of America (HCA), has mixed medicine and business skillfully enough to earn a piece of corporate history.

"I have had a burning, compulsive, almost obsessive desire to prove that it's not inconsistent for a physician to be a capable manager," says Frist. The Nashville-based company, which he helped found in 1968 — three years after graduating from Washington University School of Medicine — has also defied skeptics: It has rapidly grown into the largest hospital management chain in the U.S. In 45 states and seven foreign countries, HCA currently owns or operates 438 health care facilities. Reaching into related fields, it has also acquired an ambulance subsidiary, a nursing home company and a medical equipment leasing firm. In 1986, HCA will garner \$5 billion in revenues and employ more than 80,000 people.

Frist, a soft-spoken man with an easy southern drawl, continues to act aggressively and seize the unexpected. Last year, he surprised Wall Street by forging a giant alliance between HCA and American Hospital Supply Corp., the nation's largest distributor of hospital supplies. The merger fell apart, but HCA emerged with \$150 million, which Frist will turn to fresh advantage.

"The most recent strategy of HCA," discloses Frist, "is to develop *the* national provider network to serve the insurance industry and corporate America. We will do that through owned, managed and affiliated hospitals, both in communities where we are now and by filling gaps over the next two years in the few areas where we do not have a network."

This major new thrust for HCA, Frist hints, will mean several joint ventures within the insurance industry. It will also require state-of-the-art computer and communication systems to link hospital, physician's office, workplace and insurance company. Aided by increasingly close ties with



"Going from a cost-plus payment system to a competitive, market-driven system has changed the course of medicine," says Thomas Frist, founder of Hospital Corporation of America (HCA). (photo courtesy of HCA)

local physicians, "we will build the system of the future," he says.

Growing up in a family full of physicians, Frist learned early about health care. His father, Thomas F. Frist, Sr., was a leading Nashville cardiologist and an associate professor of medicine at Vanderbilt's School of Medicine. One brother became a cardiac surgeon; a second joined the heart transplant program at Stanford. Cousin John Frist, M.D. '66, went on to practice plastic surgery in Nashville.

From childhood, Frist had his sights set on surgery. After undergraduate training at Vanderbilt, he decided to broaden his experience and was drawn to Washington University by its strong reputation. Immediately, he was impressed by the spirit of cooperation between professors, house staff and medical students.

"The professors not only took pride in

research, they also enjoyed teaching. This combination created an exciting climate for medical students. You saw that with Dr. Carl Moore of the Department of Medicine, Dr. Carl Moyer of surgery, and Dr. [Lauren] Ackerman in pathology. They were there, participating in rounds; they made medical students feel as if they were part of a team. In business, we call that a 'corporate culture.' Washington University has a unique 'culture' for a medical center and should be the envy of all others," he says.

Returning to Vanderbilt, Frist completed his surgical internship and was beginning his residency when he was drafted to serve as an Air Force flight surgeon during the Vietnam War. That stint gave him time to ponder a lesson he'd learned from a college fraternity brother, son of a Holiday Inn founder: "Holiday Inns of America created the motel business," muses Frist. "Until that

time, travellers had two choices — boarding houses or uptown hotels. I realized that there were 7,000 independently-operated hospitals being run as a cottage industry. The same opportunity existed there as in the hotel industry.”

Discharged from the service and three months away from returning to his residency, Frist went to Vanderbilt's head of surgery with two decisions: He was not returning to complete his training, and he was going to start a for-profit hospital company. “You can imagine what the reaction was,” Frist says wryly. “I was concerned too. I knew there was tremendous potential, but there was also a great deal of risk.”

From the start, Frist had high-powered help from co-founders Jack C. Massey, whose business acumen derived from his roots in Kentucky Fried Chicken; and from the senior Frist, whose own Parkview Hospital (acquired during the 1950s) formed the nucleus of the fledgling HCA. After only 18 months, the new firm had 11 hospitals; soon, HCA developed its lasting pattern of doubling in size every three years.

At first, Frist concentrated on acquisition and development. “That was where I was able to use my background in medicine, my love of business, and my hobby of aviation,” he says. “I put all three together and went personally to visit communities, meet doctors and see hospitals.”

Frist targeted the southeast U.S., then experiencing tremendous growth. Capital-starved communities were scrambling to finance new schools or public utilities; they lacked money to improve outdated hospitals. “We were not necessarily the first or even the second choice,” Frist says. “If the local government or religious order could not fulfill the need, we were often — at least in the early years — the answer of last resort. Gradually, we built a track record which allowed us to take on larger and more prestigious projects.”

After five years in business, HCA no longer limited itself to eligible proprietary hospitals; communities began selling the firm their not-for-profit hospitals. A few years later, hospitals were seeking out HCA to manage their tax-exempt facilities. Today, approximately half HCA's hospitals are tax-able; the rest are tax-exempt.

“But in 17 years, those artificial designations have blurred, just as they have in the financial world,” reflects Frist. “It is difficult today to tell a bank from a savings and loan from an investment banking house. Likewise, you have the traditional not-for-profit hospital with for-profit subsidiaries and for-profit hospitals with not-for-profit subsidiaries.”

The scope of HCA's business has also changed. No longer simply a hospital chain, it has become a fully integrated health care system that provides wide-ranging care: in-patient, out-patient, home health, long-term and psychiatric.

And like HCA, the entire U.S. health care system is in flux, prodded by 1983 changes in Medicare reimbursement policy. “If that hadn't occurred, the alternatives were not bright,” Frist says. “We were marching down the road very rapidly toward socialized medicine — and, ultimately, a national health system — as a result of uncontrolled, double-digit inflation. This bold, dramatic change — going from a cost-plus payment system to a competitive, market-driven system — has changed the course of medicine. The system has become, in a relatively short time, far more cost-effective than I could ever have dreamed.”

That process is taking a toll, he adds. Over the next decade, probably 400 to 500 hospitals will close. Others, including university medical centers, will join hospital groups to create new kinds of affiliations — joint ventures, management contracts, equity investment, and outreach programs that stretch beyond their geographical boundaries.

HCA will play a central role in these new developments. Already, Frist says, the firm has made an important difference to the quality of American health care. In communities where HCA has built or acquired a hospital, he contends, the patients are now receiving better health care; in communities where an HCA hospital exists alongside others, its presence has given its competitors the incentive to improve.

Frist is starting to look ahead to the end of his leadership of HCA. Named president in 1978, he learned the skills of management from Donald S. MacNaughton, former

C.E.O. of Prudential Insurance who joined HCA as chairman in 1979. Frist became C.E.O. in 1982 and chairman last September: “My feeling is that a person can be effective as C.E.O. of a major company for a maximum of eight to ten years,” he says. Within five to six years, he may consider moving on to other opportunities in health care, leaving his company “. . . in an eminent position, where it will have a bright future.”

To harness the energy for the coming critical years, Frist relies on exercise. A devoted jogger who frequently runs during airport stopovers, he has completed 16 marathons. He balances his other responsibilities, which include national-level work for the United Way, with a strong commitment to his family: wife and former childhood sweetheart Patricia Gail Champion, and three children.

Although he has never practiced medicine, Frist is grateful for his medical training. It was useful through HCA's early years, facilitating his communication with physicians. But during HCA's growth spurt, it occasionally hindered him; he had to prove his mettle as a Fortune 500 company executive. With the nation's sharpened focus on health care delivery systems, however, his training has re-emerged as an asset in building his — and HCA's — credibility.

He says that he will always bear fond memories of Washington University. For one thing, HCA continues to draw on the Health Administration Program (HAP) at the School of Medicine for its managerial staff. “And I know that having attended the medical school, with its great tradition as a center of excellence, has provided me with intangible benefits greater than I can measure. I'm very appreciative of that.”

He is also thankful for his chance to shape a vital American industry. “I've enjoyed playing a role in the changing of America's health care delivery system. It has always been thought of as synonymous with quality. Now we're demonstrating that we can be effective managers as well.” ■

Candace O'Connor is a free-lance writer and frequent contributor to Outlook.

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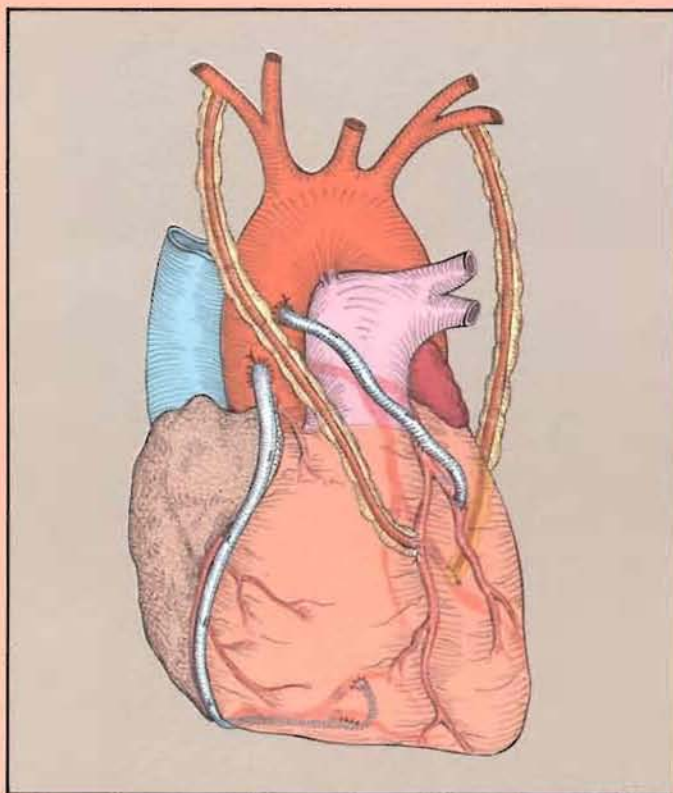
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"Speaking for the Heart" is the title of the 1985 annual report poster issued by the Washington University Medical Center. This illustration, one of more than 10 on the poster, depicts surgical treatment for coronary artery disease. In the procedure, diseased coronary arteries are bypassed with grafts, as shown. The patient's own internal mammary arteries and veins can channel an unobstructed supply of blood to ischemic heart muscle, relieving symptoms like angina.

A limited supply of "Speaking for the Heart" posters is available. To obtain a copy, please call 314-362-8258.
