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Profile:
Samuel B. Guze
Those who attended this year's alumni reunion were treated to a preview of the new Library and Biomedical Communications Center.
Outlook reflects on the career and achievements of Samuel Guze, M.D., who recently retired from his position as vice chancellor for medical affairs.

School of Medicine faculty explore the elusive link between mind and body.

Researchers trick the Sindbis virus into making proteins on demand.

Hearing researcher William Clark, Ph.D., investigates the hazards of recreational noise.
Physicians may one day rely on pictures—rather than surgery—to individually tailor treatments for patients who have breast cancer.

Scientists at the School of Medicine have created the first images of human breast tumors using positron emission tomography (PET). Breast cancer can be imaged with mammography and other radiologic techniques, but the advantage of PET is that it may enable doctors to determine—without biopsies—which tumors will respond to hormone therapy and to monitor, almost immediately, the effectiveness of that treatment.

These findings are expected to be especially important in treating metastatic breast cancer, a form of breast cancer in which the primary tumor spreads, and secondary tumors crop up at other sites in the body. The work has been reported in the journal Radiology, and will be presented at the national meeting of the Society of Nuclear Medicine, held this past June in St. Louis.

The research team—headed by radiation chemist Michael J. Welch, Ph.D., professor of radiology—created pictures of the cancer that existed in the breasts of 13 women, using PET to scan estrogen receptors concentrated in their tumors. The ability to produce those high-resolution images represents a sweeping advance in the field.

"This is the first time a tumor receptor has been imaged in humans," Welch says. "The impact could be tremendous."

In order to use PET successfully, Welch and his colleagues first had to devise a highly specific radioactive tracer, a derivative of natural estrogen called F-18 fluoroestradiol. The drug, when injected into a woman's body, binds to the estrogen receptors in her system.

When tracked on a PET scanner, it reveals the concentration of those estrogen receptors in any tumors, producing actual images of the cancer. The PET scientists confirmed their work by comparing their PET-based calculations of estrogen receptor levels to measurements obtained during subsequent biopsies: good correlation was obtained.

The concentration of estrogen receptors is what determines a breast tumor's response to treatment. Hormonal therapy, preferred by most doctors because of its relatively harmless side effects, is effective almost two-thirds of the time when estrogen receptor levels are high enough.

Knowing the nature of the tumor would allow doctors to prescribe hormonal therapy with a reasonable assurance of its effectiveness, and with a second scan, to quickly check treatment progress and make adjustments if necessary. Not knowing, they must wait for the hormonal therapy to register its effectiveness, meaning they risk wasting months of potentially valuable treatment time.

Estrogen-receptor imaging could make a crucial difference in treatment for patients with metastatic cancer, Welch says. Biopsies can provide information about primary tumors, but the PET technique is the only means available for learning about secondary tumors—those that occur in the surrounding bones, muscles and lymph nodes, and that spread rapidly to other parts of the body.

"It's the secondary tumors that kill people," he says. "The success or failure of therapy depends on the receptor status of the secondary tumor, not the primary tumor. The primary tumor can have gobs of receptors, but if the secondary has none, the therapy will not work."

"Breast cancer's not like strep throat, where you know the treatment will work if the diagnosis is correct," explains oncologist Alan P. Leys, M.D., who has referred numerous patients to Welch's study. "When the disease is cancer, the percentages are more variable—the certainty is not as great. And we can't afford to waste precious time with ineffective treatment."

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**New McDonnell Scholar arrives**

Eric C. Beyer, M.D., will serve as the School of Medicine's first McDonnell Scholar in Cancer Research.

Beyer, who joined the faculty July 1, recently was named a 1989 McDonnell Scholar by the James S. McDonnell Foundation's Program for Molecular Medicine in Cancer Research. His appointment brings with it a three-year, $375,000 grant that will enable him to pursue his research in oncology.

The McDonnell Foundation's program was established this year to develop physician-investigators who will apply
techniques of modern biology to problems in clinical oncology. It supports young physicians who have demonstrated superior potential for original basic research as well as an interest or training in oncology.

Beyer's work focuses on molecules on cell surfaces that are involved in cellular communication, adhesion and development. Using the techniques of molecular and cellular biology, he has isolated membrane proteins that form tunnel-like structures between cells. These "gap junctions" play a role in passing between cells small molecules involved in metabolic support, growth control and the development of embryos. In the heart, they permit electrical communication from one muscle cell to another. Beyer plans to study the synthesis and assembly of the gap junction proteins and to analyze their role in cell-to-cell communication in normal and cancer cells.

Before coming to Washington University, Beyer was an instructor of pediatrics at Harvard Medical School. He also served as an assistant in medicine at The Children's Hospital and as a clinical associate at the Dana Farber Cancer Institute. Since 1985, he was a research fellow at The Children's Hospital, the Farber Cancer Institute, and the departments of pediatrics and anatomy and cellular biology at Harvard Medical School.

Beyer received his doctorate in physiology and pharmacology in 1981 and his medical degree in 1982 from the University of California in San Diego. He has received numerous awards and honors for his research, including the 1987 American Heart Association's Clinician Scientist Award.

School of Medicine physicians are using a new form of echocardiography, called transesophageal echocardiography, to monitor patients during open-heart surgery and to diagnose heart problems that otherwise would be difficult to see with traditional thoracic echocardiography.

Both techniques produce images of heart function by bouncing sound waves off heart tissues. But instead of delivering sound waves from a transducer placed on top of the chest—as is the case in thoracic echocardiography—transesophageal echocardiography delivers sound waves from a tube inserted into the throat.

Because the esophagus lies directly behind the left atrium of the heart, placing the transducer down the esophagus yields a better picture than placing it on the chest, according to Drs. Lappas and Barzilai, who have been using this new technique for about a year.

Thoracic echocardiography falls short of the theoretical resolution that would be expected because the lung, ribs and chest wall block the quality of the image, says Demetrios G. Lappas, M.D., professor of anesthesia. Also, the high frequency waves needed for the best resolution cannot be used, because they would be absorbed by the chest wall.

"There's a law of physics that states that the higher the frequency, the higher the attenuation (absorption)," says cardiologist Benico Barzilai, M.D., assistant professor of medicine. "To penetrate the chest wall and go through all that murky terrain, you need a lower frequency."

Barzilai likens thoracic echocardiography to the view of the person who sits in the back row of a lecture hall. To see the speaker, he has to look through a crowd of people.

Transesophageal echocardiography, on the other hand, is like sitting on stage behind the speaker.

One obvious drawback to the esophageal method is that it involves the insertion of a tube down the throat. This is slightly invasive and requires a mild sedative and a drug to numb the throat.

Yet the advantages of the new technique far outweigh the inconvenience and discomfort, according to Lappas and Barzilai. Intraoperative use of both methods has found transesophageal echocardiography to be better at detecting clots in the chambers of the heart, locating damaged valves and assessing the pumping action of the ventricular chambers, according to Lappas, who has evaluated the use of transesophageal echocardiography in more than 200 patients.

Barzilai adds that the esophageal technique is a more sensitive and accurate method of assessing the condition of artificial valves after surgical replacement.

The School of Medicine was one of the first institutions in the Midwest to use the transesophageal method of echocardiography. Barzilai estimates that about 5 percent of all echocardiographies performed here are now done with this technique. He and Lappas are continuing to evaluate the usefulness of the technique through studies that compare it with thoracic echocardiography.

"Drs. Barzilai (left) and Lappas obtain better resolution of heart tissue when sound waves are directed from a tube that is inserted into the throat than when directed through the chest."

Echocardiographers take it closer to the heart
New psychiatry department head

C. Robert Cloninger, M.D., a scientist who is recognized worldwide for studies on the inheritance and classification of psychiatric disorders, has become the new head of the Department of Psychiatry at the School of Medicine. He is also the new psychiatrist-in-chief at Barnes Hospital.

Cloninger replaces Samuel B. Guze, M.D., who has served as head of the department since 1975.

Cloninger is perhaps best known for his work on the clinical assessment of personality and his adoption studies in Sweden. This work allowed him in 1981 to identify two types of alcoholism: with type 1, the most prevalent, drinking begins in the mid-20s to 30s, causes medical problems in later years, and is the result of both genetics and environment; with type 2, which usually occurs in men and often in criminals, inherited tendencies are the primary cause and there are rarely medical problems.

Cloninger also has studied the classification and inheritance of many other psychiatric disorders, including schizophrenia, anxiety disorders, mood disorders and personality disorders. He is working with colleagues on molecular genetic research to locate linkage markers, the specific genetic mechanisms related to susceptibility to alcoholism and schizophrenia.

Cloninger received his medical degree from Washington University in 1970, then spent three more years at the medical school as an assistant resident and a National Institute of Mental Health (NIMH) assistant and trainee in psychiatry. He joined the Washington University faculty in 1973 as an instructor in psychiatry.

From 1975-85, Cloninger conducted studies as an NIMH research scientist development awardee in quantitative genetics. During that period, he spent a year as a visiting investigator at the University of Hawaii’s Population Genetics Laboratory.

Cloninger was named associate professor of psychiatry in 1978 and of genetics in 1979, becoming a full professor in both departments in 1981. In addition, he has served as visiting professor of psychiatry and genetics at the University of Umeå School of Medicine in Umeå, Sweden.

Olson advises on human genome

Maynard V. Olson, Ph.D., professor of genetics at the School of Medicine, has been chosen as one of 12 members of the National Institutes of Health’s Program Advisory Committee on the Human Genome.

Olson will serve a four-year term on the committee, which includes members from academia, industry and non-profit organizations. The goals of the committee include the training of scientists, the coordination of the program with private sector resources, the management of the massive data processing and storage requirements that will be necessary to handle the knowledge gained through the program, and the consideration of ethical and legal issues that may arise.

It is estimated that the total cost of the human genome initiative could be $3 billion over the next 20 years. President George Bush has allocated $100 million to the NIH in fiscal year 1990 for this project.

Olson came to the School of Medicine in 1979 as an assistant professor of genetics, and was named professor in 1987. He received his doctorate in chemistry from Stanford University in 1969.
Study looks at drug use and AIDS

Linda Cottier, Ph.D., an epidemiologist in the Department of Psychiatry, has received funding to conduct the first study in the St. Louis area on the prevalence of HIV infection in intravenous drug users and their needle-sharing and sexual partners.

A research instructor, Cottier will receive a total of $797,000 from the National Institute on Drug Abuse for the project.

Until now, there have been no studies in St. Louis to determine the prevalence of HIV infection in drug users, Cottier says, because of the area's relatively low number of reported AIDS cases. However, research and educational efforts elsewhere in the country have begun to focus on IV drug users, she notes, since educational programs have stabilized the rate of new HIV infections among homosexuals.

The St. Louis study will follow some 650 subjects, including 300 IV drug users, 150 non-IV drug users and 200 sex partners. In addition to studying prevalence of HIV infection, Cottier will evaluate risk factors for HIV infection—particularly the co-occurrence of psychiatric symptoms, other substance abuse, needle-sharing, personality and high-risk sexual behaviors—to better target public education efforts.

Ultimately she hopes to determine whether education can help change high-risk behaviors and thus reduce the incidence of HIV infection in this study population.

Participants for Cottier's project will include prisoners and prostitutes, as well as clients in area drug treatment programs. Sexual partners will be recruited as well.

Inside the “visible tadpole”

Carl Rovainen, Ph.D., has a new window on blood vessel development, a phenomenon believed to play a critical role in tumor formation, eye damage in diabetics, vascular malformations in the brain, wound healing, arthritis and skin diseases such as psoriasis and scleroderma.

A professor of cell biology and physiology, Rovainen views the growth of blood vessels through the transparent skin of albino tadpoles, which he injects with a fluorescent dye while they are still embryos.

As they grow, he maps the developing spiderweb-like vessels and studies how various physical and chemical factors affect this development.

Knowing more about normal blood vessel development, Rovainen says, may eventually help scientists to understand what goes wrong in cases of abnormal blood vessel growth, and provide ways to regulate this growth.

Blood vessel growth is key to many physiological processes and diseases. The rapid growth and spread of tumors, for example, is sustained and nourished by blood vessels. Invading capillaries are thought to cause cartilage destruction in arthritics and hemorrhaging in the eyes of diabetics. Blood vessel growth heals wounds and, when malformations result, may lead to rupture of aneurysms and stroke.

Rovainen is currently mapping the normal growth of blood vessels in albino tadpoles. He then plans to test the effects of various growth factors on this development.

Lipid researcher studies proteins that carry cholesterol and fat

The director of the School of Medicine’s Lipid Research Center has been awarded a $1.1 million grant to study the role of certain blood proteins in causing atherosclerosis.

The National Institutes of Health grant was awarded to Gustav Schoenfeld, M.D., Kountz Professor of Medicine in the Department of Medicine.

The grant will support a project titled “Metabolism of Genetic Variants of Apolipoprotein B.” The study will involve looking for variants of the blood protein that are responsible for carrying cholesterol and triglycerides, with a goal of finding the structure-function relationships of apoB and its role in atherosclerosis.

In addition to directing the Lipid Research Center, Schoenfeld is head of the metabolism division at Jewish Hospital and on staff at Barnes Hospital.

A 1956 graduate of Washington University and a 1960 graduate of the School of Medicine, he joined the faculty in 1968 as an assistant professor of medicine. He became a full professor in 1977 and was named Kountz professor in 1987.

Schoenfeld belongs to many professional societies, including the Association of American Physicians, the American Society for Clinical Investigation, the American Society of Biological Chemists and the Council on Atherosclerosis, American Heart Association. He also is associate editor of the journal Circulation.
A total of 99 Washington University medical students participated in this year's National Residency Matching Program. Sixty percent of these students matched with their first choice, while 87 percent matched with one of their top three choices.

Surgery, obstetrics and gynecology, pediatrics, and anesthesia claimed a greater portion of School of Medicine graduates than last year. First-year appointments for the class of 1989 are as follows:

California
Loma Linda
Loma Linda University
Charles S. Lee, General Surgery, Otolaryngology

Long Beach
St. Mary's Medical Center
Nayyer Z. Ali, Internal Medicine

Los Angeles
UCLA Medical Center
Arthur J. Moser, General Surgery
LA County-USC Medical Center
Melvin H. Thornton, Obstetrics & Gynecology

San Diego
U.S. Naval Hospital
Elizabeth T. McKinney, Obstetrics & Gynecology

San Francisco
University of California, San Francisco
Michon Morita, Surgery Preliminary, Neurological Surgery

Stanford
Stanford University Hospital
David J. Lofts, Internal Medicine
Jonathan R. Perry, General Surgery

Torrance
Harbor-UCLA Medical Center
Catherine A. Hanlon, Internal Medicine
Holly E. Perry, Pediatrics

Travis AFB
USAF Medical Center

California
Santa Barbara
University of California, Santa Barbara

Colorado
Denver
University of Colorado School of Medicine
John B. Ebens, Internal Medicine
Thomas R. MacKenzie, Internal Medicine

Connecticut
New Haven
Yale-New Haven Hospital
Michael Apkon, Pediatrics
Tommy W. Chu, Pediatrics
Mark J. Shepard, Orthopedic Surgery

Florida
Gainesville
University of Florida Medical Center
Robert P. Quarles, Diagnostic Radiology

Paul Robiolo (left) and Richard Strauss draw their futures from the stage.
Illinois
Chicago
University of Chicago Medical Center
Miriam T. Schteingart, Internal Medicine
Preliminary, University of Illinois, Ophthalmology
Michael Reese Hospital
Mark Silverberg, Anesthesiology

Iowa
Iowa City
University of Iowa Hospitals & Clinics
Robert G. Jacoby, Internal Medicine, Neurology
Steven O. Podolsky, Obstetrics & Gynecology
Barbara Rohland, Psychiatry
Timothy C. Samelson, Pediatrics

Kansas
Kansas City
University of Kansas School of Medicine
Daniel C. Roney, Family Practice

Louisiana
New Orleans
Tulane University School of Medicine
Susan M. Berkebile, Obstetrics & Gynecology
Michael W. Carpenter, General Surgery
Mary Lee Cherry, Obstetrics & Gynecology

Maryland
Baltimore
Francis Scott Key Medical Center
Jeany Tung, Internal Medicine, Johns Hopkins Hospital, Anesthesiology
Johns Hopkins Hospital
Chandelle C. Dickey, Psychiatry

Massachusetts
Boston
Beth Israel Hospital
Nancy K. Cho, General Surgery
Brigham & Women’s Hospital
Paul A. Robiolio, Internal Medicine
Faulkner Hospital
Martin S. Arkin, Internal Medicine
Massachusetts General Hospital, Ophthalmology
Massachusetts General Hospital
Ellen M. Reynolds, General Surgery
Cambridge
Massachusetts Institute of Technology
Scott Selleck, Postdoctoral Fellow, Department of Brain & Cognitive Science

Michigan
Royal Oak
William Beaumont Hospital
Brent C. Thompson, Diagnostic Radiology

Minnesota
Minneapolis
University of Minnesota Hospitals
S. Kathi Doster, Surgery Preliminary, Neurological Surgery

Rochester
Mayo Graduate School of Medicine
Matthew G. Cary, Internal Medicine
Gail L. Knops, Family Practice
Joost L. Knops, Otolaryngology

Mississippi
Biloxi
USAF Hospital, Keesler AFB
Daniel T. Kane, General Surgery
Matthew B. Krebs, General Surgery

Missouri
Columbia
University of Missouri
Timothy L. Bartholow, Family Practice
William V. Walker, Internal Medicine

St. Louis
Barnes Hospital
Kelly M. Askins, Psychiatry
Fred J. Balis, Internal Medicine
Gregory D. Cohen, Internal Medicine
Elisa A. Crouse-Amos, Obstetrics & Gynecology
Laura E. Dyer, Internal Medicine
Michelle R. De Vera, Obstetrics & Gynecology
Nuri B. Faber, Psychiatry
Phyllis L. Faust, Anatomic Pathology
Brett R. Fink, Surgery Preliminary

Michigan
Royal Oak
William Beaumont Hospital
Brent C. Thompson, Diagnostic Radiology

Mississippi
Biloxi
USAF Hospital, Keesler AFB
Daniel T. Kane, General Surgery
Matthew B. Krebs, General Surgery

Missouri
Columbia
University of Missouri
Timothy L. Bartholow, Family Practice
William V. Walker, Internal Medicine

St. Louis
Barnes Hospital
Kelly M. Askins, Psychiatry
Fred J. Balis, Internal Medicine
Gregory D. Cohen, Internal Medicine
Elisa A. Crouse-Amos, Obstetrics & Gynecology
Laura E. Dyer, Internal Medicine
Michelle R. De Vera, Obstetrics & Gynecology
Nuri B. Faber, Psychiatry
Phyllis L. Faust, Anatomic Pathology
Brett R. Fink, Surgery Preliminary

Missouri
Columbia
University of Missouri
Timothy L. Bartholow, Family Practice
William V. Walker, Internal Medicine

St. Louis
Barnes Hospital
Kelly M. Askins, Psychiatry
Fred J. Balis, Internal Medicine
Gregory D. Cohen, Internal Medicine
Elisa A. Crouse-Amos, Obstetrics & Gynecology
Laura E. Dyer, Internal Medicine
Michelle R. De Vera, Obstetrics & Gynecology
Nuri B. Faber, Psychiatry
Phyllis L. Faust, Anatomic Pathology
Brett R. Fink, Surgery Preliminary
Gabiela Adelit Green, Anatomic Pathology
Daniel G. Hafenrichter, General Surgery

**Joost and Gail Knops find their spots on the Match Day list.**
From left to right: Gilbert Rigaud, Michon Morita and Nayyer Ali exchange news of their first-year appointments.
Rochester
Strong Memorial Hospital
David T. Harvey, Internal Medicine Preliminary
Felice A. Heller, Pediatrics
Michael P. Steinberg, Internal Medicine
Richard C. Paul, Surgery Preliminary, Urology

Stony Brook
Stony Brook Teaching Hospitals
Kenneth R. Lidonnici, Pathology

North Carolina
Chapel Hill
North Carolina Memorial Hospital
B. Todd Granger, Internal Medicine

Durham
Duke University Medical Center
Rodney J. Folz, Internal Medicine
Howard J. Ilivicky, Psychiatry

Winston-Salem
North Carolina Baptist Hospital
Janel A. Cox, Internal Medicine Preliminary, Bowman Gray School of Medicine, Radiation Oncology
T. David Cox, Diagnostic Radiology

Ohio
Cleveland
University Hospital of Cleveland
William C. Schroer, Surgery Preliminary

Oklahoma
Oklahoma City
University of Oklahoma College of Medicine
Jeffrey D. Dixon, Emergency Medicine

Oregon
Portland
Oregon Health Sciences University
John T. Berger, Pediatrics

Pennsylvania
Philadelphia
Temple University
John C. Fang, Internal Medicine
Hospital of the University of Pennsylvania
Steven C. Schmidt, Surgery Preliminary
Children's Hospital
Richard S. Strauss, Pediatrics

Pittsburgh
Mercy Hospital
Kevin D. Clark, Transitional, East Virginia Medical School, Norfolk, VA., Ophthalmology

Rhode Island
Providence Rhode Island Hospital
Bette-Jean Gillerin, Surgery Preliminary

Tennessee
Memphis
University of Tennessee College of Medicine
Kenneth A. Adams, Obstetrics & Gynecology

Nashville
Vanderbilt University
Rudolph F. Pedrizzi, Obstetrics & Gynecology

Texas
Dallas
University of Texas Southwestern Medical School
Mark H. Drazner, Internal Medicine
John R. Fitzgerald, Internal Medicine
Anthony Magalski, Internal Medicine
Glen A. Reznikoff, Internal Medicine

Rebecca Walter (left) and Peggy Klebba seem happy with their matches.

Houston
University of Texas Medical School
Teodulo M. Aves, General Surgery

San Antonio
Wilford Hall Hospital, USAF
George C. Powers, Pediatrics

Virginia
Portsmouth
U.S. Naval Hospital
Ferdinand R. Salvacion, Transitional Thomas Vaughan, Internal Medicine

Washington
Seattle
University of Washington Affiliated Hospitals
Andrew G. Batchelder, Family Practice
University of Washington
A. Gilbert Rigaud, Surgery Preliminary, Urology
Bryan E. Woods, Research
Dressed in their new white coats, the third-year medical students had planned to present a psychiatric inpatient to Samuel B. Guze, M.D., Spencer T. Olin Professor and Head of the Department of Psychiatry. They were understandably nervous; and to make matters worse, the patient in question decided to leave the hospital against medical advice. This could have made the two hours allotted for teaching rounds longer than usual. Instead, Guze turned the session into a compelling discussion of the ethical dilemma involved in involuntary commitment. "Twenty years ago," he said, "it would have been easy for a psychiatrist concerned about his patient's welfare to commit him to the hospital against his will. Because of changes in the law, this is no longer true. Nevertheless, I believe the grounds for commitment should not be the narrowest ones of potential suicide or harm to others. When judgment is impaired by mental illness, patients can do a great deal of damage to their lives and their families."

"I always wanted to be a doctor," says Guze, 44 years after he graduated from Washington University School of Medicine. During his long and distinguished career, which he began here in 1945 as an intern in medicine, Guze has fulfilled this ambition in a multitude of ways. Although his first choice upon graduating in 1945 was to train in internal medicine, by 1950 he had made the unusual switch to psychiatry. His goal, as he remembers explaining it to Drs. Barry Wood and Carl Moore—his chiefs in the Department of Medicine—was to transfer the rigor of internal medicine to the field of psychiatry.

Because he had the good fortune to be at the right medical school at the right time, Guze was able to fulfill this hope. He helped to lay the basis for a new biological approach to psychiatry and was appointed head of the department in 1975. Guze entered the administration of the medical school as assistant to the dean in 1965; he was named vice chancellor for medical affairs in 1971. His retirement from administration this year has therefore meant stepping down from two important positions—that of vice chancellor on March 1 and that of department head on July 1. Guze's satisfaction with the work he has done in both positions is expressed in the relish with which he discusses it. But he is obviously happy to give up administration to devote full-time to research, teaching and patient care.

Sam Guze, M.D., as a young resident.
Colleagues keenly appreciate the contributions he has made both to the school and to his specialty. Chancellor William Danforth (who preceded him in the vice chancellor’s position) said, “Institution building is something that I value highly. The Washington University School of Medicine and the medical center have prospered under Sam’s leadership. I know of no institution in the country that has advanced further or more rapidly, and I doubt if there is a medical center or medical school in the country better prepared for the future... Sam has set an example for all of us by conducting himself with integrity, balance and fairness.”

His partner in leading the school for the last 18 years, Dean M. Kenton King, commented: “I have known Sam for 32 years. He has always been a star in every facet of our endeavors: an excellent teacher, a superb clinician, a very good researcher and an extraordinary administrator. I want to emphasize that he was a leader in medical school affairs long before he became vice chancellor or head of psychiatry; he was responsible for a major curriculum change in 1969.”

His longtime deputy in the vice chancellor’s office, Virginia Weldon, M.D., now vice president for public affairs at Monsanto, said, “The School of Medicine has changed profoundly under Sam Guze’s leadership. It has become a much larger, more complex organization. This is, in part, due to rapid changes in the external environment, but it is also due to the emphasis Sam has put on maintaining this school as a leading research institution.”

Statistics offer convincing evidence of how the school has prospered during the 18 years he served as vice chancellor. The budget when Guze took this position in 1971 was $34,000,000; it is now in excess of $300,000,000. The number of endowed professorships has increased from 15 to 36. The number of employees has doubled. Full-time faculty has increased from 475 to 869; part-time faculty from 260 to 981. Square feet owned by the school have increased from 1,385,916 to 2,292,784—including the Clinical Sciences Research Building, which was the last major addition of space. But the size of the medical center is only one indication of its health. Its influence can be measured in other ways as well—by the number of medical students who have themselves become researchers and by the essential medical care graduates provide across the country.

In addition to overseeing this tremendous expansion, Guze’s contributions to psychiatry have been significant. He has written ten or collaborated on 175 scientific papers. While fulfilling administrative duties as department head and vice-chancellor, he continued important research. In 1972, he and co-authors Drs. Donald Goodwin and Robert Woodruff wrote a text on psychiatric diagnosis. Now in its fourth edition, it is considered a classic in the field.

Goodwin, now chairman of the department of psychiatry at the University of Kansas, says: “Sam produced first-rate scientific articles even when he was holding two jobs. He has contributed to a remarkable change in values and practices of American psychiatry in the 1960s and 1970s. Together with Eli Robins (Renard Professor in the Department of Psychiatry) and George Winokur (now chairman at the University of Iowa School of Medicine), he instilled a spirit of scientific inquiry into a new generation of psychiatrists—a number of whom now hold chairs in important universities... He is certainly among the clearest thinkers I have ever known.”

Guze is a leading figure in what has become known as the “Washington University School of Psychiatry.” It is an approach with a strong alliance to biology and a medical view of mental illness. Relying on empirical data, its practitioners seek to clarify and validate diagnoses—insisting that facts rather than theories should guide their conclusions. As Goodwin wrote in the preface to the first edition of “Psychiatric Diagnosis,” “This approach to psychiatry... is sometimes called ‘organic.’ This is misleading. A better term... is agnostic. Without evidence, we do not believe pills are better than words. Without evidence, we do not believe chemistry is more important than upbringing. Without evidence, we withhold judgment.”

Conclusive evidence that this school of thought had become influential came with the publication of the “American Psychiatric Association’s DSM III” (Diagnostic and Statistical Manual of Mental Disorders, third edition) in 1980. Its becoming an immediate best seller when previous books of this kind had very little influence indicated an important change in the way psychiatrists thought about mental illness. To quote from Goodwin and Guze’s 1988 preface to the fourth edition of “Psychiatric Diagnosis”: “Sixteen years have passed since this book was first published. In that time an interesting change has occurred in American psychiatry. Psychiatrists have become diagnosis-conscious... with the discovery of relatively specific drug therapies, diagnosis had become practical... people actually stood up at meetings and asked: ‘Where is the evidence?’ These were real changes. We like to think ‘Psychiatric Diagnosis’ anticipated them.”

The truth of this statement is clear. Washington University-trained psychiatrists made up a third of the DSM III task force, the largest contingent from any single school. The department here had been developing scientifically based diagnostic categories long before 1980. In an article titled “The Need for ‘Laughmindedness in Psychiatric Thinking,’” published in 1970, Guze answered potential criticisms to this approach: “Scientific skepticism is in no way incompatible with compassion for the sick. In fact, it is the desire to help patients that causes one to be frustrated by the lack of definite knowledge about what really helps and what does not.” Distinguishing one treatment from the other has occupied a major portion of Guze’s professional life.

The tradition of biologically oriented psychiatry had begun at Washington University during Edwin Gildea’s tenure as chairman of the department from 1942 to 1963. He encouraged biochemical and pharmacological studies of the brain at a time when the influence of Freudian theory in American psychiatric circles was supreme and largely unquestioned. His open-mindedness attracted bright young investigators to his department, among them Robins, who succeeded Gildea as chairman in 1963. Robins’ research strengthened and extended the biological approach to psychiatry. Drs. Robins, Winokur and Guze formed a formidable trio of agnostic psychiatrists, and developed the precepts and practices of what became known as the “Washington University School.” Demon-
strable and reproducible facts, rather than theories, were the key to their approach. In addition to biochemistry and pharmacology, long-term family and follow-up studies became crucial research tools. Thus, when Guze became department head in 1975, he inherited a position with a tradition of excellence in research.

Guze's intellectual promise was evident early in his academic career. Born in New York City, he attended the accelerated three-year course at Townsend Harris High School and graduated at the age of 15 in 1939. Next, he entered City College for two-and-a-half years before transferring for a final year at Washington University; he graduated in 1942 and entered the School of Medicine. World War II meant that this, too, was an accelerated course of study, and Guze obtained his medical degree in June 1945 at the age of 21.

He took an internship and residency in internal medicine at Barnes Hospital, followed by another year at a Yale-affiliated veteran's hospital in Connecticut, before returning to St. Louis as the medical center's first fellow in psychosomatic medicine.

What he learned during this fellowship was vital to his later decision to enter psychiatry: that patients with obscure illnesses could be helped if a doctor approached them with a practical and open-minded point of view. So much did he enjoy this experience, that he decided to make the commitment to psychiatry. As Guze remembers, he said to himself: "If I have to become a psychiatrist in order to do what I enjoy, okay." In addition to the extra work a second fellowship entailed, he was taking a considerable risk by switching to psychiatry at a time when it lacked the rigor, discipline and status of internal medicine.

Robins played a particularly important role in encouraging Guze's hopes for psychiatry. "What Eli did was to open up for me the literature in the tradition of his mentor, Dr. Mandel Cohen—a British and European literature in psychiatry that showed it was possible to make psychiatry a data-based (instead of theoretical) specialty." In 1955, Guze became director of the psychiatry clinic and consultant to the student health service at Washington University. "It was," he remembers, "an important symbolic step"—indicating a final professional commitment to psychiatry.

Together, Guze, Robins and Winokur divided responsibilities and created a department with a strong commitment to research and training based on fact rather than theory. As he recalls, "Because we were mavericks, we attracted unusual people to our program." One problem was obtaining research funding at a time when Freudian theory reigned supreme. However, within a few years of Robins' taking over as chairman of the department, the fruitfulness of their research findings helped turn the tide in favor of the Washington University approach to psychiatry—federal grants began to come their way.

When Guze took over the vice chancellorship from Danforth in 1971, he found in place a strong foundation on which to base his work. A new relationship with Barnes Hospital was already thriving. Much of what he has done in the last 18 years, he believes, has been adding to what Danforth had established in terms of healthy institutional relations. But there were new problems where he was able to make his own particular contribution—one of these has been the redevelopment program, started to improve and protect the neighborhoods around the School of Medicine. Richard A. Roloff, president of the Plaza Development Company, says, "Sam Guze has been the key to the success of the redevelopment program. His persistence, keen intellect, patience and sense of justice made him the perfect choice for the leadership role he has played as president of the Redevelopment Corporation."

Guze gives enormous credit to Dean King for the pleasure he's had in his job as vice chancellor. They have been partners in steering the medical school's course for nearly two decades. "It's been a ball," he says. "Ken's great virtues are fairness, integrity and open-mindedness. Even if we didn't agree, one or the other of us would compromise—and we could always talk. We met twice a week for 24 years to talk about the School of Medicine, and it was a joy."

Guze looks forward to his retirement years with keen anticipation. He plans to spend more time with his wife, Joy, and his two children and four grandchildren. But he will certainly continue being active in teaching, patient care, research and writing.

The final comments about Guze's career at Washington University are best taken from his own writing. In a 1979 article titled "Can the Practice of Medicine be Fun for a Lifetime?" (published in the Journal of the American Medical Association)

Guze wrote, "If the physician can view his practice as offering an almost infinite range of interesting problems, it is less likely that boredom and frustration will triumph. The best of education is self-education. The goal of teachers can never be higher than to help begin the lifelong process of continuing self-education and thus share in countless harvests."

During his career, Guze has indeed explored "an almost infinite range of interesting problems," and there's no doubt that he will continue to do so in his busy retirement. A leading medical educator has likened handing over administrative control of a medical center to relinquishing the reins of a horse at full gallop. The velocity of this institution's growth owes much to Guze's leadership. But it will not be slowed by the necessary transition his retirement requires.

"The transfer of institutional memory" is the phrase Guze has used to describe the briefings he gave William Peck, M.D., who succeeded him as vice chancellor on March 1. Guze's years of work as scholar and administrator are certainly a distinguished part of that memory.
Emotions and Disease: The Elusive Link

The research of Ray E. Clouse, M.D., has led him into what is perhaps the stickiest philosophical problem of all time: the relationship between mind and body.

A gastroenterologist and assistant professor of medicine at the School of Medicine, Clouse has been investigating the sneaking suspicion—held by layman and physician alike—that depression, worry or a bad day at the office are the invisible hands that wrench a patient's gut, resulting in a variety of gastrointestinal (GI) illnesses.

Clouse has found that people who suffer from irritable bowel syndrome and esophageal spasms, functional diseases with no identifiable pathology, have more emotional disorders than other physically ill people or people in good health. Patients with these GI problems also seem to improve with the help of antidepressant medications. But then comes the caveat: the antidepressants appear to help nondepressed and depressed patients alike.

Such ambiguous results characterize the research Clouse and others at the School of Medicine are conducting on the link between physical disease and emotions. It's a murky field made even murkier by unsubstantiated claims of the New Age movement—heal your body with mental images—and the attitudes of physicians toward patients afflicted in both body and mind. One attitude takes the form of blame: "Your disease is psychosomatic, so improve your state of mind." The other attitude is benign neglect: "If I had heart disease, I'd be depressed, too. It's a normal reaction."

Shining their lights into this quagmire, the medical school researchers are debunking a few myths as well as discovering some likely connections between how we feel and how our bodies function. Rather than lunging toward some unified theory for the interaction of physical disease and emotion, these physicians and psychologists are slowly building a body of evidence.

In the process, they are coming up with possible treatments for diseases they still don't understand in full. Perhaps just as important, the research is encouraging physicians to approach the emotional problems of their patients in more constructive ways.

Clouse says the psychosomatic issue presses itself upon physicians whether they like it or not. After all, people with physical illnesses are more likely to suffer from psychiatric illnesses than the population at large. Statistics on clinical depression, the most widespread major psychiatric illness, illustrate this point. Depression occurs in 20 percent to 25 percent of the physically ill, but just three percent to four percent of the total population, says Clouse.

"The problem is, doctors want to treat GI disorders. But when they ask their patients how they are doing, all they hear about are their personal problems," says Clouse. "If they had wanted to deal with emotional problems, they would have gone into psychiatry."

Clouse's jump into the psychiatric end of GI disorders wasn't without some trepidation. The subject didn't enjoy a good reputation in medical circles. "Research on ulcerative colitis did the most damage to the study of the relationship between emotion and disease. At one time, it was believed to be psychosomatic. Later research showed that it wasn't."

One 1982 study originating from the School of Medicine, for instance, indicated that lifetime psychiatric illness is no more common in ulcerative colitis patients than in other chronically ill subjects.

Another medical school study, however, came to a different conclusion about
Crohn's disease, an inflammation of the intestines that can cause diarrhea, abdominal pain and fatigue. Of 50 patients with Crohn's disease, 52 percent had some form of psychiatric illness, higher than the percentage for a medically ill control group. However, the onset of the two GI and psychiatric disorders were unrelated, and the severity of one illness did not parallel the severity of another. Such evidence did not exactly constitute a smoking gun on the psychosomatic nature of Crohn's disease.

Clouse and others discovered a similarly high rate of psychiatric illness among patients with irritable bowel syndrome (IBS) and esophageal spasms. Separate studies on each GI disorder showed that over half the patients taking antidepressants reported improved symptoms. In the case of IBS patients taking a tricyclic antidepressant, 89 percent experienced relief or complete remission. But why did the drugs work regardless of whether the patient felt less depressed?

Two possible explanations involve the role of the autonomic nervous system in governing the digestive organs.

"The bowels, for instance, don't depend on the brain for most movement," says Clouse. "The majority of the fibers between the brain and bowels are sensory, not motor in nature. They monitor bowel functions.

"Most nerve bodies for the bowels are in the bowels. It's like a mini-computer with preprogrammed activities."

The origins of IBS and esophageal spasms may reside in these nerve bodies outside the brain, says Clouse. Antidepressants may accidentally affect the bowel nerve bodies as well as the control centers in the brain for the emotions.

The two GI diseases also could have their roots in brain centers that mostly monitor and modulate the GI system. Evidence suggests these centers might overlap or border those governing the emotions, says Clouse. An antidepressant aimed at emotion centers might affect GI control centers as well.

A third explanation for the apparent efficacy of antidepressants is that, contrary to his initial studies, these drugs indeed produce an emotional change that in turn influences the GI system. In his experiments, Clouse used dosages lower than what a psychiatrist would prescribe. His studies indicated that patients experienced relief from IBS and esophageal spasms without improving psychologically, but Clouse says different psychological measures might yield other conclusions.

To test the glucose link, Lustman and McGill, an assistant professor of medical psychology in psychiatry, who collaborated with Clouse on the drug experiment with esophageal-spasm patients, has teamed up with Clouse and others to examine depression and diabetes. One study, headed by Lustman, found that 23 percent of diabetics suffered from current depression, while almost 33 percent had a major depressive episode sometime in their life. Depressed diabetics reported more symptoms of poor blood-sugar control such as sweating, frequent urination and hunger than nondepressed diabetics.

Depression also appears to take a more malevolent course among diabetics than others, he says, but the two diseases otherwise progress independently. Depressed diabetics do not necessarily develop more complications, nor do they become more depressed when complications occur.

To Lustman, these findings represent associations of fact, not cause and effect. The explanation could be behavioral. "It could be that when you're depressed, you don't take care of yourself. Or if you're depressed, you may complain more."

But Lustman has not ruled out a biological connection. After all, the bloodstreams of depressed people have abnormally high levels of insulin antagonists as well as cortisol, a hormone that may in turn raise glucose levels. Conversely, elevated glucose levels can produce a stress-like hormonal arousal observed in severe anxiety.

To test the glucose link, Lustman and
Psychologist Robert M. Carney, Ph.D., an associate professor of medical psychology in psychiatry, is searching for a possible physiological relationship between depression and coronary artery disease (CAD). It's more than a wild hunch. According to a recent study headed by Carney, 17 percent of patients with CAD were clinically depressed before the CAD diagnosis. Within a year of the diagnosis, the depressed patients had twice as many cardiac crises—heart attack, surgery or death—than their nondepressed counterparts.

Robert Carney, Ph.D.

The study stated that the cases of clinical depression do not "appear to simply be a reflection of severity of disease, degree of functional impairment, presence of other disease processes, cardiac medications or abnormalities of ventricular function."

While depression may not be a root cause, says Carney, "I think it can accelerate CAD."

Like Lustman, Carney says there may be a behavioral explanation. Depressed CAD patients may become less healthy because their illness disrupts living patterns such as sleep, or because they take less care of themselves. Also, they may complain more, leading their physicians to take more drastic actions like coronary bypass surgery.

"I'm betting, however, that the link has to do with ischemia—deprivation of oxygen to the heart," says Carney. Again, it's not a shot in the dark. Depression triggers an increase of neurotransmitters called catecholamines, associated with arteriosclerosis in animal studies. Catecholamines also can cause arteries to constrict and blood platelets to stick together. Each effect could contribute to ischemia by making someone's clogged coronary arteries even more narrow.

Carney and others have embarked on an experiment to confirm the ischemia hypothesis. Depressed and nondepressed CAD patients will undergo a stress test. Each group will have the same degree of measurable blockage in their coronary arteries. If Carney's hypothesis holds up, depressed CAD patients will experience ischemia before the nondepressed CAD patients, and perhaps more severely.

The results of Carney's and Lustman's experiments should add further twists and turns to medical thought on the mind-body connection.

The New Age movement and holistic medicine have pushed the mind-body link to an optimistic extreme. Physically ill patients aren't panned as their own worst enemies, but praised as divinities in disguise. Tap your divinity ... think positive, relaxing thoughts ... and you can heal yourself. The headline for a recent cover story of Omni magazine announces, "Mind Exercises That Boost Your Immune System."

The story includes a testimony of a woman who said she triumphed over lymphatic cancer by imagining a war between her tumor and chemotherapy drugs. The latter won by vaporizing "the cancer-causing warriors."

Medical researchers, however, are still waiting for double-blind studies to back up the claims.

"I don't think you can imagine your cancer away," says Barry A. Hong, Ph.D., an assistant professor of medical psychology in psychiatry, who is delving into the emotional patterns of AIDS and other chronically ill patients.

Mind-over-matter proponents operate "in a religious rather than scientific fashion," adds Carney. "They aren't playing the same game."

Clouse says he and his colleagues are avoiding the pursuit of some comprehensive theory explaining how the mind and body interact. Rather, their research attempts to accurately describe the symptoms and clinical expressions of physical diseases that may be psychosomatic. Even though they may not initially understand the pathology, they may discover treatments.

"If we waited for an understanding of pathology, these people would never be treated," Clouse says. "The pathology of depression wasn't known when antidepressants were developed. That happened by chance."

Unlike diseases such as cancer, depression and other psychiatric disorders can't be scrutinized under a microscope. Clouse welcomes diagnostic help from positron emission tomography, or PET. Researchers at the School of Medicine, where the technology was developed in the early 1970s, have used PET to pinpoint centers in the brain responsible for thinking and anxiety.

Advances in medical technology have subjected patients' psyches to new challenges, says Hong. Chronic illnesses such as AIDS can be detected long before the patient experiences any symptoms. The result is what Hong calls the Damocles dilemma, named after the Sicilian of antiquity who sat down at a luxurious banquet only to see a sword suspended by a hair above his head.

"The person who knows he has a chronic illness has two choices—he can go on with life—enjoy the banquet—or he can worry about the sword over his head," says Hong.

You don't have to believe that some diseases start in your head to get the point. A patient's emotional state always merits attention, whether or not it's physiologically related to his illness. Speaking about AIDS patients, Hong sums up this viewpoint well.

"We may not eradicate the virus. Our job will be to help people live more effectively despite their illness."
Henry Huang, Ph.D. The Sindbis virus as seen through an electron microscope.
Medical science takes its allies wherever it can find or create them, sometimes even from among an unlikely group such as the viruses. Parasitic and self-serving, viruses are nothing more than bits of genetic information wrapped in tiny protein shells, existing solely to produce more infectious particles just like themselves at the expense of the cells they infect. Their efficiency makes them powerful agents of disease. But viruses can’t think. And clever molecular microbiologists are tricking them into working hard for the purposes of science.
A virus subverts the cell it invades. We subvert the virus," says Henry V. Huang, Ph.D., in explaining how he and his co-investigators at the School of Medicine have engineered one particular virus to be newly useful.

Using what Huang calls "conventional cut-and-paste techniques," the researchers enter the genetic component of the common Sindbis virus and delete some of the information there. In its place, they splice a new set of genetic instructions for the product they seek. When the altered viral agent is applied to host cells, it infects them and all but "sucks them dry" in its work, says Huang, an assistant professor of microbiology and immunology. Instead of making more virus particles, however, it is fooled into manufacturing the protein dictated by the new genetic directions.

Why are such products valuable? The purpose of most of the approximately 100,000 human genes is to carry the biochemical instructions for the manufacture of a single protein. Life depends on those proteins for its form and the regulation of its systems.

So proteins made in this way can be of great value in the research lab, where the supply for study has been insufficient and time-consuming to produce.

They can be of immense clinical significance, too. The lymphokines that allow the parts of the immune system to communicate, clotting agents, growth hormones and tissue plasminogen activators that are so vital to medicine—all are proteins manufactured by the body under the instructions of specific genes.

In industry, proteins are no less important. For example, one kind of protein—the enzymes—converts corn to the high-fructose sweetener used in many food products. Gene expression using vectors, or carriers, like the Sindbis virus make it possible to generate large quantities of such products.

Commenting on the impact of the work by the Washington University researchers, Richard Mulligan, an associate professor of molecular biology at MIT, says: "They've harnessed the unique properties of the virus to make large quantities of proteins, many of which should be applicable for both basic studies and clinical procedures."

Some limitations remain. "The Sindbis virus might refuse to express certain proteins," cautions team member Charles M. Rice, Ph.D., but early tests with just two are encouraging. And the investigators have shown that there is space available on the Sindbis virus' genetic molecule to accommodate most genes specific for protein production.

The Sindbis virus itself is not a new discovery. It has been known since 1952 and is common in Europe, Asia, Africa and Australia; it is transmitted by mosquitoes. Relatively benign for humans, a Sindbis virus infection may produce a stiff neck and little more.

Unlike viruses previously employed in the engineering of proteins, however, Sindbis is an RNA virus. Its genetic instructions reside along a single strand of coiled ribonucleic acid rather than in the more commonly known double helix of deoxyribonucleic acid, or DNA. It does not go through a DNA stage as retroviruses do. Before the team can manipulate the virus' genetic information, Huang must make a DNA clone of the purified single-strand RNA. "All the tools for this work have been developed for DNA, not RNA," explains Sondra Schlesinger, Ph.D., a professor of microbiology and immunology and a member of the research team.

During that additional, intermediate step, the scientists make their changes. What Huang calls cut-and-paste technology is actually a process that begins with snipping the genetic molecule into smaller sections. Certain enzymes act to cleave the DNA only at particular junctions of the elements that form the long strand characteristic of genetic molecules. Those enzymes are the "scissors" that do the biochemical snipping.

All of the genes along the length of the Sindbis virus' genome, the name given to the complete set of genetic instructions, have been mapped. One sector carries instructions on how the virus will replicate itself. That portion, Huang does not disturb.
Huang and his fellow researchers remove the protein coat from the Sindbis virus and take out its RNA (1). This RNA is copied into double-stranded DNA and cloned (2). Then they cut the DNA and take out the portion that encodes for the virus' protein coat, replacing it with the gene for the desired protein (3). The modified DNA clone is used to produce a modified RNA. When this modified RNA is introduced to a cell, it replicates and produces a smaller RNA that is read by ribosomes and used to manufacture the desired protein instead of the virus' protein coat (4).

Another section contains the rules for building the three structural proteins that package the genome into new viral particles, or virions. To that part, Huang applies the enzyme technology that snips off the genes. In place of the originals, he supplants the gene that carries the instructions for the protein he wants to produce.

Identical RNA molecules are then transcribed from the "master copy" and saved for future production. The RNA is infectious and can be applied directly to host cells, a process called "transfection.

The techniques of producing such altered Sindbis RNA and collecting the product of the infected cells take about three days. Manipulations are fast enough that many clones can be tested simultaneously. Each may contain instructions for a different protein, or they can represent mutations of the same protein, a potential windfall for researchers who study the variants for their changes in function, stability or shape.

Previously, engineering a virus to produce experimental proteins required a minimum of two weeks, often much longer. "You can see," Huang says, "that you're more likely to do the work if it takes only three days rather than two weeks. And investigations can proceed much more rapidly."

Another advantage of an RNA virus as a vector is its relatively simple replication scheme. The processes it incites take place in the cytoplasm surrounding the host cell's nucleus rather than deep within the nucleus itself. The number of biochemical steps required for the production of the protein is thereby reduced, says Rice.

And Sindbis is a small virus, with a short and manageable set of genetic instructions. The longer the genome, the more difficult it is to manage, Huang explains. In extreme cases, even the most precise enzyme may cleave a molecule in so many places that manipulating a particular section is impossible. Researchers exploring large viruses with long genomes have had to resort to a cumbersome recombination technique.

In that approach, the gene for the protein desired is added to a host cell before infection with the virus. Via a process called "crossing over," a small fraction of the virions that result from the infection will carry the critical gene, but scientists must still identify, purify and grow those mutants. Huang calls that process "highly inefficient."

Sindbis also promises to surpass other viral vectors in its production capacity. In a paper published in the March 3, 1989, edition of Science, Huang and his co-investigators report that their viral agent produced $10^8$ (or 100 million) molecules of protein per infected cell in 16 to 20 hours. That is roughly equal to the amount of protein the virus would have produced to package new particles, had its instructions not been changed, Schlesinger notes.

Because of the speed with which gene products can be expressed by Sindbis, it may turn out to be particularly useful for generating unstable proteins—those that enzymes break down quickly, resulting in lower yields.

The quantity approaches that of baculovirus—one of the most prolific of all known viruses—that expresses up to $10^{10}$ molecules of protein per host cell. Unfortunately, baculovirus will only grow on moth cells. And the protein produced in insect cells is largely inappropriate for human applications, since it does not contain a
Birth of a virus

When Sindbis virus infects the cell (1), it replicates its RNA (2). It also produces a smaller RNA (3) that is read by ribosomes and used to manufacture large amounts of coat protein. The coat protein packages the viral RNA (4) to produce new virus particles (5).
Increasing protein production

Genetically altered RNA (1) lacks the ability to produce coat proteins, but if researchers supply the coat proteins (2), the virus can assemble into numerous infectious particles (3). Each of these infectious particles can be used to infect new cells (4), producing large amounts of the desired protein (5). Having no source of coat proteins, no infectious virus can be produced.

fundamental sialic acid group; in human metabolism, the liver quickly removes all proteins that do not display that acid group as a sort of flag for freshness.

The production of experimental proteins by means of a bacterial vector cannot compete with the Sindbis virus, either. The well-known E. coli bacteria grows at high rates, but proteins synthesized in that way often lack what are essential modifications, such as carbohydrate molecules. To clinically employ proteins expressed in E. coli would require extra, difficult biochemical processes that would adversely affect yields.

One of the Sindbis virus’ most endearing qualities — the exception that proves the rule about all viruses being eminently unlikeable — is its broad host range. Huang's team, in research supported by grants from the National Institutes of Health, the Pew Memorial Trust Fund and the Monsanto/Washington University Research Contract, has shown that the Sindbis vector operates efficiently in cultured cells from mammals, birds and some insects.

The Science paper reports on studies in which the scientists altered Sindbis to express the protein chloramphenicol acetyltransferase (CAT). The cells of chicken embryos were used as a host. CAT is not of particular importance outside the lab, but it is readily identifiable, and the amounts made are particularly easy to measure.

Control vectors of uninfected cells and cells infected with unaltered virus produced essentially no CAT. “There is no endogenous activity like it,” says Huang. “The controls are very simple and very clean.”

Though this vector represents a powerful new research tool, the investigators still confront a bottleneck: The scientists are not nearly as productive as the virus. Transfecting cells with altered RNA has been experimentally effective, but it is inefficient on any real-world scale. “If we throw in ten million molecules of RNA, we may hit one cell,” says Huang. “On a good day, we can transfect only about ten thousand cells.” And that’s not enough to manufacture commercially practical quantities of protein.

Seeking an increase in their efficiency by several orders of magnitude, team members have turned back to the virus. By adding a “helper” virus to provide the structural proteins, they again make possible the production of infectious virions carrying their new genetic information. Those virus particles will infect every susceptible cell to which they are introduced, so the success rate jumps from one in each 10,000,000 tries to a perfect one for one. Efficient packaging has been clearly demonstrated as a possibility.

But the elegance of the system is largely lost in that demonstration because the helper virus restores the missing RNA code for packaging. Therefore, the virions continue to spawn infectious generations. The Washington University team would most like to have the power of the virus combined with the safety of a “suicide” vector that dead-ends once host cells are infected. They want to keep the punchline to this most practical of jokes they play.

Toward that goal, the scientists hope to be able to make available only the virus’ packaging materials — the structural proteins — in a line of host cells. Such cells, when transfected, would yield one generation of highly infectious particles. The particles would carry the altered RNA instructions to produce the protein desired, but no genetic instructions for making more packages.

During the final stage of production in plain cells, the infectious elements would be trapped in the depleted host, unable to make shells in which to escape. As Huang puts it, in this scheme “the vector system is one-way.”

That can be an indispensable feature. “If you’re making human growth hormone, for example, the last thing you want around is a lot of virus,” says Huang. And he includes even the friendliest, most easily duped variety.
BANG BANG
You’re Deaf:
The hazards of recreational noise

BY KATHY HEINE
The federal government and private industries have gone to great lengths to protect the hearing of people in the workplace, yet myriad studies by Washington University researcher William Clark, Ph.D., indicate that workers of all types may be in more danger of losing their hearing off the job.

According to one of his more recent studies, which surveyed and evaluated the hearing of 413 workers at a major chemical, textile and pharmaceutical company with an effective hearing conservation program, recreational hunting and target shooting pose a greater risk to hearing than industrial noise. "The bottom line is that the people who worked in the noisy plant but didn't shoot had better hearing than the people who worked in the quiet office and did shoot," says Clark, an associate research scientist at the Central Institute for the Deaf. "It wasn't what they were doing on the job, but what they were doing off the job that caused the most hearing loss."

Clark's study, which was published in last summer's issue of Hearing Conservation News, tested the hearing levels of two groups of employees: office workers who were exposed to very little occupational noise and plant workers who were exposed to a lot of it.

All employees were asked if they had engaged in hunting or target shooting, and if they had any prior military service. A "yes" to any of these questions categorized them as a shooter.

The results of the tests showed that plant workers typically had hearing levels that were 5 decibels worse than the office workers, but that the hearing of shooters was about 15 decibels worse than that of non-shooters, Clark says. That is, the average difference in hearing sensitivity between shooters and non-shooters was twice as much as the difference between plant and office workers.

It's true that industrial noise can cause hearing loss, Clark says, but it's not the only cause. "There's a whole world of noise exposure that's present in the environment whether you're driving to work on a noisy freeway, running a chainsaw on the weekend, going to a noisy discotheque or wearing a Sony Walkman," he says. "While some of the federal laws we have are designed to protect the worker from excessive exposure to noise in the workplace, there are no laws that control the amount of noise he receives when he goes home." To make matters worse, studies of hearing in industrial populations indicate that people who work in noise tend to play in noise, that is, blue collar workers engage in noisy, non-occupational activities like hunting, use of power tools and motorcycle riding more frequently than white collar workers. "So unless you protect the individual from all noise—not just occupational noise—you're not going to protect the hearing of individuals," he says.

As Clark points out, shooting and other sources of recreational noise often exceed levels that would be considered a violation in an industrial setting.

This is a concern that he and his colleague Barbara Bohne, Ph.D., professor of otolaryngology, have voiced frequently. Their analysis of noise exposures at a Bruce Springsteen concert, reported in the Journal of the Acoustical Society of America, measured an average level of more than 100 decibels—a violation of the federal workplace law and enough noise to produce a temporary hearing loss in nearly anyone.

Ballparks are another arena where recreational noise levels can exceed federal workplace standards. During the 1987 World Series, Clark—and Minnesota experts—measured noise levels at the Hubert H. Humphrey Metrodome in Minneapolis and determined that they approached and at times exceeded federal workplace standards. That was enough to send most people, including Clark, home with a 20 to 25 decibel temporary hearing loss.

Exposures that cause temporary changes in hearing can and do cause permanent damage to the tissues of the inner ear, Clark explains. Sensory cells are killed by excessive noise exposure and replaced by scar tissue.

And while 30 percent to 50 percent of these cells can be killed before there's a detectable change in hearing sensitivity, it is important for people to realize early that even though they may think their hearing has returned to normal, their sensory cells have sustained permanent damage, and some of them have been killed.

Whether it be from overexposure at work, shooting, rock concerts, high noise levels at the ballpark or symphony—symphony concerts can reach highs of 105 decibels—the cumulative effect is that 20 percent to 25 percent of people in the United States will experience enough hearing loss
that they have difficulty hearing normal speech under quiet conditions by the time they turn 65. That needn’t be the case.

Clark and Bohne’s studies with chinchillas raised in a quiet environment indicate that hearing loss is almost entirely due to noise exposure, not to some intrinsic change associated with age. Their results, published as an abstract at the 1989 midwinter meeting of the Association for Research in Otolaryngology, corroborate earlier studies of hearing levels in isolated tribal populations. In the 1960s, a study of the Mabaan tribe in the Sudan that compared older and younger tribe members found identical hearing sensitivities. A more recent study among natives of Easter Island showed that living in civilized society has had a significant negative effect on hearing. “It’s tempting to conclude that humans—if they could just stay away from noise exposure—would have perfectly normal hearing when they’re 65,” Clark says.

Yet he still hears reports about high school dances where the loudspeakers produce noise levels of 115 to 120 decibels, and people at discotheques who leave with their ears ringing for days. “All these exposures count,” Clark says. “You have to ask yourself, ‘Why do people do that?’”

Clark guesses it has to do with the fact that high levels of noise cause increases in adrenalin flow and heart rate. “Noise is exciting,” he says. He also suspects that some people may seek out places such as noisy bars because they can pursue social behaviors that would be considered taboo outside loud environments. People would not normally approach complete strangers, lean on their shoulders and talk into their ears, he explains. But in a noisy bar it becomes acceptable, because people cannot hear one another unless they move closer together.

Hearing conservation programs in industry do their share of protecting people’s hearing, Clark believes. But if people are really to protect themselves from hearing loss, they must limit their exposure to noise off the job.

Piano tuners, he’s learned, do a great job of that. Last summer he tested the hearing levels of approximately 150 piano tuners who were attending a Piano Technicians Guild meeting in St. Louis. As a whole, the group had better hearing than industrial workers, the average man on the street and the highest international standard. “They had hearing levels that were even better than the best,” Clark says.

But then only 20 percent reported having noisy hobbies. The piano tuners are an exception, however. In other industries Clark has studied, about two-thirds of the workers report noisy hobbies. It makes sense, considering that piano tuners make their living from their hearing, Clark says. “One guy said he even wears earplugs while driving his car.”

Clark does not suggest people go to that extreme, but he does promote a reasonable sense of precaution. “It’s the total dose of noise you get in your lifetime that’s important,” he says. “If you work in a quiet environment you don’t need to be quite as concerned as someone who works in a noisy foundry or automobile factory.”

There are no laws that protect the hearing of people engaged in recreational activities, Clark says, nor should there be. “It’s one of those cases of caveat emptor, let the buyer beware,” he comments.

People should avoid excessive noise when they can and wear ear protectors while using firearms and handling noisy machinery. Clark forestalls a common complaint of hunters—that they can’t hear their prey when wearing ear protectors—by advising them to look for newly available protectors that not only protect the ears from high levels of noise, but also amplify the low level noises typically made by animals in the woods.

The ear responds to noise in much the same way that skin responds to sunlight, Clark adds. “We know that excessive exposure to sunlight can cause skin cancer, but that doesn’t mean we should stay in the dark all the time. We just need to avoid too much sun and use sunscreen when we’re out.”
Helen Aff-Drum, M.D. '34, and Dorothy Jones, M.D. '34, at registration.
Alumni Achievement Awards:

Richard David Aach, M.D. '59, is physician-in-chief and head of the department of medicine at Sinai Hospital of Baltimore and professor of medicine at Johns Hopkins University. He has distinguished himself through his viral hepatitis research, and his blood bank screening methods for non-A non-B hepatitis are used throughout the world. Since his days as chief resident at Barnes (1964 to 1965), he has been a pioneer and leader in shaping internal medicine house staff training programs in the U.S. He is considered to be a leading national advocate for interns and residents in internal medicine.

Charles Eckert, M.D. '39, distinguished professor emeritus of surgery at Albany Medical College of Union University, began his celebrated career at Washington University. He served on the surgical faculty from 1944 to 1956 and then as professor of surgery and chairman of the department of surgery at Albany. He has held leadership positions with the nation’s leading surgical societies. His voluminous list of publications includes the book “Emergency Room Care,” first published in 1967 and still available in a subsequent edition.

Jonathan Mann, M.D. '74, director of the Global Programme on AIDS for the World Health Organization, based in Geneva, previously served as state epidemiologist and chief medical officer for the State of New Mexico and deputy director of the State Health Department. In 1984 he became assistant to the director of the Centers for Disease Control’s AIDS Program, with responsibility for international programs. He established and directed the Zaire AIDS Research Project (Project SIDA), a collaborative Zairian, Belgian, American project encompassing epidemiological, laboratory, immunological and clinical research.

Alumni Faculty Awards:

Helen Aff-Drum, M.D. '34, works part time in the community health departments of St. Louis and Lincoln counties. She served in private practice from 1938 to 1964. She then worked for the Labor Health Institute, Children’s Hospital, the St. Louis County Children’s Tuberculosis Clinic, and county health clinics in neighboring Valley Park, Warren County and Troy. She was program manager of disease prevention services (especially TB) in St. Louis County, served two terms as president of the American Lung Association of Eastern Missouri and directed the St. Louis County Children’s Chest Clinic. She is associate professor emeritus of clinical pediatrics at Washington University.

Leonard Berg, M.D. '49, is director of the medical school’s Alzheimer’s Disease Research Center, one of only 10 centers in the U.S. funded by the National Institute on Aging to study the disease. He also is program director of the School of Medicine’s Memory and Aging Project, a long-term study of intellectual function in people aged 65 and older. Berg serves on both the national and St. Louis-chapter advisory boards of the Alzheimer’s Disease and Related Disorders Association. He became a professor in 1972.

Robert Ely Shank, M.D. '39, is Danforth Professor Emeritus of Preventive Medicine and retired head of the medical school’s department of preventive medicine. His lifelong commitment to nutrition has taken him all over the world. After joining the faculty in 1948, he also became a nutrition consultant to the U.S. government through its Public Health Service, National Institutes of Health, Office of the Surgeon General, Department of Agriculture, Indian Health Service, Interdepartmental Committee on Nutrition for National Defense, Department of State and President’s Science Advisory Committee. He also has served on the National Research Council.

Distinguished Service Awards:

“Michael Karl (M.D.) is a scholar to his core. That, according to one colleague, is the highest compliment that can be bestowed upon a physician. Karl is presently the director of medical affairs in the School of Medicine’s Department of Medicine. In his research field, hepatology, Karl’s studies have been published frequently in medical journals. He chaired the Committee on Services to the Elderly for the National Council of Jewish Federations from 1976 to 1981 and was appointed to the White House Conference on Families from 1978 to 1980. In St. Louis, he co-organized the Jeff-Vander-Lou Medical Clinic for indigents from 1967 to 1972 and served on the Municipal Nursing Board in the early ‘60s.

M. Kenton King, M.D., joined the School of Medicine faculty in 1957 as instructor in medicine and preventive medicine and achieved the rank of professor 10 years later. He also was physician in charge of Student Health Services at the Medical Center from 1957 to 1962. Simultaneously, in 1960 and 1961, he was acting head of the medical school’s Department of Preventive Medicine and Microbiology and, in 1961 and 1962, assistant dean of the medical school. King was promoted to associate dean in 1962 and dean in 1965. According to Chancellor William H. Danforth, “Dr. King has guided the school through tremendous growth both in its national stature and its physical plant. Thanks in part to Dr. King’s excellent leadership, this school is poised to further establish itself as a preeminent world-class biomedical research and training institution.”
The class of 1949 organizes for a class photograph.

The newest alumni from the class of 1989, Ferdinand Salvacion, M.D. (left) and Melvin Thornton, M.D., and guest Rose Siggs, enjoy the banquet.

Arnold Welch, M.D. '39 (left) and Bart Passanante, M.D. '39, remember when . . .

Here's to a wonderful time.
Bruce Broudy, M.D. (left) and Thomas Osteen, M.D., check reunion plans for the class of 1974.

The class of 1924's 65th reunion: Milo Tedstrom, M.D. (standing left) and Edward Halley, M.D. (right), both from California, and George Garrison, M.D., from Oklahoma.

Clifford Talbert Jr., M.D. '59, and classmates.

Ron Evens, M.D. '64 (left) presents Dean M. Kenton King, M.D., with his distinguished service award.
Members of the 50th reunion class (1939) receive lifetime membership awards to the alumni association.

Chuck Norland, M.D. '59, and his wife, Ingrid, at their class dinner.

Wesley Fee, M.D. '44, and his wife, Ann.
Members of the class of 1969 (left to right) Drs. Richard Wyatt, Barry Siegel and Robert Kolodny share a story at their class dinner.

Incoming Alumni President Roger Mell, M.D. '65 (left) accepts the gavel from Ron Evens, M.D. '64.

James Owen, M.D. (left) and Robert Rosenberg, M.D., discuss the future of the newest member of the medical class of 2015 at the class of 1979 dinner.

Steve Teitelbaum, M.D. '64, and Paul Manske, M.D. '64.

Irvin Kushner, M.D. '54 (left) and his wife, Enid, enjoy the chancellor’s alumni recognition breakfast with Julian C. Sleeper, M.D. '54.
The "Hot Docs" perform at the reunion banquet.

Vice Chancellor for Medical Affairs William A. Peck, M.D. (center) greets friends Richard Aach, M.D. '59, and Janet Aach.

Alumni scientific faculty (left to right) Carolyn Robinowitz, M.D. '64; Leonard Berg, M.D. '49; Virgil Loeb Sr., M.D. '44; Garrison Fathman, M.D. '69; and program chairman Steve Teitelbaum, M.D. '64.

Charlie Ruggieri (seated), the "father" of Phi Beta Pi, is greeted at the banquet.
Melvin Goldman, M.D. '43M (left) presents Chancellor William H. Danforth, M.D., with a gift for the medical archives.

Mrs. John Bowers and Mrs. William H. Danforth applaud award winners.

Father and son Guerdan Hardy, M.D. '29, and David Hardy, M.D. '64, celebrate their 60th and 25th reunions.
David Globus, M.D. '54 (left) and Edwin Carter, M.D. '54, at the dean's luncheon.

Enjoying the view from the Marriott Hotel, where the banquet was held.

Jean Rogier, M.D. (left) and Paul Hagemann, M.D., both from the class of 1934.
Sunny McCown picks out the young Allan McCown, M.D. '64, from an old freshman class picture.

Norman Arneson, M.D. '28 (left) congratulates Mike Karl, M.D., on his distinguished service award.

Donald Opila, M.D. '79, and his wife, Mary, dance "with baby."

Norman Leffler, M.D. (right) shares photos with M.D. '54 classmates Richard Harte, M.D. (center) and Cooper Ray, M.D.

Asa Jones, M.D. '42 (left) and Milo Tedstrom, M.D. '24, at the dean's luncheon.
“The world must have great minds, even as great spheres
Or suns, to govern lesser restless minds.”

—Philip James Bailey, “Water and Wood”
Michael Carpenter (right) helps Richard Paul with his hood prior to this year's graduation ceremony on Hilltop Campus.