Off Kilter: Developments In Balance Research
The Washington University Medical Center annual report for 1986 features “The Body in Sight,” a full-color poster illustrating the latest imaging technologies. The annual report and poster can be picked up at the Office of Medical Public Relations, Room 107 in Wohl Hospital. To receive a copy in the mail, call 314-362-8258 or write to “The Body in Sight,” Box 8065, 660 S. Euclid Ave., St. Louis, Mo. 63110. Available while supply lasts.
Balance Research Gets Patients Back on Their Feet

The new Vestibular and Oculomotor Laboratory helps physicians diagnose patients with equilibrium disorders, while providing basic information about people's ability to maintain balance.

Slim Chances

Internists and surgeons discuss weight-loss options for obese patients.

Heeding the Baby's Cry

Dr. Fran Porter's cry studies re-examine long-held beliefs that newborns do not feel the pain of circumcision.

Gems of Wisdom

Drs. Banaszak and Matthews use X-ray crystallography to determine the three-dimensional structure of proteins.

Damage from Drink: a Chemical Link

Dr. Louis Lange has discovered biochemical pathways through which alcohol can damage the heart, liver and pancreas.
Researchers at the School of Medicine are coordinating a recently launched, one-year, multi-institutional study of the growth hormone inhibitor mazindol for the treatment of Duchenne muscular dystrophy.

Funded by the Muscular Dystrophy Association, the study is part of a continuing effort by investigators at four major hospital-affiliated universities to identify drugs that can halt or slow the loss of muscular function in Duchenne's, a fatal disorder that exclusively affects males.

Boys afflicted with the disorder probably have a missing or abnormal protein in the muscle due to a defective gene on the X chromosome, according to the study's principal investigator, Michael H. Brooke, M.D., a professor of neurology who also directs the Irene Walter Johnson Institute of Rehabilitation. No one knows quite what this missing protein does, but the current speculation is that it may play some role in muscle elasticity.

Duchenne muscular dystrophy is usually recognized during the first two to three years of life, when parents notice that their sons just don't seem to walk right, according to Brooke. By age four or five, they have a hard time climbing stairs. By eight years of age, they must learn to walk with braces. And by age 12, many are confined to wheelchairs.

Improved respiratory therapy and surgical methods can extend the life expectancy of Duchenne muscular dystrophy patients to the early twenties, but the end is no less heart-rending for patients and their parents. In later stages of the disease, Duchenne boys are so totally dependent that they cannot even turn themselves in bed. Their muscles eventually become so weak that they may die from pneumonia.

Investigators from Washington, Ohio State, Rochester and Vanderbilt universities joined hands with the pharmaceutical industry to fight Duchenne's in 1976. Since then, they have tested four drugs, none of which has been successful.

Reports from South America last July, however, have given this group new reason for hope. Based on previous reports that Duchenne's is slowed by a naturally occurring shortage of growth hormone, an investigator from Brazil administered mazindol—which is known to inhibit the production of growth hormone—to one of two identical twins with the disorder.

Although both boys were weaker one year later, the boy who was given mazindol was believed to be significantly stronger than his brother. This not only prompted researchers to start treatment of the other boy, but also to plan a large, double-blind study of the drug.

The clinical trial involves 90 boys, 45 who will receive mazindol and 45 who will receive placebo. Patient progress will be measured by physical therapists, according to Brooke.

Regardless of whether or not mazindol works, Brooks holds that his research group has made marked progress in the last 10 years. The collaboration has resulted in more accurate ways of measuring the illness, knowledge of its natural history and genetic information that may one day be used in prenatal diagnosis.
Kilo Foundation Endows Lacy Lecture

The Kilo Diabetes & Vascular Research Foundation has endowed a pathology lectureship at the School of Medicine to honor internationally recognized diabetes researcher Paul E. Lacy, M.D., Ph.D.

The Lacy Lectureship, which will be delivered annually by a Kilo Scholar, began March 25 with an address on “Control of Proteins and Membrane Traffic in Eukaryotic Cells,” by George E. Palade, Ph.D., professor of cell biology at Yale University School of Medicine.

“The Lacy Lectureship enables internationally known figures in pathology, particularly of diabetes and vascular diseases, to visit Washington University School of Medicine,” says Emil R. Unanue, M.D., Edward Mallinckrodt Professor and head of the pathology department. “It also is an opportunity for School of Medicine researchers to interact and exchange ideas with notable scientists.”

The lecture series was named for Lacy to honor his many contributions in pathology and diabetes research and to recognize his collaboration over the years with the co-founders of the Kilo Foundation.

Diabetologist Charles Kilo, M.D., ‘59, and pathologist Joseph Williamson, M.D. ’58, both trained under Lacy, who introduced them and suggested they become partners in diabetes research.

Their collaboration led to the creation of the Kilo Foundation, which supports research on diabetic and atherosclerotic vascular disease. One of the foundation’s most important achievements has been proving the necessity of normalizing blood sugar levels in diabetics.

The foundation, which conducts its research in an independent laboratory at Washington University Medical Center, also sponsors pathology fellowships at the School of Medicine to train physicians in the care of patients with diabetes and related disorders.

Robert L. Kroc Professor of Diabetes and Endocrine Diseases at Washington University School of Medicine, Lacy is especially noted for his studies on the morphologic and metabolic events involved in insulin secretion by beta cells, transplantation of islets and the development of procedures that modify the immunogenicity of the islets, thus preventing rejection of islet transplants and the need for continuous immunosuppression of recipient animals. These basic advances have led to the initiation of islet transplantation as a possible therapeutic approach to human diabetes.

Lacy stepped down in 1985 as head of the Department of Pathology, a position he held for more than 20 years, to concentrate full-time on his research. He remains on staff at Barnes, Children’s and Jewish hospitals at Washington University Medical Center.
At the head of the class

Twenty-three students were honored for academic achievement at this year's student awards luncheon. Fred J. Balis, M.D. '89, received five awards: the George F. Gill Prize in Anatomy, the Kehar S. Chouke Prize in Anatomy, the Edmund V. Cowdry Prize in Histology, the Antoinette Frances Dames Award in Cell Biology and Physiology and a McGraw-Hill Book Prize.

Other awards included the Dr. James L. O'Leary Neuroscience Prize to John A. Butman, M.D. '89; Carl F. and Gerty T. Cori Prizes in Biochemistry to Jonathan H. Hughes, M.D., Ph.D. '91, and Miriam T. Scheingart, M.D. '89; Antoinette Frances Dames Awards in Cell Biology and Physiology to Ted D. Cox, M.D. '89, and Sanjay Arvind Desai, M.D. Ph.D. '91; the Howard A. McCordock Book Prize in Pathology and the Dr. Margaret G. Smith Award to Paula J.Chor, M.D. '88; Medical Center Alumni Scholarship Fund Prizes to Laura J. Bierut, M.D. '87 and Laura A. Rokusek, M.D. '87; the Washington University School of Medicine Academic Achievement Award to Elizabeth T. McKinney, M.D. '89; the Oliver H. Lowry Prize in Pharmacology to Iris L. Wagman, M.D. '88; and another McGraw-Hill Book Prize to Scheingart.

Lange Medical Publications Book Prizes went to first-year students, Ellen M. Reynolds and James K. Bischoff; second-year students, Robert J. Optician and Robert G. Kaniecki and third-year students, Edward W. Frank and Gary M. White.

Richard S. Brookings Medical School Prizes were given to Katherine D. Holland, M.D. '90; Kenneth M. Zabel, M.D. '89 and Timothy J. Pluard, M.D. '88; Dr. Robert Carter Medical School Prizes were received by Michael P. Steinberg, M.D. '90; Brian A. Armstrong, M.D. '89 and Jesse S. Little Jr., M.D. '88.

Diabetes study underway

The National Institutes of Health have awarded the School of Medicine an eight-year grant totaling $2,586,761 to proceed with the Diabetes Control and Complications Trial.

Washington University is one of 27 leading diabetes research centers in North America participating in the study, which is designed to determine whether highly intensive forms of treatment can prevent or stop the progression of early eye, kidney and nerve damage that occurs commonly in patients with insulin-dependent diabetes.

During the feasibility phase of the study, researchers learned that differences in blood glucose can be obtained safely with intensive forms of diabetes treatment. "We hope that we can reproduce and extend our early success as we progress from 278 to 1,400 patients studywide," says Julio V. Santiago, M.D., professor of pediatrics and principal investigator for the study. "Right now we simply don't know if patients really benefit from this form of treatment. . . . other studies have been too short or too small to show any definite benefits in terms of eyesight, kidney function or nerve damage."

To participate in the study, patients must be between the ages of 13 and 39, and have been taking insulin for more than one year but less than 15 years. Patients accepted into the study will receive their diabetes care from diabetes specialists at the Washington University Medical Center. All diabetic care and management supplies will be provided free of charge; included are frequent evaluations of eye, kidney, nerve and cardiac function as well as periodic physical examinations and a 24-hour "hotline" for advice or help in diabetes and general medical management.

Persons interested in more information should call the Washington University Diabetes Control and Complications office at 454-6025.
Researchers help define Alzheimer's

Four Washington University researchers are helping to design a new national program to develop uniform diagnostic criteria for Alzheimer's disease. The Consortium to Establish a Registry for Alzheimer's Disease combines efforts of physicians and scientists at 15 leading institutions, including all 10 federal Alzheimer's Disease Research Centers (ADRCs).

Funded by the National Institutes of Aging and coordinated through Duke University in Raleigh, N.C., the consortium also plans to establish facilities for training professional and technical personnel.

Washington University's ADRC, like other participating centers, will contribute 40 patients and 40 control subjects to the study. The four faculty members who are playing a key role in the study design are John Morris, M.D., assistant professor of neurology; Leonard Berg, M.D., professor of neurology and director of the Washington University ADRC; Martha Storandt, Ph.D., professor of psychology; and J. Philip Miller, associate professor of biostatistics in preventive medicine.

In addition to his role in the consortium, Berg has recently been elected to the National Alzheimer's Disease and Related Disorders Association (ADRDA) Medical and Scientific Advisory Board. The ADRDA is the national voluntary health agency dedicated to aiding victims of Alzheimer's disease and their families through a program of research, patient and family services, education and advocacy.

Kodner elected to surgical board

Ira J. Kodner, M.D. '67, associate professor of surgery, has recently been elected a Director of the American Board of Surgery, representing the Board of Colon and Rectal Surgery.

Kodner completed his surgical internship and residency at Jewish Hospital after receiving A.B. and M.D. degrees at Washington University. He then spent a year as a fellow in colon and rectal surgery at the Cleveland Clinic before joining the School of Medicine faculty in 1976.

In addition to his new appointment on the American Board of Surgery, Kodner holds memberships in several other professional societies, among them the American College of Surgeons, the American Society of Colon and Rectal Surgeons, the American Gastroenterological Association and the American Medical Association.

McCleskey elected Young Investigator

Edwin W. McCleskey, Ph.D., assistant professor of cell biology and physiology, is among 200 researchers nationwide to receive Presidential Young Investigator Awards from the National Science Foundation.

As such, he will receive a base grant of $25,000 each year for five years and is additionally eligible to receive up to $37,500 per year to match industrial support on a dollar-for-dollar basis. In its three years of existence, the Presidential Young Investigator Award has been given to 500 of the country's most promising young scientists and engineers, encouraging them to remain in academia.

McCleskey joined the School of Medicine faculty in November of last year after completing a postdoctoral fellowship at Yale University. His research interest is the biophysics of calcium channels, which play an important role in generating electric signals in heart muscle, skeletal muscle and nerves. In previous work he helped describe how calcium channels pass calcium.

Present research focuses on the modulation of calcium channel function by hormones and neurotransmitters.

McCleskey holds a bachelor's degree in biophysics from the University of California, Berkeley and a doctorate in physiology from the University of Washington in Seattle.
Fifteen senior medical students and three faculty members (two of them alums) were initiated into the medical honor society, Alpha Omega Alpha, during the annual banquet last January at the University Club.


Faculty initiates are: Dan M. Granoff, M.D., professor of pediatrics, Dixie J. Anderson (Aronberg), M.D. '71, associate professor of radiology and Edward J. Campbell, M.D. '72, assistant professor of medicine.

Lithostar uses sound shock waves to crush kidney stones without immersing patients in water.

Mallinckrodt tests stone smasher

The Mallinckrodt Institute of Radiology and the Division of Urology will be the first to test a new kidney stone treatment system that uses sound shock waves to crush kidney stones without immersing patients in water. One major advantage of the new Lithostar system is that it triggers localization of the stones and release of the shock waves in rhythm with respiratory motion. Because the kidneys move with respiration, accuracy of aim is improved, fewer shock waves are required and healthy tissue is preserved. Another important advantage is that, as the new method eliminates the water bath, follow-up radiographic examinations can be done without moving the patient. Lithostar, which may also be effective at disintegrating gallstones, is expected to reduce the cost of treatment. "Lithostar can be a major improvement in technology for the treatment of kidney stones," Ronald B. Evens, M.D., Elizabeth E. Mallinckrodt Professor and head of radiology, and Director of the Mallinckrodt Institute of Radiology, says, "and should be of interest to everyone—patients, because it should be less traumatic; physicians, because it should allow a less complicated treatment; and medical insurance programs, because it should be less expensive."
Ruediger Thalmann, M.D., professor of otolaryngology, has received a $1.75 million Program Project grant to pursue research on inner ear disorders that affect hearing and balance.

The five-year grant is from the National Institute of Neurological and Communicative Disorders and Stroke, part of the National Institutes of Health (NIH). The NIH awards only a few of its prestigious Program Project grants each year, and only to schools judged as having outstanding investigators, research programs and facilities. The School of Medicine currently has 20 Program Project grants.

Thalmann’s research project, “Inner Ear Fluid Dynamics in Health and Disease,” explores basic mechanisms underlying disorders of the inner ear fluids, such as Meniere’s disease. This disease is characterized by fluctuating hearing loss and by disabling attacks of dizziness that can occur without warning. Eventually, Thalmann and his colleagues hope to devise more effective medical treatment for such disorders, striving to cure dizziness and restore hearing.

Thalmann’s co-investigators on the project are Daniel C. Marcus, Ph.D., assistant professor of otolaryngology, and research assistant professors, Alec N. Salt, Ph.D., and Isolde Thalmann, Ph.D.

Thalmann received his medical degree from the University of Vienna, Austria in 1954. He came to Washington University in 1963 as an assistant professor of otolaryngology and director of the audiology division. He was named professor in 1972 and served as director of the School of Medicine’s division of experimental otology. He also is a research collaborator at the Central Institute for the Deaf, a sponsoring institution of the Washington University Medical Center.

Stephen fund created

A special fund has been created at the School of Medicine to honor C. Ronald Stephen, M.D.C.M., professor emeritus of clinical anesthesiology, who established and headed the school’s Department of Anesthesiology in 1971.

The C. Ronald Stephen Lectureship and Clinical Research Fund in Anesthesiology will be used to support clinical research in anesthesiology and to sponsor annual visits by distinguished speakers in anesthesiology and related fields.

“There have been four or five pioneers in the field of anesthesiology, and Dr. Stephen is one of them,” says William D. Owens, M.D., Mallinckrodt Professor and head of the Department of Anesthesiology. “He has engineered so many significant clinical breakthroughs that it is impossible to enumerate them. Through his research, teaching, writing and speaking engagements throughout the world, he was a major force in bringing the field to the high level that it has achieved.

Stephen came to the School of Medicine in 1971 as the Mallinckrodt Professor of Anesthesiology and head of the department, also serving as chief of anesthesiology at Barnes Hospital. After retiring from Washington University in 1980, he served five years as chief of anesthesiology at St. Luke’s Hospital.

Stephen received his medical degree from McGill University in Montreal, Canada, in 1940 and received a diploma and certification in anesthesiology from the Royal College of Physicians and Surgeons in 1946 and 1947.

The founding editor of Survey of Anesthesiology, one of the leading journals in its field, Stephen served as editor from 1957-1984 and is still a member of the editorial board. In 1982, he received the Distinguished Service Award from the American Society of Anesthesiologists.

He is a member of numerous professional societies, including the International Anesthesia Research Society, and is a fellow of the American College of Anesthesiology and of the Faculty of Anesthetists, Royal College of Surgeons. A world-renowned lecturer and writer, Stephen has written more than 160 scientific papers, with an emphasis on pediatric and geriatric anesthesia.

Dwight Towler receives fellowship

Dwight Towler, a student in the M.D./Ph.D. program at the School of Medicine, has been named the 1986 recipient of the Gerty T. Cori Predoctoral Fellowship and Prize.

The Sigma Chemical Company established the award in honor of the late Gerty T. Cori, providing support for a student in biochemistry who has displayed outstanding research abilities in carrying out his or her thesis project.

Towler was the first person to identify, characterize and purify an enzyme involved in the attachment of the 14-carbon fatty acid myristate to the amino terminal end of specific proteins. He has designed a variety of inhibitors of the enzyme from yeast and has identified an analogous enzyme in cultured mammalian cells. This work is of great importance because a number of these enzymes—including some encoded by oncogenes—play important roles in regulating cellular metabolism.
Dorothy didn't plant geraniums last spring. For the first year in memory, the pink and purple blossoms did not adorn her backyard garden. That’s because Dorothy’s lawn—like most lawns—gently dips and waves. Most people navigate such minute shifts in terrain with unconscious ease. But for Dorothy and other people with balance disorders, a walk across the lawn can resemble a frightening ride on a runaway roller coaster.

During an attack,” Dorothy says, “the world just spins. You can’t stand up; you’re completely out of control. It’s all you can do to call for help.”

Her problem was initially misdiagnosed as a viral infection, then as a heart condition, then as a clogged artery. But it wasn’t until she was examined by otologist Peter Smith, M.D., Ph.D., assistant professor of otolaryngology, who referred her for evaluation at Washington University School of Medicine’s new Vestibular and Oculomotor Laboratory, that Dorothy began to climb out of the swirling nightmare that had become her life.

The culprit was Meniere’s disease, a condition of the vestibular system—that portion of the inner ear which helps us maintain balance. Meniere’s is thought to be a progressive imbalance of pressure within the vestibular system that causes the brain to receive faulty information about balance and motion.

Dorothy’s condition, which had deteriorated over a period of 20 years, began to improve after her surgeons divided that portion of the eighth nerve in her right ear that had been transmitting bad information to the brain. “Today, I walked outside without a cane for the first time since surgery,” the 65-year-old resident of Rockford, Illinois, reports. “I think I’ll even plant geraniums this spring.”

Balance disorders like Dorothy’s are not uncommon. According to the Dizziness
A tightly controlled, closely monitored rotational chair with accurate tracking of eye movements allows Dr. Paige to better assess what's happening in the inner ear. The chair is located in the new Vestibular and Oculomotor Laboratory at the School of Medicine.
and Balance Disorders Association of America, 42 percent of adults over the age of 40 report episodes of dizziness or vertigo to their doctors. In about 85 percent of these cases, the problem lies in the vestibular system.

This system is made up of two types of organs. One is a series of fluid-filled, semicircular canals that monitor angular head movement. When the head rotates in the plane of a certain canal, the fluid presses against a neural sensor that dispatches messages to the brain about the size and velocity of the head movement in that plane.

The other type of organ consists of a disc weighted down by small stones, so that it is heavier than the fluid in which it is suspended. When the head is tilted, the disc falls in the direction of gravity, yielding specific information about head orientation in space. The disc also responds to changes in linear forces, such as the acceleration of a car.

The brain receives information from both types of organs and, in turn, sends messages to the muscles responsible for maintaining posture, balance and eye position in space. The latter assures a clear visual image despite rapid head movements.

When these organs are not functioning properly, a person may experience rapid or jerky eye movements, double vision, nausea, diminished hearing, or a spinning sensation.

Yet these organs are not the brain's only source of information about motion. Messages from the eyes, joints, skin and muscles also help maintain balance. In lieu of vestibular information, these other sources—often enhanced by adaptive mechanisms—become extremely important.

Vital to the recovery of patients with vestibular disorders, these mechanisms are the primary focus of the new Vestibular and Oculomotor Laboratory. "Our goal," says its director Gary D. Paige, M.D., Ph.D., assistant professor of otolaryngology, and ophthalmology, "is to identify and measure the patient's adaptive capabilities."

The lab opened in 1986 and recently received a five-year, $700,000 grant from the National Institutes of Health to study mechanisms underlying disequilibrium and falls, particularly in the elderly, as well as to help people with inner ear problems. For people like Dorothy, who have lost some input from the vestibular system, the lab can reliably project how much time it will take for the remaining vestibular input and adaptive mechanisms to compensate for the deficit.

"Different people have different capacities for adaptation," Paige explains. "The immediate goal of this lab is to identify and measure this capability in people who are losing, or are about to lose, input from the vestibular system."

Paige likens the process to the blind man who develops an acute sense of hearing. "When a person loses vestibular input from one ear, the plastic adaptive mechanisms can turn up the volume of input from the remaining good ear," he says. "The process is the same whether the input is lost through surgery, or in an auto accident or through natural degeneration as the person ages."

Accurate measurements of plastic adaptive mechanisms can also be used by physical therapists to help people learn to rely more on other sensory input when their vestibular systems begin to fail.

In addition, the work done by Paige and his colleagues, Malcom H. Stroud, M.D., professor of otolaryngology, and Joel Goebel, M.D., instructor in otolaryngology, can be invaluable to a surgeon who deals with the inner ear. Dorothy's physician and surgeon, Smith, has been using evaluations from the new lab for several months. "The results from the lab can give me a reasonable indication of the extent of the damage, and tell me whether one or both ears are involved," Smith says. "This is information that I use to guide me in treating patients with dizziness."

Tests at the lab give patients a better prediction of the length of their convalescence. After surgery, patients are sometimes dizzy until adaptive mechanisms begin to compensate for the deficit. "Will the patient be unable to work for six weeks or for six months?" Paige asks. "This is a question we're just now trying to answer."

The lab may even provide physicians with optical "tricks" to aid the adaptive process. Before surgery, for example, a patient may wear special glasses that optically exaggerate the movement of the head. This forces the brain to adapt. After surgery, when vestibular input from one ear is lost, the patient has a head start on the recovery process.

"Almost everyone experiences some dizziness after surgery," Smith says, "and a sense of imbalance can last for several months. So the development of these techniques to shorten that period is a tremendous help to the patient."

In the past, detailed study of the vestibular system has been difficult compared to the study of other systems. "It's relatively
The moveable platform throws patients off balance, so that Dr. Paige can observe how well they can regain their balance.

Paige spent much of last year outfitting his new lab with equipment that can evaluate and quantify vestibular function. A rotational chair that manipulates a subject's sense of angular motion, a platform that lurches back and forth under a subject's feet, a tiny tube that circulates warm and cold water through the ear—Paige's lab, for most people, resembles a high-tech fun house. But for those with balance disorders, it is much more than fun and games.

This was the case for James, a 46-year-old computer sciences student from Hillsboro, Missouri, who arrived at Barnes Hospital last October in an ambulance. He'd had a few dizzy spells in the past, but that morning at school he was so ill with vertigo that some classmates mistook his episode for a heart attack. A few days later, he was evaluated at the new laboratory.

James is certain his laboratory evaluation was worth it. Results from the lab were used to direct treatment that brought his dizziness under control with medication. These tests are more useful than in the past, according to Paige, thanks to computer techniques that allow precise control of patients' motion and equally precise assessment of their physiological response. "You can't just sit people on a record player, spin them around and ask them questions," he says. "But a tightly controlled, closely monitored rotational chair with accurate tracking of eye movements allows us to better assess what's happening in the inner ear."

"I hardly ever have attacks now," James says. "And when they come, they're far less frightening." Fear is a common denominator in the lives of Paige's patients. "Most people don't realize how terribly debilitating this dizziness can be," he says. "These people know they might become dizzy at any time, and the anxiety that goes along with that knowledge is tremendous."

Yet the work of researchers at the Vestibular and Oculomotor Laboratory is taking some of the fear out of the lives of people with vestibular disorders. And indirectly, it's putting geraniums in one backyard garden in Rockford, Illinois.
SLIM CHANCES

Beating the slender odds for weight loss
Last spring Richard Hellan weighed 333 pounds and had to admit for the first time that he was fat. When he tried to play golf, he had a hard time swinging. On business trips, he could no longer buckle standard airline seatbelts. His wife was afraid that he'd die young. And on his 40th birthday, he too felt niggling worries about his mortality. "Suddenly life didn't seem as long as it once had," he says.

Across town, Margaret McKnight, 45, dreaded the three-block walk to the supermarket. Panting, she felt that he'd die young. And on his 40th birthday, he too began when her father died. "I'd just sit around all the time and cry and eat," she says.

Obese patients typically come into Skor's office worrying about hidden hormonal or glandular conditions. During an initial exam, Skor, who treats a large number of obese patients, checks for early-stage diabetes, thyroid disease, over-production of cortisone and other physiological causes of obesity. But only 1 percent have them. For the rest, the cause is more obvious.

"The common denominator is caloric intake over and above an individual's metabolic need. Without calories, you can't form fat." Period," Halverson says.

Why does a person overeat? The answer may lie in the brain's "eating center," the hypothalamus, which responds to two circulating chemicals that control appetite: the endorphins, which stimulate eating, and their counterpart hormones, which create a feeling of satiety.

"We don't know whether obese people have a high setpoint for safety and need to eat until they reach it, or whether they have abnormalities in their circulating hormones that alter their eating behavior," Skor says. "It is clear that certain people will eat at the sight of food and not because they are hungry, while others will eat only when hungry."

Causes of Obesity

Richard Hellan blames his obesity, in part, on slow metabolism. Years ago, a doctor told him he could eat one apple and it would last him all day. Mrs. McKnight says that her problem began when her father died. "I'd just sit around all the time and cry and eat," she says.

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Heredit also plays a part. Studies have shown that twins raised in markedly different environments—one having fat and the other thin parents, one well-fed and the other poor—show similar patterns of obesity. With one obese parent, a child has a 50 percent chance of growing up obese; with two, there's an 80 percent likelihood.

Physicians hotly debate the extent to which psychology is a factor in obesity. "Clearly, some people drown their sorrows in booze, some in food and ice cream," Halverson says. "In fact, many health professionals will tell you that extreme obesity always grows out of psychological disorders. I violently disagree. Obesity, even morbid obesity, can occur in the absence of psychiatric illness or other psychological factors."

At the very least, though, his patients have developed elaborate systems of rationalization and denial. A 400-pound man will come in swearing he "eats like a bird." Another will claim that his wife is a great cook and that he would hurt her feelings by refusing food.

"Early prevention of obesity is crucial," Skor says. During childhood, fat cells proliferate twice—once in the first two years, then again at puberty. "Those of us who raise children must encourage good eating habits and physical fitness. We must get away from the idea that a fat baby is healthiest, or that kids have to eat a lot to grow up big and strong. That can create weight problems later in life."
When he should have been enjoying Paris, Richard Hellan found himself resting his painful feet. Standing for any length of time was difficult. Margaret McKnight was plagued with arthritis, which restricted her activities and made simple movement painful.

"Every organ system is placed under strain by obesity," Halverson says. "The greater the obesity, the greater the likelihood that one or more organ systems will be affected."

The health risks of obesity are substantial: cardiovascular disease, stroke, hypertension, myocardial infarction, and the list goes on. Diabetes may also develop, as well as reduced lung function. In morbid obesity, joint pain and osteoarthritis, abnormal liver function, dermatitis, infertility and loss of menstruation may result.

Obese men face an excess mortality rate of 42 percent. Across all age groups, the highest risk is in the 25- to 34-year-olds, where the morbidly obese have a twelvefold risk of dying compared to people of normal weight in the same age group. In the 35 to 44 age range, the probability drops to 5.6, and by 65 to 74 it is twofold.

Why are the youngest most affected and the oldest, least? "Possibly because morbidly obese people in the older age groups are constitutionally stronger," Halverson says, "the less strong having already died."

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**METROPOLITAN RELATIVE WEIGHT (%)**

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This Framingham Study graph illustrates the 26-year incidence of cardiovascular disease among men and women younger than age 50, and age 50 or older. The first bar in each Series represents those who are less than 10 percent overweight. The last bar in series represents obese individuals. N represents the number of people in each category.
To do that, most adults need to combine diet with a solid dose of exercise. Initially, Skor encourages patients in good health to walk regularly in indoor malls if they are bothered by cold. A patient who cuts 200 calories out of his diet each day and burns off 300 more will lose one pound a week.

"Most people need reassurance, though, that losing a pound a week is not too slow," he says. "The usual conception is that if I don’t lose five pounds a week, I haven’t lost anything." That’s not right. Losing a pound a week takes a great deal of effort.

Because of possible cardiovascular complications, Skor never prescribes amphetamines for his patients. Occasionally, he will suggest that a patient investigate surgery if that patient has conscientiously tried to lose weight, has lost some, then has reached a weight plateau. Few fall into this group. "If a patient can’t follow a diet now," Skor asks, "is he likely to follow one after surgery?"

### Surgical Options

Several times before, Richard Hellan lost weight—then regained it, plus a little extra. This time, he read about gastric restriction surgery and consulted Halverson. After screening and tests, Hellan underwent surgery last August. Within two weeks, he was back to work on a restricted diet.

Morbidly obese patients who come to Halverson must meet his strict requirements for surgery. They must not be blindly committed to surgery. They must be in good health and stable psychologically, with a history of supervised weight loss attempts and a realistic idea of what surgery can change in their lives.

"If they think the operation is a magic wand and that they can eat whatever they want afterwards, they won’t comply postoperatively as they should," he says. "I’ve also grown to be skeptical of: ‘Doctor, you have to operate because my life is in a shambles, my love life doesn’t exist and I can’t get a job. But everything will be all right if you take the weight off me.’"

He admits that this winnowing process places him on the conservative side of most obesity surgeons. The American Society for Bariatric Surgery, of which he is current president, recently formulated its own criteria for surgery: essentially any patient who is 100 pounds overweight and can come through the operation safely.

The scope of surgery, itself, has changed. Twenty years ago, physicians began performing the intestinal bypass, which set aside much of the bowel and "short-circuited" food from the upper to lower intestines in an effort to impede absorption. In 1978, a protocol initiated at the School of Medicine by Walter Ballinger, M.D., and Leslie Wise, M.D., and continued by Halverson after Wise’s departure, culminated in an article demonstrating severe long-term problems with that approach.

Surgeons have since turned to a variety of gastric restriction procedures all designed to reduce food intake by producing satiety. In gastric bypass, a line of staples closes off the top of the stomach, creating a one-ounce pouch: a nearby loop of small intestine is sewn to the pouch to absorb food. In gastroplasty, outflow from the pouch takes place through a channel into the more distant stomach.

Some two-thirds of all bariatric surgeons are now using vertical banded gastroplasty, in which a vertical line of staples creates the stomach pouch, and a band reduces the outlet tract to approximately one centimeter. Without that banding, the outlet would stretch as the patient eats, eventually allowing him to fill the entire stomach.

After surgery, patients must reduce their food intake, follow a well-balanced diet, eat slowly, stop eating when full, drink no liquids with meals and avoid high-calorie liquids. Exercise is also important. If patients continue to overeat, they may vomit frequently, stretch their pouches or even pop out the line of staples; there is also a 2- to 3-percent complication rate from stomach juice leaking into the abdomen, causing peritonitis.

Perhaps due to his careful screening, Halverson’s patients show unusually good long-term results. Two-thirds of them will permanently shed at least 65 percent of the excess weight. “Once patients reach their maximum loss, only slight regain of weight occurs in the majority,” he says.

Plastic surgery offers a number of procedures for the obese, formerly obese and the overweight. Many involve a rapidly developing technique called blunt suction lipectomy, in which physicians use high-powered instruments to suction fat from concentrated areas and re-shape the body.

“Suction lipectomy has been a major breakthrough in our ability to do body contouring and sculpting,” says V. Leroy Young, M.D., associate professor of plastic and reconstructive surgery. “We can now do it proficiently and accurately, with minimal morbidity and risk. And we have added a whole new spectrum of patients we could not treat before.”

The best known application is the removal of localized fat deposits from the abdomen and lower extremities, which resist diet and exercise.

“Saddlebag” thighs become slim, and bulging stomachs flatten with a minimum of scarring. Other parts of the body may need this treatment too, especially breasts and arms.

But liposuction is also used in the head and neck area as part of a facelift, or on an isolated pocket of fat, such as a double chin. “It has been an important adjunct to other surgical procedures,” says J. Regan Thomas, M.D., assistant professor of otolaryngology in the division of facial plastic surgery.

“We can now do a lot of work involving the removal of fat through very small incisions.”

Only a few years ago, suction lipectomy was not recommended for patients over 40 or for the generally obese. As the benefits and limitations of the procedure become better understood, however, those strictures are changing. “We can no longer say point-blank that an overweight person is not a candidate. Sometimes they are excellent candidates depending on their goals and anatomical situation,” Young says.

“All you have to do is talk to them and see how much benefit they get from it,” he adds. “I have seen patients go down as much as two sizes, and they are not going to regain fat in those areas. They get excellent results and they are usually very satisfied.”
The Gastric Bubble

The Garren-Edwards Gastric Bubble is a new weight-loss device, consisting of a plastic balloon that is inserted into the stomachs of patients and inflated to make them feel full. The bubble was recently approved by the FDA for use in patients who are morbidly obese. Fredric G. Regenstein, M.D., assistant professor of medicine, has a lukewarm response to the bubble. "It appears to have some value over the short-term, but it has not been clearly demonstrated to be effective," he says.

After the initial weight loss, regardless of the procedure or method employed, patients frequently regain weight. A disadvantage of the gastric bubble is that it must be replaced every three months. If left in longer, the bubble may deflate and migrate into the intestine or esophagus, where it can cause an obstruction that might require surgery.

As of last September, 17,000 bubbles have been inserted in the United States, yet no carefully controlled studies on the device have been published. Preliminary data compiled by investigators in conjunction with the manufacturer, American Edwards Company, was favorable. Of 59 patients, 97.5 percent reported that their appetite had decreased, while 92 percent said their weight loss was easier than with past experiences.

To insert it, the physician first examines the upper intestinal tract with an endoscope, checking for any abnormalities and noting the distance from the teeth to the upper portion of the stomach. The endoscope is then removed, and a plastic tube containing the deflated bubble is inserted through the mouth into the stomach. The balloon is then inflated with a syringe, and the insertion tube is removed. The cylindrical balloon remains free-floating in the stomach until it is punctured and removed by a physician.

Like all weight loss systems, the bubble requires a significant change in eating habits. To accompany bubble insertion, its developers provide an intense program of dietary modification, exercise, psychotherapy and support groups. A typical weight-loss program lasts from six months to a year and requires the insertion of two to four bubbles.

The Results

In five months, Richard Hellan has lost close to 90 pounds, 10 inches from his waist alone. As his size changes, he's been spending quite a bit on new suits. But he's also buying off the rack for the first time. Walks to the store are now routine for an 85-pound-lighter Margaret McKnight. Though her goal is still 160 pounds away, she is already delighted with her progress. "My friends brag on me; Dr. Skor's office brags on me," she says. "To have someone say 'oh, you've lost so much weight,' sure feels great."

One Florida study underscores some of the social and emotional benefits of post-surgical weight loss: 97 percent of patients were more hopeful and less depressed; 92 percent had more harmonious marriages; 96 percent reduced their alcohol intake and 71 percent improved sexual function.

Yet many patients don't seek help, and recidivism is high. Patient Hellan complains that many physicians are indifferent to the obese and unaware of treatment options. "I believe that 99 percent of the physicians in the U.S. don't know a darned thing about weight loss and related behaviors," he says.

In turn, some physicians say that the obese often make poor patients, blaming everyone, including the physician, for their problems. And anyway, they say, physicians are only human. It's natural to become discouraged in the face of such slender odds for success.

On the other hand, Halverson says, there are rewards. "Someone will walk into your office two years after surgery—looking normal, feeling better than they ever have and giving some indication that their lives have changed. Their bosses have suddenly promoted them, or they've started dating, even gotten married. Some, previously infertile, have pictures of their new babies. 'That's absolutely wonderful,' he says. 'And that, in the end, is probably why anybody's in it.'"
The shrill cries from the small room off the newborn nursery cannot be ignored. The baby boy lying restrained on an infant-sized table is being circumcised, and judging by the high pitch of his cry, he's in pain. He is, indeed, not taking it like a man. But then, any adult male would be anesthetized.
Each year nearly one million male babies undergo circumcision—the most common elective surgery performed in America—without anesthesia. Historically, physicians have believed that anesthesia is not only too risky, but also may not be needed for babies because their immature nervous systems keep them from feeling pain.

New evidence that newborn babies do feel circumcision is being amassed at the School of Medicine by researchers who are analyzing behavior patterns in infants.

"I studied the baby’s cry," explains Fran Porter, Ph.D., a research associate in pediatrics. "By measuring changes in the cries in response to a broad range of stimuli, we have a better understanding of what babies are experiencing.

In her study of 50 healthy infants undergoing circumcision, Porter found that the babies’ cries changed in very dramatic ways as procedures became increasingly invasive.

"There’s absolutely no evidence to support the notion that infants don’t feel pain," Porter says. "And now we have evidence that they respond to what adults would find painful." Porter’s cry studies support previous studies on circumcision that indicate babies do undergo behavioral and physiological changes when stressed.

Although the American Academy of Pediatrics and the American College of Obstetrics and Gynecology find no real evidence to support the need for circumcision and do not recommend it, the controversy over whether or not to circumcise continues. Some physicians, for example, argue that circumcised male babies have fewer urinary tract infections. According to Porter, most parents agree to circumcision for their baby because they feel it is the socially acceptable thing to do. And despite her findings that circumcision is extremely painful, she stresses that the acute pain experienced during the procedure does not last long. Computer displays of babies’ crying patterns indicate that normal, healthy, full-term babies recover within five minutes of circumcision.

Why not just anesthetize babies before circumcision? Infants, because of their small weight, can be very sensitive to anesthesia, says John E. Forestner, M.D., assistant professor of pediatric anesthesiology. "Under anesthesia, infants are very fragile with respect to respiratory distress and their ability to maintain heart rate," he explains. "Of course infants are anesthetized for major surgery, and dosages are carefully distributed and monitored—as they are with adults. But for routine procedures such as circumcision, spinal taps and insertion of chest tubes, it is more expedient for physicians to perform the procedure without anesthesia."

Forestner adds that it has been documented that local anesthetic blocks do stabilize a newborn’s heart rate and oxygen levels during circumcision, but that it is usually up to the obstetrician performing the procedure to use anesthesia. Because of the short duration of pain, most obstetricians do not use anesthesia and, as Forestner believes, will continue not to use it.

Forestner does stress, however, that the use of anesthesia for infants undergoing major surgery is more common today than it was 10 to 20 years ago. "There is ongoing work to establish dosages that will decrease the infant’s negative response to..."
an unstressed cry

anesthesia," he says. "It gets safer and safer all the time."

A baby's cry is loaded with information that adults are capable of recognizing, Porter comments. "Some might say that we've known this all along, but there's the history of treating babies as though they don't feel pain. At least acoustically, they're telling us that they do."

For her study, which was funded by the Edward Mallinckrodt Jr. Foundation, Porter recorded the vocalizations of babies throughout the various stages of circumcision: before the surgery while the baby rests in his bed, during a preparatory period when his arms and legs are immobilized by restraints, during the circumcision itself and then during postcircumcision restraint and resting periods.

The most invasive procedures, when foreskin was clamped then severed, were associated with the most statistically significant changes in several aspects of the infants' cries. In addition to becoming higher pitched, the cries also became shorter, more rapidly repeated, more turbulent and less harmonically melodic.

To measure the changes in cries, Porter produced sound spectrograms, which provide visual pictures of the sounds. These spectrograms illustrated definite changes in the pitch of the cry, its harmonic structure and its duration and pattern in response to increasingly invasive procedures. Computer displays of the cries were also generated at the Central Institute for the Deaf (CID) at Washington University Medical Center, and these confirmed the sound spectrograms.

According to Porter, the normal healthy newborn's non-stressed cry is approximately 450 Hertz (cycles per second). She equates this to the first A note above C on the piano. "The cries of the infants during the most invasive procedures reached pitches of about 2,000 Hertz, which is three full octaves above middle C and beyond the known range of most adult female vocalists," Porter explains.

The idea that babies don't feel pain is based on the fact that their nervous systems are immature, Porter says. Traditionally, she explains, it's been believed that until nerves are covered in myelin—a protective sheath—they cannot transmit an impulse, or at least can't transmit it well. Within the last five years, research on immature human nerve fibers and on nerve fibers which were partially stripped of their myelin have shown that non-myelinated fibers can conduct impulses such as pain, she points out.

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"We now know that babies are not physiologically protected against painful stimuli," she says. "Although their nerves are to some extent immature, and the organization of their central nervous system may also be immature, we should not assume that it's not processing information."


"Most physicians are aware that babies do feel pain when undergoing invasive procedures, as communicated by their small patients' cries," he commented. "But many aren't aware of the physiological changes—the abrupt increase in blood pressure, for instance, that these babies experience during the procedures. The increase in blood pressure and blood flow to the brain, in some instances, can provoke intraventricular brain hemorrhages."

"It is hoped that in the near future, infants will be provided the same treatment as older children and adults," Volpe says. "Any studies that further elucidate Dr. Porter's work, as well as studies on proper anesthesia dosages for infants, are very important."

Porter's findings could have a major impact on the treatment of premature infants who, unlike healthy newborns, can be subjected to more frequent procedures that are equally invasive as circumcision during their sometimes lengthy stays in neonatal intensive care units.

Porter recently received a two-year, $150,000 grant from the National Institutes of Health to study the impact of required, but presumably painful medical procedures on premature newborn infants in intensive care. She also will evaluate the efficacy of using local anesthesia—routinely used in older children and adults for these same procedures—to minimize pain and physiological fluctuations in the infants.

Pediatrician Richard Marshall, M.D., now at Cleveland Metropolitan Hospital in Cleveland, Ohio, collaborated extensively with Porter in her research on the reliability of crying as a mark of pain in newborn infants.
Protein crystallography holds many fond memories for Leonard J. Banaszak, Ph.D., who likes to recall his classic experience with the clawed toad, Xenopus.

Years ago, when he first started working on a protein found in egg yolk, Banaszak decided to use Xenopus as the source of eggs, because he had read that a single female toad can produce thousands of eggs within 24 hours after injection with an ovulation-stimulating hormone.

Encouraged by this bit of information, Banaszak spent almost an entire day collecting the necessary equipment and chemicals to inject a half dozen toads, only to discover that he had picked up a tub of male toads by mistake.
Banaszak never was able to grow large enough crystals from Xenopus eggs, although he has had success with the eggs of Missouri lamprey eels.

At least 50 protein crystals—each no less than .5 millimeters wide in all directions—are needed to determine the three-dimensional structure of a protein through crystallographic methods. If proteins crystallized perfectly, the necessary crystals could be derived from a one milligram sample. But in reality, it takes about 10,000 times that amount, according to Banaszak. "And finding the right conditions for growing the crystals is so full of witchcraft that people either give up or switch to another source."

"After all, you can't write a paper saying you couldn't grow the crystals," his friend and colleague, F. Scott Mathews, Ph.D., adds.

Even so, Banaszak and Mathews consider protein crystallography well worth the time and effort, as it is currently the only way to confirm the three-dimensional structure of proteins.

The three-dimensional arrangement of a protein molecule is critical during biological reactions regulated by proteins called enzymes. The substance, or substrate, that is acted upon by an enzyme fits into a specific reaction site on that enzyme like a key in a lock. The human body requires thousands of these lock-key relationships to accomplish all of its important metabolic reactions.

Banaszak and Mathews believe that a more detailed understanding of the locks and keys to these reactions, coupled with recombinant-DNA methods that alter a protein's genetic code—may one day enable man to preside as locksmith of his own body and environment. "Once you know the structure of a protein, you can begin to tinker with it," Banaszak says.

Such tinkering may someday repair genetically misshapen proteins, ready-make new proteins to work on different substrates or alter proteins to work faster or more efficiently on existing substrates, according to Mathews. Imagine new and faster-acting drugs, tastier foodstuffs and sudser soap.

The practical benefits are not likely to emerge anytime soon, however, considering that it takes one to three years just to analyze a single, large protein. "And that's only after you have good crystals," Banaszak adds.

Still, 30 years is a marked improvement over the 22 years it took the first protein crystallographer, Max F. Perutz, to determine the structure of hemoglobin. In a 1964 Scientific American article, "The Hemoglobin Molecule," Perutz jokingly admits: "Fortunately the examiners of my doctoral thesis did not insist on a determination of the structure, otherwise I should have had to remain a graduate student for 23 years."

Perutz, Mathew's mentor, shared the Nobel Prize with Banaszak's teacher, John C. Kendrew, in 1962. Using methods developed by Perutz, Kendrew was first to actually complete the three-dimensional analysis of a protein (myoglobin).

The Nobel Prize-winning methods Banaszak and Mathews learned from Perutz and Kendrew at Cambridge's Laboratory of Molecular Biology exploit very slight variations in the surface charges of protein molecules. Under certain conditions, Mathews explains, these charge differences may cause ordinarily separate molecules in a protein solution to align and attach themselves into crystals that can be analyzed by X-rays.

X-rays create "snapshots" of crystals in almost the same way that visible light produces images in a microscope. Banaszak continues. When shone through an object on a slide, light is diffracted, then magnified and refocused into a visible image by a glass lens. X-rays, similarly diffracted by crystals, pass unaltered through glass and therefore cannot be refocused into an image by a lens.

The X-rays diffracted by crystal are instead recorded as spots on film and "refocused" by a computer, which assigns numerical values to these spots on a spectrum of light to dark. Counting devices, called scintillation detectors, are often used in place of film, speeding things up by simultaneously detecting and assigning values to the diffracted X-rays.

The images that result from such "computer refocusing" resemble topographical maps, except that the contour lines depict electron density instead of height above sea level. When such map sections are photocopied onto clear plastic boards and stacked, a three-dimensional map of the electron densities within the crystal results. To make such a map, Banaszak and Mathews must make thousands of X-ray measurements, sometimes as many as 500,000 different crystal orientations.

Even with their special "goniostats" that move crystals into any possible orientation with a precision of .01 degrees of
Dr. Mathews peers through an electron density map section. Several such sections, when stacked, reveal the three-dimensional shape of a protein.

angle, it still takes at least one-and-a-half minutes for each measurement, and an additional 20 seconds to move the crystal from one position to the next.

This time adds up—one of Banaszak’s students spent an entire year just collecting X-ray data for a project requiring 200,000 measurements.

Things are getting better. This spring, Banaszak and Mathews will be participating in a consortium of five crystallographers at the Argonne National Laboratory, where new devices for data collection are 50 to 100 times faster.

One such innovation is “electronic film”—a grid of wires in a chamber that records hundreds of X-ray events at a time. Mathews has already sent three of his proteins to the national facility at the University of California-San Diego for electronic film analysis, as the proteins he studies are just “too large and take too long to do here.”

Once all of the X-ray data has been collected, refocused into topographical map sections and assembled into a three-dimensional electron density map, Banaszak and Mathews can begin to build a molecular model.

Looking down into the three-dimensional map, they try to trace a continuous line that might correspond to the backbone structure of the protein molecule. The line is then recorded as points on a grid and fed into the computer. The computer reproduces the grid as a series of electron density clouds along a stick model, which can be manipulated until it’s in line with the clouds.

This stick model can be seen in three-dimensions by wearing special stereo glasses, or by staring cross-eyed at two opposite images on the screen. Banaszak prefers the latter method, because he can switch back and forth between the computer screen and his laboratory notebook without taking the glasses on and off.

Before computer graphics, Banaszak recalls, protein crystallographers created three-dimensional models by hand, drawing electron density maps onto huge, wall-sized sheets of glass. These sheets were then stacked in rows before a gigantic half-silvered mirror and behind a light source. Standing on the other side of the mirror, a crystallographer holding up a wire model could see its three-dimensional image between the glass sheets. He would then bend the wire until its image matched up with the drawings.

Researchers rarely worked on more than one protein at a time with this method. Banaszak recalls, not only because it took so much time to hand draw the maps, but also because they took up the space of an entire lab. Computer graphics are some of the many improvements Banaszak and Mathews have witnessed in their field since they arrived at the School of Medicine in 1966. Together, these innovations have shortened the analytical process from almost a quarter of a century to a going rate of two months for a small protein, and one to three years for a large one.

To date, they have determined molecular structures for eight proteins, one of which contains 9,000 atoms, not counting hydrogen. Mathews is currently working on an enzyme important in yeast metabolism. Banaszak, on the other hand, is interested in lipid-binding proteins found in the heart, liver and other organs as well as the infamous Xenopus eggs. How these soluble lipoproteins bind lipids may ultimately be related to heart disease, which is characterized by changes in the concentrations of serum lipoproteins.

The molecular model of which Banaszak is most proud, however, hangs in his lab like a modern icon for tenacity. The 35-pound, brass-rod stick model of malate dehydrogenase, after all, required no less than five years, thousands of dollars in equipment, loads of computer time, a little “witchcraft” and the patience of a saint.

Banaszak is a professor of biological chemistry, and associate professor of cell biology and physiology.

Mathews is a professor of biological chemistry, and cell biology and physiology.
Dickey “Orients”  
Fellow Medical Students

Chandlee Dickey, M.D. ’89, will probably never use acupuncture in her medical practice. But it did relieve the pain of her patella tendonitis. And the sophomore School of Medicine student from Rocky River, Ohio, is sure there must be some physiological basis for why it works.

Dickey had the opportunity to observe both traditional and modern forms of Chinese medicine last summer, as one of the first American medical students to be hosted by Beijing Medical College in Beijing (Peking), China.

The six-year medical school is part of a medical education system that has only recently been re-instituted, according to Dickey. The Cultural Revolution from 1966 to 1976 almost completely obliterated modern medical education and other forms of Western intellectualism in China. Physicians and other intellectuals were sent to the countryside to work hard labor, or were beaten to death. And for an entire decade, medical practice fell into the hands of peasants, called barefoot doctors, with little to no medical training.

Since then, Chinese medical schools like Beijing are only now beginning to graduate their first students. At Beijing, Dickey and the dozen other medical students she led on the American Medical Student Association-sponsored trip to China found themselves highly accommodated on both medical and personal levels. “We were able to see brain surgery, mitral valve replacement, adrenalectomies and lobotomies,” she says. “We were literally able to see anything we wanted to see.” Because Dickey did not yet have any clinical experience at the time she was there, she does not feel she could accurately assess the medical equipment and facilities at Beijing. But she was impressed with how sophisticated they appeared.

Even so, the Chinese students seemed hungry for any medical knowledge from the West. Dickey and other members of her group brought some of their textbooks to share, and the Beijing students “took just about anything they could get their hands on.”

What they might have been missing in knowledge, they made up with pure intelligence, according to Dickey. On the average, she says, Chinese medical students appear brighter than their American counterparts. Education is so restricted in China, Dickey explains, that only about four percent of high school graduates go on to pursue higher education. An even smaller portion of that four percent goes to medical school. “We’re talking the cream of the cream,” she says. “There’s no way I’d ever get in there.”

Chinese medical students are accepted directly from high school into four-, six- or eight-year programs in which they study the same subjects as American students, except that they spend six months studying traditional Chinese medicine.

Dickey and her crew learned more about traditional Chinese medicine at Chengdu College of Traditional
Medicine in the capital of Sichuan. Although some Western-trained physicians don't put much credence in it, traditional Chinese medicine is offered at most medical centers. Ideally, modern and traditional doctors work cooperatively.

Traditional medicine, which has been practiced relatively unchanged for 4,000 years, diagnoses patients in terms of dialectics, according to Dickey. Diseases are characterized as hot or cold, acute or chronic, excessive or deficient. The three modes of treatment: acupuncture, muxabuston and deep massage attempt to bring these dialectics into harmony. For example, the acupuncture treatment for menstrual cramps—which are considered a problem of excess—is to stimulate so-called deficiency points on the body by inserting needles of various lengths. Muxabuston stimulates similar points with a cigar-like mux leaf, while deep massage realigns body asymmetries.

In the province of Sichuan, Dickey and the others also visited Sichuan Medical College, one of China's leading institutions for the teaching of Western medicine. Dickey, who spent her junior year of college in China during a more restrictive period from 1981 to 1982, found the Chinese young people much more open and relaxed this time than on her previous visit. "In '81 we talked about cafeteria food and bicycles," she says. "This time we talked about God, politics and the direction they want to see the new policies take." Dickey was surprised by how increased consumerism has almost eliminated the need for a black market. "We saw computers on sale, where before you couldn't even buy a tape deck. And instead of blue cotton trousers and army jackets, the women were wearing bright colors, even some pretty risqué dresses." While they seem to be enjoying their new freedoms, Dickey says, the Beijing students worry that too much consumerism may be a bad thing. "They don't want people to lose that sense of working for the common good."

In addition to the week Dickey and her tour group spent in Beijing, they spent two weeks traveling in Chengdu, home of the poet Du Fu; Kunming, where the famous Stone Forest is located; Guilin, known for its picturesque landscapes; and Guangzhou, the most important industrial and foreign trade center in southern China.

Dickey's interest in the Orient stems from her high school years, when she lived in Thailand through the foreign exchange program. Her undergraduate major at Oberlin College was, in fact, East Asian studies. She decided on medicine as a career when she enrolled in a "biology for poets class" during her senior year in college. She had been considering public health, but her biology teacher convinced her otherwise. "Someday you're going to be far from the nearest village, and some child is going to need an injection," he said. "Only you won't be able to do it, because a public health degree does not equip you to do so."

Dickey is glad that she was able to share her interest in the East with other medical students. She recommends such an experience for those medical students who "don't want their medical education to just come from a textbook." Anyone desiring such an experience, however, should be prepared to give up some creature comforts. "Students who want America should stay in America," she says. "But for those who really want to see China as it is and the people as they are, you just can't beat a tour like this."
Damage from Drink: a Chemical Link

BY LINDA SAGE

Louis Lange, M.D., Ph.D.

Countless alcohol abusers—more than 10 million in the United States alone—are dying a slow death as excessive drinking destroys liver, heart or pancreas. How alcohol damages the liver has been well understood for more than a decade, but its insidious harm to other organs has long perplexed medical scientists.

Washington University School of Medicine researchers now have evidence that a newly discovered biochemical pathway operates in organs susceptible to alcohol damage. The pathway joins alcohol to fatty acids, forming a toxin that is different from the one made from alcohol in the liver. This discovery provides the first viable explanation of how organs other than the liver sustain damage from alcohol, and it has practical implications. Detection of the toxin could help forensic scientists identify alcohol use in victims of accidents and child abuse, and studies of the pathway’s pattern of inheritance may shed light on the genetic basis of alcoholism.

Current theories about the destructive effects of alcohol metabolism focus on a compound called acetaldehyde, which is made in the liver from ethyl alcohol and reaches other organs only in minute amounts. “Our discovery points to the fact that there have to be other agents involved,” says Louis Lange, M.D., Ph.D., the study’s principal investigator, “because you can’t find a way for acetaldehyde, produced primarily in the liver, to explain why one alcoholic has pancreatic damage but no brain damage, or why another had heart damage but no damage in the pancreas. There are a lot of these cases in the literature, and if you apply current theory of how alcohol is metabolized in the liver and produces injury, you just can’t explain them. So there has to be something in an organ that makes it selectively susceptible to damage.”

In the early 1980s, Lange, associate professor in medicine and pathology, looked at the fate of alcohol in susceptible organs. Working with rabbit hearts, he made the intriguing observation that heart muscle cells metabolize alcohol by com-
bining it with fatty acids to form substances called esters. He and Stanley Mogelson, M.D., now a physician with Kaiser Permanente Group in South San Francisco, California, purified the responsible enzyme—which turned out to be a relative of the enzyme that makes esters from fatty acids and a more complex alcohol—cholesterol.

A more recent Science paper bridges the gap between this laboratory research and human disease by showing that the alcohol-derived esters are linked to drinking in humans. Lange and Elizabeth Laposata, M.D., now an instructor in pathology at the Hospital of the University of Pennsylvania, assayed the esters in samples of body fat, skeletal muscle and various organs of cadavers with different histories of alcohol use. They found that concentrations of the esters in the pancreas, brain, liver, heart and body fat were significantly higher in persons who died while acutely intoxicated than in persons who died with no alcohol in the blood or history of drinking. Moreover, the ester concentrations mirrored the levels of blood alcohol. Chronic alcoholics with no alcohol in the blood at death also had high concentrations of esters, but only in body fat. None of the subjects had esters in organs such as the kidney and thyroid that are not susceptible to alcohol damage.

“Our results show that fatty acid ethyl esters are present in high concentrations and are synthesized at high rates in human organs frequently damaged by alcohol,” Lange says.

“It seems,” Laposata adds, “that when one ingests alcohol, waves of fatty acid ethyl esters are made in certain organs. Then they disappear, whereas in adipose tissue, they stay around. And the waves compare in magnitude and frequency roughly to the amount of ethanol ingestion. So people who drink more frequently would have potentially more tissue damage.”

And the mechanism of this damage? Naturally, Lange wanted to know if fatty acid ethyl esters are actually harmful to the organs in which they form. So he looked at heart muscle, which contracts feebly in many alcoholics because it cannot obtain enough energy. In 1983, he and Burton Sobel, M.D., the Tobias and Hortense Lewin Professor of Cardiovascular Diseases in the Department of Internal Medicine, reported that the esters are capable of causing such an effect by clinging to the mitochondria that provide muscles with much of their chemical energy. When the esters bind to the mitochondria, they release their fatty acids, which interfere with energy production. Thus ethyl alcohol, by combining with fatty acids in the blood and splitting away from them in mitochondria, bring inhibitors of energy metabolism into muscle cells.

Although the pieces of the puzzle fit so snugly together, Lange doesn’t claim to have all the answers. “I think it’s extremely unlikely that this pathway accounts for everything that alcohol does,” he says. “We are just saying that there have to be factors other than damage from acetaldehyde involved. The model that is going to explain alcohol-induced organ damage has to be based on a widely prevalent pathway that takes many years to produce a toxic effect, because an awful lot of people can develop endorgan damage if they drink enough.”

Meanwhile, the discovery has opened up new fields of research. For pathologist Laposata, it raises the possibility of establishing alcohol use as a cause of death. “Individuals often have heart disease of no known etiology or other diseases that may be related to alcohol ingestion,” she says. “By being able to test samples of subcutaneous adipose tissue for fatty acid ethyl esters, one could show that there has been long-term ethanol exposure. Before this, it was all word of mouth, and one could not document a history of drinking.”

Such a test would also be useful to forensic scientists, Laposata says. For example, some parents regularly sedate their children with alcohol. But if the children die with no alcohol in the bloodstream, such chemical abuse cannot be proven. Assaying fatty acid ethyl esters could reveal prior alcohol intake and even indicate its extent.

Lange’s top priority at present is to see if the inheritance pattern of the ester-forming enzyme is related to that of alcohol abuse. He is collaborating with Robert Cloninger, M.D., professor of genetics and psychiatry, who has studied the inheritance of alcoholism in adoptees. Cloninger has identified two inheritance patterns for alcohol abuse. One affects both men and women and is strongly dependent upon the environment in which a child grows up. The other affects mainly men, who have a nine-out-of-ten chance of inheriting it if their biological fathers abuse alcohol.

Research on susceptibility to alcoholism has concentrated on the inheritance of various forms of the liver enzyme that makes acetaldehyde from alcohol. But Cloninger and Lange believe that inheritance patterns of other enzymes—such as the ester-forming enzyme—should also be studied. Therefore they are looking for variations in level or subtype of the new enzyme in the white blood cells of 300 families attending Jewish Hospital’s alcohol clinic. Each of these families has at least one alcohol abuser.

“If you could show that there was a genetic link between this pathway and any alcohol abuse syndrome,” says Cloninger, “then you could do a blood test and tell individuals whether or not they were predisposed to a certain problem with alcohol.”

The researchers have not established a link between fatty acid ethyl esters and craving for alcohol. But, unlike acetaldehyde, the esters are formed in the brain. “The main problem in alcohol research is why people drink to excess, which comes down to how alcohol can affect brain function and therefore behavior,” Lange says. “This is the only alcohol metabolism pathway that has been described in the brain, so I would say that some basis has been laid for examining it.”
Life as the Patient’s Advocate

The high cost of medical school, exorbitant malpractice insurance premiums, DRGs and a purported physician oversupply have caused many to take a dim view of the future of medical education, but not Ceylon S. Lewis Jr., M.D. ’45.

When asked why young people should go into medicine today, the 66-year-old cardiologist and President of the American College of Physicians replies: “For the same reasons I did when I decided to go.

“There was the thrill and intellectual stimulation of the biomedical sciences for one,” he says. “And I viewed medicine as a profession in which I could have a primary relationship with other individuals and be of help to them.” Lewis also admits that the status afforded physicians by society was not by any means an unpleasant aspect.

“These things are all still true,” he asserts. “A lot of young people are concerned that medicine will be different than it used to be as it becomes more corporate—when in fact, the basics of medicine haven’t really changed,” he says. “Tomorrow’s physicians will learn to live with these economic changes, while continuing their role as patient advocates.”

Lewis himself has demonstrated a vociferous patient advocacy—through his own cardiology practice of 36 years, his introduction of new heart care technologies in his community and the Third World, and through his numerous contributions to medical education.

Lewis’s own medical education began at Washington University School of Medicine, where he says he was “impressed with the degree to which the intellectual atmosphere was brought to bear on improving the level of individual patient care.” At the School of Medicine, Lewis met hematologist Carl Moore, M.D., who exhibited the “care and concern for each individual patient” that Lewis later used as a model for his own practice. There he also met his wife, Marge, whose father was president of Missouri-Pacific Railroad.

Upon receiving the M.D. degree, Lewis studied under one of Moore’s colleagues, Maxwell Wintrobe, at the University of Utah in Salt Lake City. But after three years with Wintrobe, Lewis decided to switch from hematology to cardiology because he “preferred looking at electrocardiograms to looking into a microscope.”

After completing his cardiology fellowship in 1951, Lewis returned with his wife to his home state of Oklahoma, where he set up the first heart catheterization laboratory in the Tulsa area, helped establish the University of Oklahoma Tulsa Medical College teaching facility and worked to attract more physicians into Tulsa residency programs. Vital to this recruitment were the
Dr. Lewis talks with medical students at University of Tulsa Medical College. A 1945 graduate, Lewis is current President of the American College of Physicians. (photo credit: Graphic Arts Department, University of Tulsa Medical College)

physician manpower studies he pioneered, which correctly predicted that physicians completing their residencies in Oklahoma would tend to stay in the state. As chairman of the Legislature’s Physician Manpower Training Commission, Lewis used this information to ensure matching funds for training primary-care physicians.

Long before the advent of DRGs, Lewis helped devise the Oklahoma Utilization Review System, which in 1975 resulted in a pilot program for the state that dramatically decreased the number of Medicare claims denied, the number of hospital days utilized per 1,000 possible Medicare and Medicaid beneficiaries and the actual number of hospital claims.

Beyond these and many more contributions to his own community, Lewis has been instrumental in improving patient care on a national, even international level. As President of the American College of Physicians, Lewis has worked to improve continuing medical education by incorporating computers into self-assessment programs so that, using floppy disks, physicians can review and evaluate their knowledge of current medical developments.

On a global level, Lewis has made several trips for the Presbyterian Medical Mission Fund, Inc., surveying the development of community health programs and maternal-child health clinics in Third World countries. His work with the Mission has taken him and his wife to Egypt, Ethiopia, Cameroon, Sudan, Afghanistan, Pakistan, Nepal and Thailand. One of his most memorable trips was a two-month stint at a 400-bed teaching hospital in Miraj, India, where he led a cardiac clinic, taught a course in electrocardiography and set up a cardiac catheterization lab.

Yet the most important thing in Lewis’ life, he says, is his family, which includes three children and six grandchildren. During family gatherings at his home-away-from-home on Grand Lake in the Cherokees, he often finds himself in the role of water ski instructor. “At this age, I’m spending more time as a teacher than a doer,” he says.
J. Robert Mangum, M.D. '38, has spent a total of 18 months at church-related hospitals of New Guinea, Central India and the Republic of South Africa since his retirement in 1979.

T. Eugene Ruff, M.D. '38, retired in 1977, but writes that he is still very active in community organizations, among them the Shriners, Kiwanis and the Genealogical and Historical Society.

Benjamin Milder, M.D. '39 is editor of Time Oph, a poetry section in the medical journal, Survey of Ophthalmology.

Roland R. Cross Jr., M.D. '40, retired from his position as associate clinical professor and chairman of urology at Loyola University last June. He writes, "Loyola has a rule—"Age 70 and out"—so I'm now out." He still spends two hours a day at Hines Veterans Administration Medical Center as a urology consultant, and last summer he and his wife, Helen, spent three weeks touring the Orient.

Melvin Gibbel, M.D. '42, retired last year from his general surgery private practice in Arlington Heights, Illinois. He now lives at Keowee Key in Salem, South Carolina.

C. Barber Mueller, M.D. '42, is Vice President elect of the American College of Surgeons.

Jack D. Weaver, M.D. '42, retired in October 1986, after practicing in the same office started by his grandfather, Dr. J. Dorsey, in 1896.

James H. Cravens, M.D. '43, was recently elected to a three-year term as president and chairman of the Illinois Chapter of the American Academy of Pediatrics.

Don E. Miller, M.D. '44, retired from practice in Wichita, Kansas and moved to Tampa, Florida.

Robert A. Huckstep, M.D. '48, was voted the 1986 Employee of the Year at Farmington State Hospital #4 in Farmington, Missouri and declared Missouri State Employee of the Month for December 1986.

J. Neal Middelkamp, M.D. '48, is President elect of the American Board of Pediatrics. He also was the first Wyeth International Visiting Professor of Pediatrics to Southeast Asia, participating in seminars before Singapore, Malaysian and Thai pediatric societies, as well as lecturing and leading rounds at medical schools in those countries.

Warren L. Felton II, M.D. '49, has been named medical director for the Oklahoma Foundation for Peer Review.

William N. Chambers, M.D. '50, withdrew from active clinical practice and teaching last year, but is still active in forensic psychiatry. He lives alone now since the death of his wife, Fran, and spends a good bit of his time in France—"beyond English and the tourist curtain when possible."

Wendell C. Kirkpatrick, M.D. '51, has two sons who graduated from medical school last year—Donald, M.D. '86, and Jeff, M.D., a graduate of the University of Washington in Seattle. His son, Steven, graduated from Washington University School of Dental Medicine in 1982.

Oscar Pinsker, M.D. '51, writes that his wife, Bonnie, died October 15, 1986.

Harry S. Jonas, M.D. '52, is the new author of the nationally read newspaper column, "Woman's Health," and President of the American College of Obstetricians and Gynecologists.

Paul E. Siebert, M.D. '52, retired from full-time practice as chief of radiology at Denver Administration Hospital in August, 1985. Last year he was appointed clinical professor at University of Colorado Medical School.

Wayne O. Buck, M.D. '55, is the new president of the Western Occupational Medical Association, which represents physicians in California, Nevada, Utah, Arizona and Hawaii.

Harriet S. Kaplan, M.D. '56, is president of the section on psychiatry for the Los Angeles County Medical Association.

Byron J. Masterson, M.D. '58, was presented an Award of Excellence by the Association of Medical Illustrators for his second edition of Manual of Gynecologic Surgery.
Richard D. Aach, M.D. '59, has been elected to the nine-member Governing Council of the Association of Program Directors of Internal Medicine.

Floyd E. Bloom, M.D. '60, was recently elected to the Council of the Institute of Medicine and to the Board of Directors of the American Association for the Advancement of Science.

Dick D. Briggs Jr., M.D. '60, was elected President of the Association of Pulmonary Program Directors.

John D. Rich, M.D. '62, was appointed chief of plastic surgery for the U.S. Army and consultant in plastic surgery to the Surgeon General.

Jeannie J. Kinzie, M.D. '65, recently became an associate editor of the International Journal of Radiation Oncology, Biology, and Physics. She also was recently made a consultant to the Food and Drug Administration's Center for Devices and Radiological Health.

Michael Treister, M.D. '67, has been elected President of the medical staff at St. Mary of Nazareth Hospital in Chicago, Illinois.

Earl D. Hearst, M.D. '69, practices psychiatry in Virginia Beach, Virginia and writes investment columns for Surroundings magazine in Norfolk, Virginia and Style Weekly in Richmond.

W. B. Jerry Younger, M.D. '69, is an assistant physician in the medical oncology division at Massachusetts General Hospital and an instructor in medicine at Harvard Medical School.

David J. Carlson, M.D. '73, has recently completed his term as president of the medical staff at Deaconess Hospital in Evansville, Indiana.

Eugene M. Shepherd III, M.D. '73, is a neurologist in Melbourne, Florida. He has three sons—15-, 12- and 9-years-old—and writes that he is “still a wonderful person despite my incredible success.”

Roslyn K. Yomtovian, M.D. '74, who is medical director of the St. Cloud Hospital Blood Bank in St. Cloud, Minnesota, writes that the blood bank’s autologous blood program was featured on “CBS Morning News” last October.

Gregory L. Hemphill, M.D. '75, holds ophthalmology teaching appointments at several medical schools, including the University of Texas, Baylor and Texas A & M.

Robert G. Armbruster, M.D. '77, is director of obstetrics and gynecology at Lawrence Hospital in Bronxville, New York.
Gary L. Baker, M.D. '77, has been named a Diplomate of the American Board of Surgery, making him the 10th individual to be certified by both the American Board of Surgery and the American Board of Internal Medicine. Baker is the Amelia Brown Frazier Fellow in Reconstructive Microsurgery at the University of Louisville.

Jonathan William Horstmann, M.D. '77, is a family physician in private practice with three other physicians in San Bernardino, California. He lives in Redlands with his wife, Nancy, and daughters, Amy and Melanie.

Robert Eliot Silverman, M.D. '78, and Randi Leavitt, M.D. '78, were expecting their second child in February. Silverman is chief of the Diabetes Programs Branch at the National Institutes of Health in Bethesda, Maryland. Leavitt is senior investigator in the laboratory of immunoregulation at the NIH.

Stephen K. Bradley, M.D. '79, and his wife, Betsy, have a new baby daughter, Lauren Elyse Bradley.

Raymond A. Roden, M.D. '79, has been elected to the American College of Cardiology.

Patrick D. Gerstenberger, M.D. '80, has been practicing gastroenterology in Durango, Colorado since August 1985. When he's not skiing or otherwise enjoying the San Juan mountain country, he's active on the voluntary faculty at the University of New Mexico and University of California—San Francisco. Suzanne Lee, M.D. '81, recently joined the medical staff at Saint Margaret Hospital in Hammond, Indiana. She also has a private practice in ophthalmology.

Raymond W. Phillips, M.D. '81, is chief of internal medicine at General Leonard Wood Army Community Hospital. He and his wife, Marian, have two daughters: Rachel, 4, and Laura, 2.

Jeffrey V. Winston, M.D. '81, is an ophthalmologist for a multi-specialty group in Orange County, California. His wife's name is Susan.

Beverly Logan-Morrison, M.D. '82, is practicing internal medicine in St. Louis, while serving as a faculty member for the residency program at St. Luke Hospital.

T. Chelimsky, M.D. '83, writes "Mayo's neurology program is the most outstanding I have seen anywhere, and I'm enjoying it thoroughly."

Michael Kastan, M.D. '84, is doing a clinical and research fellowship in pediatric hematology and oncology at Johns Hopkins Hospital. He and his wife, Kathy, are enjoying their first child, Benjamin, who was born November 4 of last year.

Barry J. Linder, M.D. '84, was recently selected by NASA as executive secretary for the Clinical Medicine Study Group in the Life Sciences Strategic Planning Study Committee of the NASA Advisory Council.

Edward R. McCluskey, M.D. '85, is continuing his medicine residency at Barnes Hospital.

Judith Mclear, M.H.A. '83, recently had her design for the USS Louisville—one of the fastest attack submarines in the world—selected for the ship's official insignia. Her design was picked from more than 300 entries in a contest sponsored by the Chamber of Commerce in Louisville, Kentucky.

Three couples have established named loans through the School of Medicine's new Medical Scholars Loan Program. They are: Dr. and Mrs. Edward J. Kloess, Dr. and Mrs. Robert F. Merger and Drs. Barbara and Julius Shier.
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Nine School of Medicine faculty members are traveling to Tokyo this April to inaugurate a research exchange agreement with the Tsukuba Life Science Center at the government-sponsored institution of RIKEN. Washington University is the first American university to form such an agreement with a Japanese research institution. Extensive coverage of this new research tie is planned for a future issue of Outlook.