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HOPKINS CONTRIBUTIONS TO SCIENCE AND CLINICAL MEDICINE

Hopkins contributions to medicine include dozens of firsts. Among them:

Combined hospital and medical school — In the late 1800s, the concept of designing a hospital as the teaching laboratory for the medical school, and by extension, as part of a university, was the novel and wise contribution of Johns Hopkins and served as a model for all future academic medical institutions.

Medical education elevated to the graduate level — The Hopkins School of Medicine, opened in 1893, drastically reformed medical education by demanding a college degree for admission, requiring applicants to have mastery of the basic sciences, and offering a four-year graded curriculum. Both men and women students were accepted. While most medical schools simply lectured students, Hopkins professors took them into the wards to observe diseases they were learning about, letting them actively care for patients in their senior year. Until The Johns Hopkins University opened its School of Medicine, most medical schools were proprietary institutions, which "taught" students for a period of approximately eight months, then sent them out to practice medicine without having so much as seen a patient. As late as 1900, less than 20 percent of the medical colleges even required a high school diploma.

Research a part of medical education — Hopkins attracted the best faculty available in the world, men capable not only of teaching but of developing new knowledge through research, then freed them of the responsibility for earning a living from the practice of medicine by putting them on full-time salaries, a radical departure from the tradition of employing local practitioners who taught on a part-time basis. Medical research by both faculty and students was part of the educational process.

Introduction of postgraduate, specialty training — Before Hopkins opened, specialty training after medical school — through internship, residency or research fellowship — was virtually unknown in the United States. Hopkins set up a pyramidal training system, with interns and assistant residents in a particular field guided by a chief resident who in turn learned from the chief of service, or department head, assuring expert supervision. Residents, in the early days, lived under the Hospital's dome. Almost all teaching hospitals eventually adopted the system, which is still in use today.

Halsted radical mastectomy for breast cancer — Surgeon William S. Halsted developed his famous operation for breast cancer in 1889. The technique, which included removal of the tumor, all the breast tissue, the pectoral muscles and the lymph glands in the armpit, was the most extensive procedure for breast cancer ever attempted; when it became clear that Halsted's patients were surviving after the operation, the procedure was quickly adopted all over the world. Halsted's own five-year cure rate rose from 20 percent to 45 percent, and then

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to 72 percent when he was able to treat the disease before it spread to the lymph glands.

Standard procedure has since been modified; the major pectoral muscle rarely is removed today even in radical mastectomies. Halsted's suggestion that the operation be performed immediately when a biopsy proves positive has won wide acceptance.

First American use of X-rays in surgery — On Nov. 6, 1896, a woman was rushed to Hopkins after her combative bartender husband shot her. The bullet seemed to have lodged somewhere in her spine, doctors could tell, because she had no feeling on one side, and the other showed signs of paralysis. But because bullets tend to wander, neurosurgeon Harvey Cushing had no idea where the bullet had finally landed. So he brought in his fluoroscopy tube — a new piece of equipment he had brought with him from Massachusetts General earlier that year, much to the consternation of his Harvard colleagues — and took several X-rays, each of which took about 35 minutes. The images pinpointed the bullet at C6, her sixth neck vertebra.

Widely considered the founder of modern neurosurgery, Cushing was a junior resident under William Halsted and practiced at Hopkins from 1896 to 1912. During his training, he picked up two Halsted hallmarks: he used rubber gloves, and he was exceptionally careful to seal off blood vessels, as the biggest drawback to brain surgery in those days was that patients often bled to death during surgery. Cushing's meticulousness made him so slow, in fact, that a general surgeon, watching him, once teased: "Harvey, do these tumors ever recur on you during the operation?"

Cushing also was the first to identify the pituitary as the master gland, and to link a variety of clinical disorders to trouble in the pituitary. He also is credited with introducing a new practice in surgery: recording of blood pressure.

First perineal prostatectomy — In 1902, Hugh Hampton Young designed one of the best early treatments for what in those days was politely called "male weakness" — bladder problems caused by an enlarged prostate. Just 10 years before, castration was the treatment in vogue, and thousands of men had their testes removed. Young considered that method far too extreme, and anyway it didn't seem to work for very long, so he tried simply shelling out the knotty excess tissue in the prostate gland, leaving the healthy part of the prostate intact. The procedure not only restored older men's ability to void, but it was rarely fatal. By contrast, suprapubic prostatectomy, the most favored operation at the turn of the century, carried a mortality rate of 20 percent. Young performed his transurethral prostatectomy on grateful patient "Diamond Jim" Brady — so grateful that he gave the money to build an entire urology institute (see chapter on famous patients).

First culture of living cells outside the body — Test-tube babies owe their births in no small way to an anatomist named Ross Granville Harrison who coaxed a bit of embryonic tadpole to grow on a drop of lymph fluid. This event, in 1907, was the first success of the so-called in vitro (on glass) technique — also known as tissue or cell culture — which scientists now use as much as the microscope. The technique provides a stunningly simple way to study living cells and tissue with as few confounding variables as possible. As well as opening the door to in vitro fertilization and to the development of the polio vaccine, the method holds out hope for routine harvesting of healthy skin for compatible skin grafts for burn victims.

Development of the first continous cell-culture line, HeLa — The name HeLa memorializes a young woman named Henrietta Lacks, whose cervical biopsy lives on in research labs all over the world. HeLa,

which has endured as the first established cell line, was cultivated in 1951 by George Otto Gey, director of the tissue culture laboratory in the Department of Surgery. It was used to determine much of what we know about human cells and remains a standard cell for many studies, particularly in the fields of molecular cell biology and genetic disorder.

First American children's hospital built as part of an academic medical center — Pediatrics was generally considered part of internal medicine, not a field in its own right, and no children's clinic in the country was set up for pediatric instruction and research until 1912, when the Harriet Lane Home for Invalid Children opened at Hopkins. (The interest of the benefactors, Henry Elliott Johnston and Harriet Lane Johnston, arose from the loss of their two sons to rheumatic fever.) John Howland, the clinic's first head, is credited with modernizing the field of pediatrics by promoting biochemical studies for the investigation of disease in children. The clinic has evolved into the 11-story Johns Hopkins Children's Center, which serves as the regional trauma center for children.

First psychiatric clinic in a general teaching hospital — Founded by Pennsylvania steel magnate Henry Phipps in 1913, the Phipps Psychiatric Clinic was instrumental in revealing the role of personality problems in physical as well as mental illness, and in launching a new emphasis on looking for biological factors in mental illness. The clinic is now part of the Adolf Meyer Center for Psychiatry and the Neurosciences, reflecting Hopkins' emphasis on weaving together interrelated specialties.

First development of a method of renal dialysis — John Jacob Abel, Hopkins' first professor of pharmacology, developed an artificial kidney first used successfully on a rabbit in 1913 — 33 years before a dialysis technique was tried on humans. Abel's invention consisted of a cylinder filled with a series of collodion tubes, an idea he had described to friends over lunch a year earlier. Onto the table he had rolled out pieces of bread, to show how arterial blood from an animal would flow through these tubes, impurities would be diffused out into a saline solution and the cleansed blood would be injected back into a vein. (About that time, Abel also came up with the idea for a blood bank for operating-room emergencies, a plan that took 25 years to institute.)

Development of ventriculography, the forerunner of modern brain imaging — In 1917, it was practically impossible to see a brain tumor without digging for it; the cancers were rarely distinguishable on X-ray plates. Brain surgeon Walter Dandy figured out a way to improve the images, by pumping air into the liquid-filled cavities of the brain, and ventriculography was born.

Discovery of vitamin D and its role in preventing rickets — To figure out what causes rickets, scientists had to figure out what keeps calcium salts from being deposited in bone and cartilage. After trying about 300 experimental diets on rats, scientists working in 1918 on a joint project of the pediatrics department, under John F. Howland, and the School of Public Health's biochemistry department, under Elmer V. McCollum, determined that lack of a fat-soluble vitamin, which they called vitamin D, was to blame.

Crystallization of insulin — In 1926, after insulin was discovered, the nation's first professor of pharmacology, John Jacob Abel, isolated the hormone in a chemically pure crystalline form and proved that it is a protein. That was an important discovery, as until then it wasn't thought that proteins could act as enzymes, or that the protein

Abel isolated could perform the functions of a hormone.

Discovery of biorhythms — Psychobiologist Curt Richter coined the phrase "biological clock" for the cyclical internal mechanisms that drive people's eating, drinking and sexual behavior. His interest was kindled as a graduate student when he noticed that rats, which are active at night, doze during the day even if they are kept in total darkness and have no external cues about night and day. Richter described mammals' internal clock in 1927, as part of his doctoral thesis.

Prevention of rheumatic heart disease — Well into the 20th century, large numbers of children died from rheumatic heart disease until Caroline Bedell Thomas earned her place in history with the discovery of the value of sulfanilamide in the treatment of strep throat to prevent rheumatic fever. She found that sulfanilamide interrupted the disease-damage-disease cycle that frequently caused premature death from this heart disease. Other antibiotics since have replaced sulfa drugs, but the concept of preventing heart disease was established.

"Blue baby" operation developed, opening heart surgery era — No one dared operate on the cardiovascular system until 1944, when surgeon Alfred Blalock rerouted a major artery coming out of a baby's heart and connected it to one going into her lungs. The surgery, suggested by pediatric cardiologist Helen Taussig as a way to correct a congenital defect that decreased blood flow to the lungs, has since saved thousands of babies and paved the way for modern heart surgery.

Discoveries concerning such drugs as Dramamine, Adrenalin and Heparin — Dramamine's powerful protection against motion sickness was discovered by a fluke. Allergist Leslie N. Gay had prescribed a new antihistamine known as compound 1694 for one of his allergy patients in 1948; he knew he was onto something when the woman returned, telling him the pills hadn't cleared up her hives, but certainly seemed to wipe out the nausea she usually felt on the trolley car. Intrigued, Gay stuck the woman with some sugar pills and sure enough, the next time he saw her, fresh from her ride to the Hospital, she was ashen-faced and deeply disappointed. After a few more tests, Gay got in touch with General Omar Bradley, who agreed to let Gay test the drug's suspected stomach-settling property on troops ill from motion sickness on ocean crossings. The young men were delighted; not only did this new potion prevent nausea, it settled a stomach that was already overcome. Thus was Dramamine introduced.

Adrenalin, also known as epinephrine, owes its discovery largely to pharmacologist John Jacob Abel, who in 1897 was the first to isolate the hormone from the adrenal gland. Purified by the Japanese chemist Takamine, Adrenalin was then used therapeutically.

Heparin, the anticoagulant used to prevent blood clots during heart surgery, among many other uses, was isolated in the laboratory of Hopkins' first physiology professor, William Henry Howell, aided by a medical student, Jay McLean. The work was done after Howell noticed that mammals are the only vertebrates whose plasma contains clotting factor — and therefore must also contain anti-clotting factor.

Identification of three types of polio virus, making the polio vaccine possible — One of the top polio research teams in the country, David Bodian and Howard Howe, isolated three versions of the virus in 1949, and showed that they were genetically stable, unlike influenza virus. The team, joined by Isabel Morgan, daughter of Nobelist Thomas Hunt Morgan, already had shown that immunity could be induced ar-

tificially in monkeys; later, Bodian showed that gamma globulin contained antibody to all three types and could be used to immunize animals. The work led to development of polio vaccines for people.

Development of closed-chest heart massage, or CPR — Cardiopulmonary resuscitation, which has saved thousands of heart attack victims, was devised by accident. During the mid-1950s, an electrical engineer, G. Guy Knickerbocker, was testing a defibrillating machine — another Hopkins invention, which uses electrodes to shock the heart into regular rhythm through paddles placed on the patient's chest. Knickerbocker, working in William Kouwenhoven's lab, had hooked up an unconscious animal to a blood pressure monitor and noticed that the animal's blood pressure rose simply from the weight of the paddles on its chest. Intrigued, Knickerbocker, Kouwenhoven and James Jude found that they could keep a cardiac-arrested dog alive by rhythmically pressing on its sternum with 80 pounds of pressure once every second for 10 minutes. The day after Valentine's Day in 1958, Hopkins surgeon Henry T. Bahnson tried the technique to revive a 2-year-old child whose heart was beating erratically. The next morning Bahnson told Kouwenhoven: "Bill, your theory works."

Organization of the human gene map — Since the early 1960s, pioneer medical geneticist Victor McKusick has helped lead the worldwide effort to assign genes to their proper chromosome. The map now includes thousands of genes, with several now added each week. Knowing the location of faulty genes and normal genes to which they are linked is a crucial step toward eventual diagnosis and therapy for inherited diseases.

Pioneer in bone marrow transplantation, often the only cure for many people with blood diseases — George Santos became known for use of transplants of blood-forming bone marrow to treat leukemia, aplastic anemia, and certain genetic disorders. In 1968, he was one of the first scientists in the country to do marrow transplantation in humans. He was also one of the first researchers to realize the importance of using immunosuppressive drugs in marrow transplants to avoid graft-versus-host disease and marrow-graft rejection, two serious and often fatal complications of marrow transplantation.

Identification and elimination of leading causes of blindness — Ophthalmologist Arnall Patz revolutionized eye surgery by turning to the laser in 1969 to seal leaking blood vessels for some of the most common causes of blindness, including diabetic retinopathy, macular degeneration and certain forms of glaucoma. Patz has encouraged the use of portable laser machines in rural areas and developing countries to fight blindness. He also discovered that excess oxygen pumped into incubators of premature infants was responsible for an overgrowth of blood vessels in the eye. This observation curbed the leading cause of blindness in children.

First total knee replacement — Lee H. Riley, now director of the Department of Orthopedic Surgery, was a leading member of a team that developed the first practical, artificial total-knee joint, used initially on a patient at Hopkins on May 26, 1971. The device's design served as the model for several subsequent total-knee replacements.

Development of increased accuracy and reduced radiation of X-rays — Long before the present-day discipline of biomedical engineering emerged, Russell H. Morgan combined his knowledge of mathematics, physics and engineering to create a timer that automatically regulated X-ray exposure.The Morgan timer reduces the need for retakes and increased the ac-

curacy of each X-ray film for optimal interpretation. Morgan also adapted television technology to enhance X-ray images, again with the result of reducing radiation exposure and improving image. Morgan's work with image intensification proved as revolutionary in the '50s as CT scans were to be in the '70s.

Discovery of the opiate receptor — Using radioactive tags, neuroscientist Solomon Snyder and colleagues at Hopkins and in Britain in 1973 traced the neural pathways that opiates travel to reach receptors where these chemicals deliver their painkilling messages to the brain. Snyder's discovery, a hallmark in neuroscience, has driven efforts to identify and measure the brain's entire chemical communication network. He showed that brain cells "talk" to one another through the exchange of neurotransmitters, which act on receptor sites on the surface of cells the way keys fit into locks. These messages are responsible for every brain-controlled process, from thinking and breathing to addiction, pain control, anxiety, love and mental illness.

Discovery and use of restriction enzymes as a chemical scissors to cut genes — Molecular biologists Daniel Nathans and Hamilton O. Smith won the 1978 Nobel Prize in Medicine, shared with Werner Arber of Switzerland, for finding and using restriction enzymes to divide DNA molecules at specific locations. The discovery came about when Smith noticed that something in his test tube was slicing apart the genes he was studying in very specific ways. Instead of tossing out his experiment as a flop, Smith related his observation to Nathans. Both realized that this "something" could be a so-called restriction enzyme, the type of specialized gene cutter that Arber had been seeking. Nathans showed that it was, using the cutters to analyze a cancer-causing virus. The enzymes can be used to map the complex messages of the gene strand; cut-up fragments can be used to determine the order of genes on chromosomes, to analyze the chemical structure of genes, and to recombine genes by chemical means. The three men's findings launched the field of recombinant DNA and genetic engineering, offering new leads for prevention and treatment of malformations, hereditary diseases and cancer. Already, the discovery has led to the manufacture of synthetic human insulin and other products for therapeutic use, such as t-PA (tissue plasminogen activator).

First effective treatment to desensitize people highly allergic to stinging insects — Convinced by meticulous immunologic studies of the uselessness of giving extracts of whole insect bodies to patients who get severe reactions to insect stings — the standard treatment in the early 1970s — immunologist Lawrence Lichtenstein experimented with venom therapy. By 1979, he showed that periodic injections of venom desensitize patients with this kind of allergy. Later, Lichtenstein identified a key biochemical switch — the lipoxygenase pathway — that turns on most allergic reactions. Scientists now are closer to developing allergy-control drugs that block release of all mediators at once, instead of just a few, as antihistamines do.

Development of the automatic implantable defibrillator — The device, about the size of a deck of cards, electrically senses dangerously irregular heartbeats and shocks a heart into normal rhythm. The defibrillator was developed in the late 1960s by Michel Mirowski and first implanted by cardiac surgeon Levi Watkins Jr. in 1980.

Invention of a bonelike total knee replacement — The problem with the first knee replacements was that after awhile the cement that held them to the patient's bone loosened and the whole artificial joint needed to be replaced. In 1982, orthopedic

surgeon David S. Hungerford announced success with a new knee he had helped develop: a prosthesis coated with chrome cobalt beads into which the patient's own bone would actually grow, knitting a tight bond.

First use of a PET scanner to image neuroreceptors in the living brain — Scientists led by Henry Wagner and Michael Kuhar used positron emission tomography in 1984 to see neuroreceptors in a living brain — namely, Wagner's. The technique holds out potential for better diagnosis and possibly treatment of numerous brain disorders, including Alzheimer's disease and schizophrenia.

First use of genetically engineered t-PA, a human protein that stops heart attacks — Tissue plasminogen activator can dissolve fresh blood clots in 15 to 20 minutes if it is given to a patient intravenously within hours of the start of a heart attack. While the substance is naturally produced, the body does not secrete enough to prevent an attack before heart muscle is destroyed. Using recombinant DNA techniques, Genentech, a genetic engineering firm, produced a supply it sent to Hopkins cardiologists who were the first to use it successfully on a patient.

First rechargeable cardiac pacemaker — In the late 1960s, pacemakers were lasting an average of 18 months in human subjects, usually because the batteries wore out. It occurred to Robert Fischell, Hopkins Applied Physics Laboratory scientist, that the problem could be eliminated if the rechargeable nickel cadmium batteries that were being used in satellites could be used instead. With NASA support and working with Hopkins physicians, Fischell developed a rechargeable pacemaker with just such a battery. Lithium batteries later replaced the nickel cadmium ones in rechargeable pacemakers.

First implantable insulin pump — A programmable implantable medication system (PIMS) was developed by Hopkins physicians and physicist Robert Fischell for the treatment of diabetes and first used on a patient in November 1986. Instead of daily insulin injections, a computer controls the release of insulin in a device that is implanted under the skin of the abdomen and needs to be refilled only four times a year. Before each meal, wearers dial the type of food they are going to eat on a hand-held device and it electronically tells the pump the amount of insulin to release, in an action that mimics a normally functioning pancreas.

DISTINGUISHED FACULTY

will be chief Marshall at ceremony
member of President's Council of Advisors on Science + Tech.

Here are a few of the Medical Institutions' current award-winning faculty:

DANIEL NATHANS and HAMILTON O. SMITH, professors of molecular biology and genetics, shared the 1978 Nobel Prize for Medicine with Werner Arber of Switzerland for their discovery and application of restriction enzymes, the chemical scissors used to cut genetic material at precise points. (See "Contributions" for more background.) Both have spent their entire careers at Johns Hopkins. What they didn't share, despite a close working relationship that continues to this day, was a common background. Nathans' father was a man who, as a headstrong Russian boy of 15, in 1900, rebelled against his Orthodox Jewish family and left for Philadelphia. He was 43 when his American son was born in Wilmington, Del., and the family was storybook poor and loving. "My father lost his small business," Nathans said in his Nobel acceptance speech, "and was for some time unemployed. Our house was cold and leaky, and (I learned later) my parents sometimes went hungry." Smith's parents, by contrast, were both professors of education at the University of Illinois in Urbana, and until he headed to Hopkins for medical school in 1951, he spent all his life in that comfortable, predictably demanding Midwestern academic community. "At home, an atmosphere of intense intellectualism was maintained. My father was perpetually working and writing," Smith wrote. "My brother and I received private French lessons during our preteen years. I began piano lessons at age 8."

VERNON B. MOUNTCASTLE, known as America's dean of neurophysiology, has traced the codes and signals of the nervous system from the fingertips to the brain's cerebral cortex. He has made fundamental discoveries about the cellular organization and architecture of the cortex, the outer layer of the brain essential to the most sophisticated mental processes — thought and memory, learning and cognition. Director of the Bard Laboratories of Neurophysiology, Mountcastle received the National Medal of Science from President Ronald Reagan in 1986 for his research on how the brain perceives information gathered through the somatic sensory system.

"Each of us," Mountcastle has written, "confronts the world from a brain linked to what is 'out there' by a few million fragile sensory nerve fibers, our only channels, our lifeline to reality." Hailing from Virginia, he graduated from Roanoke College at 19. In explaining how he happened to finish so young, he tells this tale on himself: He got a head start in school through exposure, at age 3, to his older sisters' home instruction course from Baltimore's Calvert School. "On my first day of school, they asked, 'Who can read?' I said I could and they moved me up a grade. On my second day they asked, 'Who can write?' I said I could and got moved up another grade."

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ARNALL PATZ, director of the Wilmer Eye Institute, was a young ophthalmologist in private practice when he noticed that most of the blind babies he saw had something in common: they had been born early and then put in an oxygen-rich incubator. That oxygen, Patz realized after a series of experiments, was to blame for abnormal overgrowth of blood vessels in the infants' eyes, which leaked and caused permanent damage. Warned of this danger, doctors turned down the oxygen levels, and the condition, retrolental fibroplasia, virtually vanished from nurseries around the nation.

Since Patz joined the faculty in 1955, the Wilmer Eye Institute has solidified its reputation as the world's No.1 eye clinic. Patz, a Lasker Award winner, has pioneered laser therapy for treating some of the most common forms of adult blindness, including diabetic retinopathy, a complication of diabetes, and senile macular edema, which steals away all but peripheral vision. Like the newborn blinding disease, both conditions result from blood vessel overgrowth, which prompted Patz and his colleagues to look for chemicals that can prevent it. Such inquiries, still under way, have drawn the attention not only of eye specialists but of cancer researchers, who would like to rob tumors of their blood supply.

SOLOMON SNYDER was only 31 when he was promoted to full professor, an age when most medical academicians are at the bottom of the promotional ladder, trying to prove themselves. Now director of the Department of Neuroscience as well as professor of psychiatry and pharmacology, he is credited with touching off the modern revolution in neurochemistry. Snyder mapped chemical pathways that brain cells use to communicate with each other; in 1978 he won the Albert Lasker Basic Medical Research Award for his work on the mechanism of action of opiate drugs and for showing that the brain contains naturally occurring morphinelike substances called enkephalins. Both contributions should lead to better pain relief and ways of controlling narcotic addiction. The scientific and technological methods Snyder developed to ask and answer questions about opiate receptors also provided the tools for discovery of many chemical "locks" and molecular "keys" that fit them. Among these: Valium and other drugs in the benzodiazepine family, calcium-releasing proteins and odorants.

VICTOR McKUSICK is probably best known for his catalog of genetic traits and defects: with more than 4,000 entries, it is to genetics what the *Oxford English Dictionary* is to English.

Trained as a cardiologist, McKusick practically invented the field of medical genetics, which wasn't recognized as a real medical discipline until the 1950s. He was the first, for instance, to suggest that the unusual height and eye and heart problems of Marfan syndrome (sometimes called basketball player's disease) all were caused by a single gene defect in connective tissue. Mapping on chromosomes the gene locations for such inherited diseases soon became a consuming interest; now the Howard Hughes Medical Institute taps McKusick's home computer to make his constantly updated compendium, *Mendelian Inheritance in Man* (otherwise known as "McKusick's catalog") available to doctors and scientists nationwide.

Many of the world's most noted geneticists were trained by McKusick. Other medical geneticists from the U.S. and abroad have been exposed to his annual summer "Short Course in Medical Genetics and Experimental Mammalian Genetics" that he founded with staff at the Jackson Laboratory in Bar Harbor, Maine in 1960. The 30th session will take place in his native Maine during the Centennial year.

PATRICK WALSH, Hopkins' chief urologist, became discouraged at the long parade of prostate-cancer patients who came

to him too late to benefit from surgery. Many, dreading impotence and incontinence if their whole prostate gland had to be removed, put off treatment until the cancer had spread beyond hope. The best way to draw such patients in earlier, Walsh knew, was to figure out an operation that would spare them those side effects. Working with a Dutch anatomist, Walsh determined exactly which nerve bundles must be left intact when the gland is cut out. Based on his findings, he trained surgeons from around the world in the refined technique, which also has been applied to surgery for bladder cancer.

BRUCE REITZ led the nation's first "domino donor" transplant surgery, in which an organ recipient gave up his own healthy heart to another patient, in the spring of 1987. In the 17-hour operation, a set of heart and lungs from an accident victim were given to a cystic fibrosis patient, whose own heart, in turn, was removed and grafted, piggyback, onto the diseased heart of a man with congestive heart failure.

The two men, previously near death, returned home within weeks, fortified with immunosuppressive drugs that heart surgeon Reitz also had helped pioneer in his years at Stanford, where he performed the first heart-lung transplant. Now he is studying whether the walnut-size hearts transplanted in infants will grow as the babies mature.

KIMISHIGE AND TERUKO ISHIZAKA, a married team of Japanese-trained immunologists, in 1966 discovered the immune molecules that trigger allergic reactions. Called immunoglobulin E — IgE for short — antibodies, the substance is the most potent mediator of the sneezing, itching and wheezing seen in allergy and asthma. Since the discovery, allergists have been able to measure not only a patient's response to particular allergy-causing proteins but the success of therapy. They also have been able to design better drugs to suppress allergy symptoms.

DONALD AINSLEE HENDERSON, dean of the School of Public Health since 1977, directed the World Health Organization's successful, decade-long smallpox eradication program. Under his leadership, more than 700 advisers from 69 countries and 200,000 national health staff volunteers worked on one of medical history's most ambitious undertakings. Smallpox killed or crippled millions of people around the world over the 3,000 years it was known to exist. At the end of the WHO campaign, Henderson said, "After so many years and so many cases, it is all but impossible to comprehend that smallpox now exists only in glass vials in two laboratories." The worldwide savings on vaccination alone is estimated at $2 billion annually.

Henderson received a medical degree from the University of Rochester, and abandoned plans to specialize in internal medicine after spending his two years of military service at the Centers for Disease Control.

For his contributions to the health of the world, Henderson has received the National Medal of Science, the Japan Prize, the Albert Schweitzer International Prize for Medicine, and the Dana Award for Health and Higher Education. Other honors have come from Great Britain, Germany, Afghanistan, Ethiopia, Pakistan and India and from numerous colleges and universities around the globe.

Today, the effort to eliminate polio from the Western Hemisphere takes a great deal of his time, as does leading the world's foremost school of public health.

REVOLUTION IN AMERICAN MEDICINE

Until Johns Hopkins opened a century ago, most medical students were taught in "trade schools" which, because they were set up to turn a profit, often accepted high school graduates who would have had trouble getting into a liberal arts college. After two, at most three, years of attending typically repetitious lectures by part-time teachers, students were free to apprentice themselves to older doctors or simply hang out a shingle, even if they had never laid a hand on a patient.

Hopkins earned its reputation by radically transforming medical education and the practice of medicine and medical research. With the opening of the Hospital in 1889, followed four years later by the School of Medicine, Hopkins ushered in a new era marked by rigid entrance requirements for medical students, a vastly upgraded medical school curriculum with emphasis on the scientific method, the incorporation of bedside teaching and laboratory research as part of the instruction and integration of the School of Medicine with the Hospital through joint appointments. The new model also created standardized advanced training in specialized fields of medicine with the creation of the first house staff fellowships and postinternships.

To wage this revolution, Hopkins recruited four impressive young physicians — William H. Welch, William Osler, William S. Halsted and Howard Kelly — the so-called Big Four — by offering them rare and tempting research opportunities. The basic scientists and later the clinicians were free to do research by a full-time salary, a departure from the tradition of employing part-time local practitioners to teach classes. Another innovation which assured higher quality applicants: rigid entrance examinations after prerequisite college education, heavy on basic science — chemistry, physics, biology — and rigid entrance examinations, were expected of all students who ventured into a Hopkins medical school classroom.

Classes were small and involved hands-on training with patients, a departure from the old lecture format. From the start, talented women were permitted to enroll, breaking a prohibition that many older schools held for decades. Medical research by both faculty and students was fostered as part of the educational process and as integral to patient care. The "clinician-scientist" became a Hopkins hallmark.

Study was rigorous and lasted four years, including unprecedented hours of bedside learning at the side of experts, original research projects guided by respected clinicians, and extensive laboratory training. Then came postgraduate education in the Hospital for interns and residents, an innovation which became the model for the postgraduate clinical education of the 20th century. Hopkins' "products" soon were in demand across the country.

The Hopkins reforms in American medical education were pushed further after 1910, when the Carnegie Foundation asked educator Abraham Flexner to survey the 150 medical schools then operating in the United States and Canada. Flexner found

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only five that he thought were adequate, and he held up Hopkins as the model.

"The influence of this new foundation can hardly be overstated," Flexner wrote. "It has finally cleared up the problem of standards and ideas and its graduates have gone forth in small bands to found new institutions or to reconstruct old ones." In fact, Washington, Vanderbilt, Iowa, Duke and Rochester universities patterned their medical schools directly after Hopkins; Duke went so far as to hire all but one of its first chairmen and chiefs of service from the Hopkins faculty.

In turn, Hopkins had modeled itself largely after German universities, where medical science was highly valued and laboratories well-equipped. Few facilities like this were available in the United States in the late 19th century, but slowly, with Hopkins in the vanguard, the belief spread that medicine would not advance unless doctors were firmly grounded in basic science and applied research methods to the study of disease.

It was perhaps fortunate that the opening of The Johns Hopkins Hospital was delayed for 13 years after the opening of the University in 1876. These years gave Daniel Coit Gilman, the University's first president, a chance to get a program of postgraduate education well-established.

The delay also gave William H. Welch, the first professor at the School of Medicine, time to get up and running before the wards opened. The emphasis on research was well-established before a single patient was admitted. The bacteriologic era came into full bloom during those years, as well. Robert Koch discovered the tuberculosis organism in 1881, launching a new awareness of the role of germs in disease, which strongly influenced the practice of medicine.

The School of Medicine opened four years after the Hospital and, in retrospect, this gap, too, was an advantage, for it gave the innovative residency system time to get firmly established. When the first medical students came along, they could easily be incorporated into the wards, caring for the patients. One other great benefit emerged from the delays. They gave Osler the time he needed to write his classic textbook, *The Principles and Practice of Medicine.*

Hopkins continues to buck national trends in medical education. In a somewhat controversial move in 1985 designed to expand the access of broadly educated students to medical careers, the medical school dropped the Medical College Admissions Test, or MCAT, as a requirement for admission, because Hopkins officials felt premeds were focusing their undergraduate educations too heavily toward science in order to pass the examination. More than 25 students apply for each available place in the medical school, while nationwide the pool of applicants has dropped to 1.8 for every available medical school seat. While not all applicants meet the school's rigorous entrance standards, Hopkins attracts enough highly qualified entrants to avoid admitting applicants with lesser credentials, as some medical schools have been forced to do.

Another mark of a great academic medical center is its commitment to research. Hopkins for years has been among the top three or four medical schools in the amount of competetive research grants awarded by the National Institutes of Health.

SELECTED BEDSIDE TALES OF FAMOUS PATIENTS

Hopkins' reputation for first-rate care has always drawn large numbers of the internationally famous. Here are a few bedside tales that can be told without violating patients' wishes for privacy and confidentiality.

• "Diamond Jim" Brady, so known in New York social circles because he was always bedecked with jewels (he had 35 jewel sets, each with about two dozen pieces, and he wore a different set every day of the month), had serious prostate gland trouble in 1912. Doctors in Boston and New York turned him away, unwilling to risk a tricky operation on a grossly obese man who also had high blood pressure, diabetes, angina pectoris and a chronic urinary tract infection. Full of trepidation over what surgery could mean for his sexual function, yet dogged by urogential problems that mattered to him even more, he sought the help of Hugh Hampton Young, the Hopkins urologist who had made a name for himself by refining prostate surgery. (A New York surgeon once joked, "The prostate makes most men old, but it made Hugh Young.")

Young's surgery was a success, and so grateful was Brady that the operation restored one function without robbing him of another that he had an entire urology institute built for Young at Hopkins. Named for Brady, the institute opened its doors in 1915. It was the first time in this country that a surgical subspecialty had its own building for patient care, teaching and research. Wrote H.L. Mencken of Brady, who was vice president of Standard Steel Car Co.: "When he threw a party for railway executives it made Broadway history and doubled the sale of headache powders." Brady himself was a teetotaller, but loved to see his friends enjoy themselves.

A portrait of Brady, with the requisite diamonds — some of them three-quarters of an inch in diameter — now hangs in the library in the Brady Institute.

• F. Scott Fitzgerald had recurring tuberculosis and a nearly unshakable attachment to gin. Treating the first was the province of internist Louis Hamman; his younger partner, Benjamin M. Baker, was enlisted to try to wean the novelist off alcohol, which he was able to do once for a stretch of several months. During the 1930s, Fitzgerald was admitted to Marburg, the private patient pavilion at Hopkins, at least nine times, sometimes because a tubercular lesion had flared up in his left lung, but more often because the writer had been on a binge and wanted "a fresh start."

Experiences based on one of those hospitalizations, and weekends and holiday nights spent sitting at a table set up for him in a corner of the emergency room, led Fitzgerald to write "One Interne." Like most of his tales, the story was woven from snippets borrowed from life. Fitzgerald created Bill Tulliver, a brash but sensitive doctor in training who falls in love under a gigantic statue of Christ which "gestured in marble pity" at the hospital entrance, just like the statue that has stood in Hopkins' rotunda since 1896. Tulliver's thoughts reflected hours Fitzgerald had spent quizzing young

For media inquiries, contact Ghita Levine, Centennial Office, The Johns Hopkins Medical Institutions, (301) 955-6680.

Hopkins physicians and internalizing their attitudes and medical slang.

• In 1941, the Duke of Windsor paid a call at Hopkins. His Baltimorean wife, Wallis Warfield Simpson, was consulting a Hopkins stomach specialist when the duke remarked that he'd like to have a general medical exam, himself. Referred to internist Benjamin M. Baker, the abdicated king paid for health services rendered with a $50 check drawn on the Bank of England, signed simply, "David."

• Welterweight boxing champion Sugar Ray Leonard was in training for a match in May 1982 when the sight in his left eye went fuzzy. Whether a stray practice punch knocked his retina loose or it simply detached on its own has never been determined. In any case, on May 9, 1982, ophthalmologist Ronald G. Michels repaired the damage and gave him a clean bill of health, clearing the way for Leonard's return to the ring.

• Prince Rainier of Monaco could not easily have forgotten his stay as a Hopkins patient in 1956, because directly after his discharge he went north to Philadelphia to propose marriage to actress Grace Kelly. Rainier came to Baltimore with a princely entourage, including his personal priest, and while at Hopkins enlisted the advice of Hopkins personnel to develop a list of current medical supplies and instruments to take back with him to his own country.

• Undoubtedly the oldest patient ever to be seen at Hopkins is Boris, a 2,500-year-old Egyptian mummy brought here for radiologic scans in May 1988. CT scans had been used on mummies before, but The Johns Hopkins Hospital was the first to employ a sophisticated computer program to enhance the images into three dimensions.

• Cary Grant came to Hopkins one summer in the '50s. In those days, the hospital used to close an entire floor at a time in the private Marburg pavillion for a thorough cleaning. The actor was admitted to one of those floors and had the whole place to himself.

Other famous patients included Sarah Kleberg, whose Texas husband owned the largest ranch in the world. When their horse won the Dixie Handicap at Pimlico, they donated the entire winnings to Hopkins to create a fellowship fund in neurosurgery.

Many Du Ponts came here for treatment, as did/and do members of Congress, industrialists such as Harvey Firestone and Champion McDowell Davis, the Atlantic Coastline Railroad magnate.

When Joe DiMaggio was a patient here, a United Press photographer took pictures of him on a stretcher and was barred from photographing at Hopkins for a year because of his breach of Hopkins' strict rules governing patient privacy. Many other baseball players have sought treatment at Hopkins.

Walter Dandy, the famous neurosurgeon, took care of George Gershwin and Thomas Wolfe, who both had brain tumors. Dandy also went to Mexico to see Leon Trotsky after he was shot in 1940, but arrived too late to save his life.

Many Hopkins physicians went abroad to treat the famous. A.E. Walker went to the Soviet Union to see composer Dmitry Shostakovich, A. McGehee Harvey spent two weeks in the U.S.S.R. to see Nikita Khrushchev's daughter who was ill with lupus. Ophthalmologists Ronald G. Michael and Walter Stark went to the U.S.S.R. to treat a top Soviet official whose name has never been released. And back in the U.S., Dean Richard Ross, a cardiologist, went to California to examine President Richard M. Nixon.

Other famous Hopkins patients: publishers William Randolph Hearst, Alfred Knopf and Katherine Graham, Mme. Chiang Kai-Shek, Zelda Fitzgerald, civil rights leaders Ralph Abernathy and Rosa Parks, rocket scientist Werner von Braun, Federal Reserve chief Arthur Burns, labor leader Lane Kirkland, chicken king Frank Perdue, actors Clark Gable, Carole Lombard, Marie MacDonald, Dick Powell and Yul Brynner, Evening Sun columnist H.L. Mencken, South Pole explorer Admiral Richard Byrd, poet Ogden Nash, writer Pearl Buck, cellist Pablo Casals, Whitey Ford of the New York Yankees, football star O.J. Simpson, U.S. Rep. Helen Delich Bentley, Supreme Court Justice Lewis Powell, "All My Children" producer Agnes Nixon, and at least two presidents of the Philippines, Elpidio Quirino and Remon Magsaysay.

THE FOUR FOUNDING PHYSICIANS

Every one of the "Big Four," as they are known at Hopkins, was a character, a larger-than-life personality: pathologist William Henry Welch, a stout bachelor whose favorite pastime was a week of swimming, carnival rides and five-dessert dinners in Atlantic City; surgeon William Stewart Halsted, whose severity with students masked an almost debilitating shyness; internist William Osler, king of pranks; and gynecologist Howard Kelly, snake collector and evangelical saver of souls.

As Hopkins' most famous medical school professors, they sat in John Singer Sargent's London studio in 1905 for a portrait that now hangs in the Welch Medical Library. (Lore has it that much of Halsted's figure was painted in disappearing pigment, so disgusted was Sargent with Halsted's strident objection to having blue shadows painted under his eyes. Halsted does, in fact, appear a bit fuzzier than his colleagues, but curators and art experts insist that is only because Sargent painted him farther in the background, and used a thinner wash, for perspective.) Each of the doctors, in his own way, had a profound and lasting influence on American medical education and research.

Welch (1850-1934) joined the faculty first. He came by a necessarily tortuous route, because the last thing he had wanted as a youth was to follow in his country-doctor father's footsteps and take up medicine. The sight of blood, he said, had always made his knees weak. From age 13 he yearned to teach classics, preferably at Yale, where he eventually went to college. No job awaited him after graduation, however, and, at a loss for what else to do, he enrolled at the College of Physicians and Surgeons in New York, to the delight of his father, who expected they might practice together when Welch was graduated. The New York college was then considered one of the best medical schools in the country, even though its only entrance requirement was that an applicant be able to read and write. Welch, always a diligent student but a lifelong procrastinator, found the program so amazingly simple that he didn't have to study for the final, most critical test. "To tell the truth," he admitted to his sister Emma, "it was the easiest examination I ever entered since leaving boarding school." Such was the sorry, undemanding state of American medical education in the mid-19th century that Welch would overturn.

Upon graduation, Welch put off unwelcome talk of joining his father in Connecticut by sailing for Germany to train in pathology and bacteriology. Then came a dreary teaching job at Bellevue College in New York, where extravagant promises of a hefty research budget and a lab turned out to mean $25 and three small rooms furnished with kitchen tables. A popular intellectual who enjoyed New York's nightlife with his many friends, Welch made the best of it, combing upstate marshes for frogs for his students to use as pathology specimens. With a boxful of croaking creatures in tow, he would ride the train back to New York City and, not wanting to be found out, make a showy pretense of being distracted by all the noise from reading his newspaper. "I ap-

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peared to be as ignorant and much astonished as the other occupants of the sleeping car," Welch wrote.

Welch had high hopes that organizers of the proposed Hopkins medical school might want to recruit him. A friend had earlier praised him to the president of the University, Daniel Coit Gilman, and a chance meeting with John Shaw Billings in Leipzig, Germany, when Welch was still in training, seemed to him to have boosted his chances. Billings, the administrator of the Surgeon General's Library, and an authority on hospitals, had been asked to design and organize the proposed hospital and medical school and was busy studying various German laboratories and methods in 1876 when he came upon the 26-year-old Welch hard at work in a German laboratory. The two met that night for beers, and Welch sensed that Billings was delighted by his attitude toward science and his mastery of German technique. In fact, as soon as he got back to his hotel, Billings told Francis King, the hospital trustee who had come with him on the fact-finding trip: "The young man should be, in my opinion, one of the first men to be secured when the time comes to begin the medical school."

So when the call from Hopkins finally came, complete with assurances of an all-expenses-paid, German-style laboratory, as many research assistants as he needed and freedom from seeing patients unless he cared to see them, Welch couldn't resist. (Unlike his garrulous father, whose life revolved around midnight house calls and trading gossip with his patients' families, Welch preferred the pure science of work with cadavers to treating patients.)

Knowing well Welch's weakness for fine food, his cosmopolitan friends teased him relentlessly, begging him not to move to a wasteland like Baltimore. "Well, goodbye," he remembered one saying, finally, at his farewell dinner. "You may become a connoisseur of terrapin and madeira, but as a pathologist, goodbye."

Welch didn't take long to prove the man wrong. He arrived in 1884, five years before the Hospital and nine years before the medical school officially opened, and headed back to Europe for more grounding in scientific method. By 1886, he had opened his laboratory and was training 16 graduate students — committed research scientists who already had medical degrees and were attracted by Welch's reputation for serious scientific study. His was the first graduate training program for doctors in the country.

Bringing Welch to Hopkins set the precedent of importing top-flight faculty from other parts of the nation at the risk of antagonizing the Baltimore community. But Welch's immediate popularity prevented such resistance.

His students found him a bit eccentric: an inveterate night owl, he had trouble waking up in the morning and sometimes missed his own lectures. According to one of his proteges, Simon Flexner, he completely ignored his students at first, leaving them to their own devices in the laboratory, until on their own each came up with a bit of research that excited him. He always maintained an affable distance that prompted the nickname "Popsy," which they rarely dared to use in his presence. As far as they knew, he had no romantic attachments, but he was such a private man they couldn't be sure, and they devised a little ditty they sang behind his back:

"No one knows where Popsy eats,
No one knows where Popsy sleeps,
No one knows whom Popsy keeps,
But Popsy."

Welch awed his students with his seeming grasp of any subject. Said Flexner, reflecting on Welch's rather one-sided conversations on those rare evenings when he dined with some of his most promising students: "He often became so absorbed that the ash from his perpetual cigar dropped un-

noticed onto his swelling waistcoat to join the thick grey powder that was already there. A spell fell over the room as the quiet voice talked on, and the young men, some of them already a little round-shouldered from too much peering into the microscope....resolved to go to art galleries, to hear music, to read the masterpieces of literature about which Welch discoursed so excitingly." Welch's students needn't have felt quite so overwhelmed, however. Like many intellectual conversationalists, Welch had a gift for steering the subject to one with which he was deeply acquainted — or at least seemed to be. At holiday dinners, he amazed his relatives with long, involved discussions of the most esoteric topics -- until someone finally realized his words of wisdom came straight from the Encyclopedia Brittanica, which he read right before he came to the table.

Osler may have been the supreme prankster, but Welch liked to play a good joke himself. Once, by studying aerodynamics, he convinced a few of his friends, and even some of his closest relatives, that he had a pilot's license and that, in fact, one of the Wright brothers had taught him how to fly in Atlantic City. He was delighted that they bought his story even though they knew that all his life he had never even learned how to drive a car. On another occasion, he primed Halsted for a wicked joke by complaining for days about a vague discomfort in his chest. Finally, one day when the two were climbing the steps of the Maryland Club, Welch stopped as if stunned, and told Halsted the pain was now very sharp. Wasting no time, Halsted pressed his ear against Welch's chest and felt the most inhuman, resounding thumps. Under his shirt, Welch had hidden a rubber bulb connected to another in his pocket, which he rhythmically squeezed for a monstrous pseudoheartbeat.

While Welch made some notable research contributions — he discovered the gas bacillus — probably his greatest legacy lies in having trained some of the most eminent scientists of the time. Among them were Walter Reed, James Carroll and Jesse Lazear, who showed that yellow fever is transmitted by mosquitoes. Their finding, considered one of the greatest achievements of modern medical science, led to the virtual eradication of the disease. Medical schools and institutes across the country vied for Welch's former students and graduate scientists to fill top posts, and Welch served as a sort of national placement officer for academic physicians. It is somewhat ironic that the medical institution committed itself to supplying highly trained researchers to "rival" schools, because it never had room for all its trainees. Trainees understood that few could stay on as faculty members. But the result was the rapid expansion of the revolution in quality of American medical education and research that Hopkins wrought. Wherever these Hopkins doctors went, they took with them higher standards and expectations.

Welch also played a key role, with University President Gilman and medical institutions planner Billings, in pulling together the original medical school faculty, including Halsted and Osler. In 1916, Welch also founded the nation's first school of public health at Hopkins, and 10 years later he headed Hopkins' Institute of the History of Medicine, now lodged in the medical library that bears his name. He also was instrumental in the founding of the Rockefeller Institute for Medical Research, and served as the first chairman of its board, and of the *Journal of Experimental Medicine*.

Halsted (1852-1922) came to Hopkins next. An almost excruciatingly slow, meticulous surgeon known for his gentle handling of tissue at a time when bloody slashing, and no thought of germs, were more common, the aristocratic Halsted fought a lifelong battle against drug addiction — including cocaine — after a bout of self-experimentation with its newfound anesthetic properties. Although in practice

in New York, Halsted had discovered that an injection into a major nerve trunk could numb a whole limb, or block the spinal cord. While his experiments led to modern dental anesthesia, he personally landed in a hospital for mental disorders. Welch approached him in New York after the surgeon's release from the hospital in 1886 and offered him a research position while he recovered.

Welch's unswerving support helped Halsted start his career, but though he was appointed to the job of chief surgeon, his formerly dazzling personality and surgical approach were permanently altered. Gone were the daring, inimitable speed, the willingness to take risks he'd been known for in New York. Instead, Halsted became shy and reticent even with his students, and in surgery he stressed a whole new method — control of bleeding, absolute cleanliness and careful reconstruction of tissue. His insistence on perfection took on mildly eccentric proportions in his home life; he insisted on personally selecting the leather from which his European shoes were cut, and shipped dozens of his dress shirts to Paris or London every year for laundering. He also sent his wife out regularly to scout Baltimore's lumberyards for the only wood he cared to burn in their fireplaces — white oak and hickory.

Halsted's knowledge of surgical anatomy and dissection, which he passed on to his students by operating before them on an old wood army hospital table left over from the Franco-Prussian War, was unparalleled, his technique precise. Today, most laymen are familiar with the eponymous "Halsted radical," the initial life-saving surgical treatment for breast cancer, which he first described in 1891. In his day, however, a "Halsted" meant something quite different. His colleagues used the term to mean any drawn-out procedure that seemed to take longer than absolutely necessary. So involved and slow would Halsted become during surgery that a single instance seemed to sum it up: during a particularly tedious procedure, with his colleagues getting restless and irritated, he asked the man working next to him if he'd mind scooting over. "You've been standing on my foot for the last half hour," Halsted informed his fellow surgeon.

Halsted revolutionized surgery by insisting on skill and technique rather than brute strength. Using an experimental approach, he developed new operations for intestinal and stomach surgery, gallstone removal, hernia repair and disorders of the thyroid gland.

Thanks largely to Halsted, surgeons worldwide began wearing gloves during operations. That shift came about after one of his nurses — Caroline Hampton, whom he later married — complained that the mercuric chloride she was supposed to wash with gave her a rash. He asked the Goodyear Rubber Co. to try to make two pairs of thin rubber gloves to protect her hands. His surgical assistants were quick converts and began to wear them during operations, swearing that the gloves made them more dextrous. The idea that the gloves also might help in germ control actually didn't occur to any of them for years, which Halsted remarked on, somewhat bemused, long after. "Operating in gloves was an evolution rather than an inspiration or happy thought," Halsted said, "and it is remarkable that during the four or five years when as operator I wore them only occasionally, we could have been so blind as not to have perceived the necessity for wearing them invariably at the operating table."

Halsted had been at Hopkins seven years before he convinced the trustees that he had kicked his drug habit. They made him full professor of surgery in 1892. Until then, he had been given the title of "acting professor." But about six months after Halsted was promoted, he confided in Osler, who had been surprised to find Halsted one day shivering unnaturally, that he was still taking morphine. "Although he had never been able to reduce the amount to less than

three grains daily," Osler wrote, "on this he could do his work comfortably and maintain his excellent physical vigor (for he was a very muscular fellow). I do not think that anyone suspected him — not even Welch." He remained addicted the rest of his life.

Osler (1849-1919) had arrived in 1888, as physician in chief. A British Canadian, Osler was already considered America's premier doctor and was known as a superb clinical teacher. He was famous for using alliteration to help his students remember what they needed to know. "Four Fs," for instance, lead to typhoid fever, he told them: fingers, food, flies and filth. His landmark 1892 text, *Principles and Practice of Medicine*, became the landmark text of internal medicine and has been continually updated. The 22nd edition, published in 1988, is a lineal descendant with the same name and same publisher, edited by A. McGehee Harvey, Hopkins professor emeritus.

A short, wiry man with a handlebar mustache, Osler had an uncontrollable urge to pull practical jokes that constantly got him into trouble. Two years before he arrived at Hopkins, he had bamboozled a respected medical journal into printing the outlandish medical findings of Egerton Yorrick Davis, an imaginary retired Army surgeon who supposedly had set up practice in Canada; after that, its editor refused ever to publish any of Osler's legitimate work — or even believe it. While Osler's jokes didn't always backfire, plenty of people failed to find them funny, including some naive first-time female patients. Osler delighted in "consoling" these unsuspecting women as they waited nervously for their appointments with the newly arrived Dr. Kelly. You are in the most capable hands, Osler would assure each of them; and don't worry, old Kelly's senile tremor disappears as soon as it's time to operate. Doubt, then puzzlement would cross their faces when in walked the rather baby-faced Kelly, the youngest of the "Big Four." Osler remains the Will Rogers of the medical world, "Osleriana" appearing regularly in the *Journal of the American Medical Association*. He was the first to say, "A physician who treats himself has a fool for a patient."

Perhaps Osler's greatest contribution to medicine was the establishment of the medical residency program, an idea that spread across the country and remains in place today in most training hospitals. Through this system, doctors in training make up much of the Hospital's medical staff. The success of his residency system depended, in large part, on its pyramidal structure with interns, fewer assistant residents and a single chief resident, who originally occupied that position for years.

Osler also instituted another first by getting his medical students to the bedside early in their training; by their third year they were taking patient histories, performing physicals and doing lab tests — examining secretions, blood and excreta — instead of sitting in a lecture hall, dutifully taking notes. He diminished the role of didactic lectures and once said he hoped his tombstone would say only, "He brought medical students into the wards for bedside teaching." He himself liked to say, "He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all."

Osler was a staunch advocate of good nursing, hygiene and prevention, and his stature as the outstanding American internist of the time made him instrumental in getting U.S. doctors to prescribe only those drugs that were proved effective. He also fought against low-standard profit-making medical schools before he left for Oxford in 1905.

Billings, the Hospital's planner, generally is credited for having recruited Osler, but according to Simon Flexner, Welch's biographer, Osler was actually a second choice. When Welch plead Osler's case, Billings agreed with reluctance, believing Osler to be far too interested in pathology, a field Welch had well-covered. Hopkins

chronicler Augusta Tucker relates this account of Osler's job interview in 1888, when Osler was still at the University of Pennsylvania:

"Dr. Billings, stopping off between trains in Philadelphia, went to Dr. William Osler's rooms on Walnut Street and without sitting down, said, 'Will you take charge of the Medical Department at the Johns Hopkins Hospital?' Dr. Osler, without a moment's hesitation, answered, 'Yes.' Dr. Billings replied, 'See Welch about the details; we are to open very soon. I am very busy today, good morning.' He left, having been in the room approximately two minutes; and while there he altered the course of medical education in the United States forever." (Osler had not been caught off guard, having been sounded out already by Welch.)

Osler brought Kelly (1858-1943), a skillful gynecological surgeon, into the fold in 1889 from the University of Pennsylvania Medical School. Kelly was a reptile collector and a bible-thumping fundamentalist Christian who read the good book in the original Greek and Hebrew and called a prayer meeting before every operation.

Kelly was only 31 when Hopkins hired him, and he gave his house staff, the gynecology residents, great responsibilities, much as Osler did. Kelly is credited with establishing gynecology as a true specialty; he concentrated mainly on new surgical approaches to women's diseases and to understanding underlying pathology. He invented numerous medical devices, including a urinary cystoscope. When radium was discovered, Kelly was among the first to try it for cancer treatment (he is said to have gotten a sample straight from Marie Curie), and he founded the privately owned Kelly Clinic in Baltimore, once one of the country's leading centers for radiation therapy. He introduced the use of absorbable sutures to Hopkins, and was partly responsible for bringing the German artist Max Broedel, the father of medical illustration, to Baltimore. Broedel later headed the nation's first Department of Art as Applied to Medicine, at Hopkins.

Kelly's home crawled with children — he and his wife had nine — and exotic varieties of snakes, and he was recognized as an expert among amateur herpetologists. Social reform attracted his attention as well; Kelly battled energetically for election reforms, often standing guard at the polls to keep people from voting two and three times. He fought organized prostitution and worked diligently to help rehabilitate "ladies of the evening." He was an avid Bible quoter who frequently locked horns with the irreverent Baltimore columnist H.L. Mencken, who had this to say about his energetic "old sparring partner" in 1921, when Kelly was 63:

"Before cock-crow in the morning he has got out of bed, held a song and praise service, read two or three chapters in his Greek Old Testament, sung a couple of hymns, cut off six or eight legs, pulled out a pint of tonsils and eyeballs, relieved a dozen patients of their appendices, filled the gallstone keg in the corner, pronounced the benediction, washed up, filled his pockets with tracts, got into a high-speed automobile with the Rev. Dr. W. W. Davis and started off at 50 miles an hour to raid a gambling house and close the red-light district at Emory Grove, Maryland." But, Mencken admitted (writing under a pseudonym), "put a knife in his hand, and he is at once master of the situation, and if surgery can help the patient, the patient will be helped."

Directory

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G.W.C. Whiting School of Engineering
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3400 North Charles Street
Baltimore, Maryland 21218
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East Baltimore Divisions

School of Hygiene and Public Health
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School of Medicine
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School of Nursing
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One East Mt. Vernon Place
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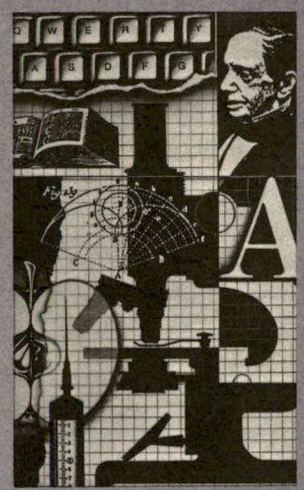
FACTS ABOUT

HOPKINS



1989

Athletics

Through the comprehensive facilities of the Newton H. White, Jr. Athletic Center on the Homewood campus and the Denton A. Cooley Center in East Baltimore, Johns Hopkins offers both students and faculty ample opportunities for team sports and individual athletic programs. Undergraduates can compete in a full range of intramural and intercollegiate sports.

Since the 1880s, championship lacrosse has been the hallmark of Johns Hopkins athletics, and the fencing and swimming teams have built outstanding championship records over the years as well. In recent years the baseball, soccer, and women's lacrosse teams have had successful seasons and have been selected for the NCAA playoffs.

Lacrosse Highlights

- 42 national championships either won outright or shared
- 76 winning seasons, with only 15 losing ones and 11 even
- 149 first-team All-Americans since the teams were first selected in 1922
- 46 members in the Lacrosse Hall of Fame
- The United States representative in the only two Olympic lacrosse competitions, tying for first place in 1928 and finishing first in 1932

Fall 1989

Figures shown are for 1988-89 unless otherwise indicated.

Marks of Distinction

- Over the years 16 alumni and faculty members have been named Nobel laureates; three are current faculty members.
- Approximately 50 current faculty members have been elected to the nation's most important honorary body for scientists, the National Academy of Sciences, and its sister groups, the National Academy of Engineering and the Institute of Medicine.
- In the past decade, 10 Johns Hopkins students have been named Rhodes Scholars.
- The Peabody is America's oldest chartered music conservatory, and its faculty and students have won virtually every prestigious international music award and competition.
- Based in the nation's capital, the Paul H. Nitze School of Advanced International Studies serves as a major research resource for foreign affairs policy makers and offers graduate professional education distinguished by access to national and world leaders.
- The School of Public Health is the first and largest in the world.
- The Johns Hopkins University Press is the oldest continuously operating university press in North America.
- Homewood campus is the site of the Space Telescope Science Institute, the ground base for NASA's 95-inch space telescope.
- The School of Medicine altered the course of medical education, changing it from proprietary training to a graduate-level university enterprise.
- The Johns Hopkins Hospital established the first medical residency system in the United States.
- Interdivisional work in biomedical engineering has led to the development of a robotic arm, argon lasers for eye surgery, the rechargeable pacemaker, and PIMS, the Programmable Implantable Medication System, which automatically delivers medication to specified body locations.
- In addition to prominent scholars in languages and literature, the School of Arts and Sciences has included the founders of fields such as pragmatism and behaviorism, as well as scientists whose practical contributions have included methods of cracking gasoline, groundwork in fluorescence leading to development of the laser, and precise instruments for measuring and exploring natural phenomena, such as the precision diffraction grating.
- The School of Continuing Studies led the country in graduate degree offerings, and the G.W.C. Whiting School of Engineering now has the nation's largest part-time graduate degree program in engineering.

Highlights of Contributions to Medicine and Public Health

- First use of surgical rubber gloves
- Purification of insulin
- Discovery of vitamin D
- Discovery of epinephrine (Adrenalin) and the anticoagulant heparin
- Discovery of biological clocks
- Discovery of Dramamine's effectiveness against motion sickness
- Development of tissue culture and first culture of cancer cells
- Development of corrective surgery for "blue babies," opening era of modern heart surgery
- Discovery of three types of polio virus, making vaccine development possible
- Invention of timer to reduce x-ray exposure
- Discovery of techniques to image receptors in the brain
- Discovery of restriction enzymes, "chemical knives" that cut genes into fragments
- Development of gene mapping
- Development of oral rehydration therapy to save victims of diarrheal diseases
- Development of modern methods of water purification
- Identification and control of leading causes of blindness in infants and the elderly
- Development of nerve-sparing prostate surgery
- First use of drugs to prevent rheumatic fever
- Development of implantable, rechargeable cardiac pacemaker and programmable, implantable medication system
- First use of bone marrow transplants and radioimmunotherapy against some cancers

Johns Hopkins

When Baltimore merchant Johns Hopkins died in 1873, he left a bequest of seven million dollars for the establishment of The Johns Hopkins University (1876) and The Johns Hopkins Hospital (1889). Considered from the beginning to be among the nation's foremost private research universities and teaching hospitals, the Institutions and their affiliated enterprises have grown to comprise several graduate and undergraduate academic divisions, a major health system, a university press, a music conservatory and international centers of study. Separately and jointly, these Institutions have earned Johns Hopkins a reputation for leadership in education, research and patient care that is world renowned.

Institutional Locations

Baltimore. *University:* Arts and Sciences, Engineering, Continuing Studies, Medicine, Public Health, Nursing, Peabody Conservatory; *Health System:* Johns Hopkins Hospital, Francis Scott Key Medical Center, Homewood Hospital Center, Johns Hopkins Health Plan, Hopkins Preferred Network.

Howard County. Applied Physics Laboratory, Columbia Center of the School of Continuing Studies

Montgomery County. Johns Hopkins Montgomery County Center

Washington, D.C. Nitze School of Advanced International Studies

Italy. Center for European Studies in Bologna, Center for Italian Studies in Florence

China. Hopkins-Nanjing University Center for Chinese and American Studies

University Divisions

School of Arts and Sciences (1876)
G.W.C. Whiting School of Engineering (1913; reestablished 1979)
School of Continuing Studies (1909)
School of Hygiene and Public Health (1916)
School of Medicine (1893)
School of Nursing (1889; reestablished 1983)
Paul H. Nitze School of Advanced International Studies (1943; affiliated 1950)
Peabody Conservatory and Preparatory School (1857; affiliated 1977)
Applied Physics Laboratory (1942)

Major Academic Centers and Affiliated Enterprises

Centers for specialized research and study—often interdisciplinary—operate throughout the University. The major centers and affiliated enterprises include:

Center for the Advancement of Academically Talented Youth
Institute for Policy Studies
The Johns Hopkins University Press
Space Telescope Science Institute
Mind/Brain Institute
National Foreign Language Center

Libraries

	Volumes
Milton S. Eisenhower Library	2,064,720
Welch Medical Library	326,947
Institute of the History of Medicine	42,243
Lilienfeld Library (Public Health)	19,071
Mason Library (SAIS)	96,406
Bologna Center Library	74,768
Peabody Conservatory	82,589
R.E. Gibson Library (APL)	60,452
Villa Spelman Collection	17,390
Total	2,784,586

The Johns Hopkins Health System

Formed in 1986, the Johns Hopkins Health System includes three hospitals—The Johns Hopkins Hospital, The Francis Scott Key Medical Center, and Homewood Hospital Center—as well as the Johns Hopkins Health Plan (a health maintenance organization) and the Hopkins Preferred Network (a preferred provider organization). One of the first and largest of its kind, the Johns Hopkins Health System provides a full range of services with the goal of making high quality medical care convenient and affordable.

Patient Care Statistics

Discharges	57,813
Deliveries	4,464
Patient Days	541,816
Average Length of Stay	8.0 days
Average Daily Census	1,484
Outpatient Visits	773,302
Emergency Visits	122,650
Operating Room Procedures	
Inpatient	19,354
Outpatient	11,439
Uncompensated Patient Care	$48.6 million

Inpatients by Region (FY88)

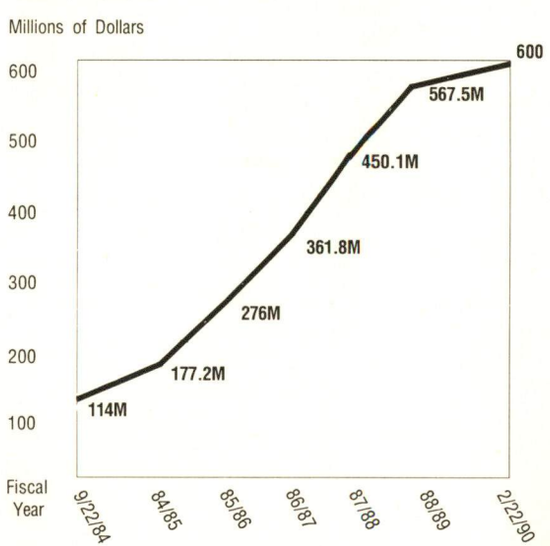
Baltimore City	19,642	55.7%
Surrounding Counties	5,144	14.6%
Rest of Maryland	4,759	13.5%
Other States and Countries	5,726	16.2%

The Campaign For Johns Hopkins

On September 22, 1984, the five-year Campaign for Johns Hopkins was publicly launched, seeking to raise $450 million from private sources for the University and Hospital. Because the Campaign surpassed its original goal in July 1988 and because new needs had arisen since its launch, the Trustees voted in October 1988 to raise the goal to $600 million and to continue the Campaign through its slated completion on February 22, 1990. As the chart below shows, Hopkins is nearing the achievement of the revised goal.

Campaign Commitments

9/22/84 - 6/30/89



Campaign Commitments as of June 30, 1989
$567,519,887

Finances

Current Fund Expenditures

Health System	$481,271,000
University (excluding APL)	$629,589,000

University Endowment

Market Value	$527,200,000
Investment Return* Averages	
3 Years (FY86-FY89)	6.43%
10 Years (FY79-FY89)	15.10%

*Income plus appreciation

Gift Support

Cash receipts	
Alumni and Friends	46,900,000
Corporations	9,200,000
Foundations	20,300,000
Organizations	7,800,000
Total	$84,200,000

Economic Impact on Maryland

The Johns Hopkins Institutions, including the Johns Hopkins Health System, is the largest private employer in the state.

The University alone is the third largest private employer in the state, providing more than 11,000 jobs in Maryland each year and indirectly providing employment for another 25,000 residents.

In 1986, the University injected $1.7 billion into the state's economy, accounting for nearly 2 percent of the state's total economic activity.

Faculty

	Full-Time	Part-Time
Arts & Sciences	255	143
Engineering	92	255
Continuing Studies	16	441
Medicine	1250	1150
Public Health	321	252
Nursing	21	19
SAIS — Washington, D.C.	51	88
SAIS — Bologna Center	8	35
Peabody Conservatory	65	57

Student/Faculty Ratios	
Arts & Sciences	10.9 to 1
Engineering	7.8 to 1
Continuing Studies	6.6 to 1
Public Health	2.8 to 1
Medicine	.6 to 1
Nursing	4.6 to 1
SAIS (D.C.)	4.9 to 1
Peabody Conservatory	2.7 to 1

Alumni

Living Alumni by Division	
Arts and Sciences	26,787
Engineering	12,819
Continuing Studies	14,719
Public Health	8,208
Medicine	6,643
Nursing	3,152
SAIS	5,234
Peabody	4,464
Living Alumni by Region	
Baltimore	23,729
Washington, D.C.	9,038
Metro New York City	5,673
Middle Atlantic	9,731
North Central	3,567
Northeast	5,078
South/Southeast	6,109
West	8,748
U.S. Possessions and Other Countries	6,159
Total Alumni	**77,832**

Students

Regional Origin (Full-time Undergraduates)

Maryland	20.2%
Other States	75.0%
Outside U.S.	4.8%

Enrollment

Full-time Programs	**Men**	**Women**	**Total**
Arts and Sciences			
Undergraduate	1193	814	2007
Graduate	588	359	947
Total	1781	1173	2954
Engineering			
Undergraduate	549	160	709
Graduate	273	67	340
Total	822	227	1049
Peabody			
Undergraduate	106	126	232
Graduate	97	134	231
Total	203	260	463
Medicine			
Graduate	436	276	712
Public Health			
Graduate	428	568	996
Nursing			
Undergraduate	4	63	67
Graduate	1	30	31
Total	5	93	98
SAIS			
Graduate			
Washington, D.C.	233	197	430
Bologna, Italy	74	62	136
Total	307	259	566
Total Enrollment			
Full-time Programs	**3982**	**2856**	**6838**

Note: 36 Chinese and 26 American students were enrolled at the Hopkins-Nanjing University Center for Chinese and American Studies.

Part-time Programs			
Continuing Studies			
Undergraduate	619	873	1492
Graduate	758	1350	2108
Total	1377	2223	3600
Engineering			
Undergraduate	398	98	496
Graduate	1769	547	2316
Total	2167	645	2812
Total Enrollment			
Part-time Programs	**3544**	**2868**	**6412**

Tuition (1989-90)

Arts and Sciences	$13,000 (returning) $14,000 (entering)
Continuing Studies	$165/credit hour
Engineering	$13,000 (returning) $14,000 (entering)
Public Health	$13,000
Medicine	
Ph.D.	$13,000
M.D.	$15,500
Nursing	
Undergraduate	$11,000
Graduate	$11,800
Peabody	$10,350
SAIS	$13,000

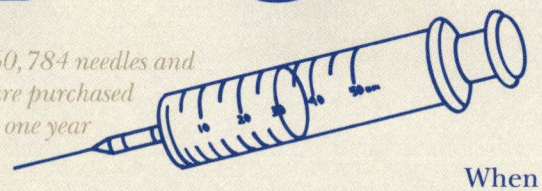
Student Financial Assistance

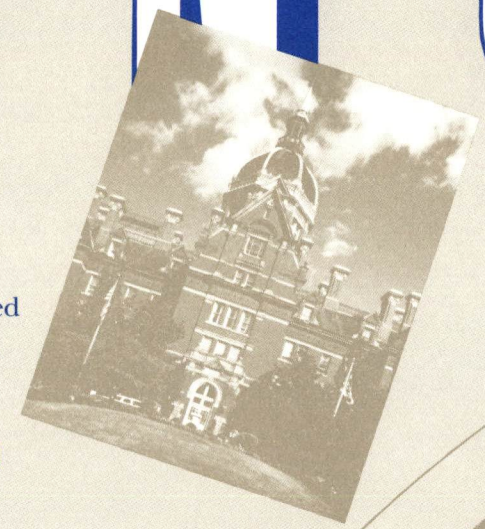
(In thousands of dollars)

Direct Aid	
Government Grants and Contracts	$4,571
Private Gifts and Grants	5,062
Endowment Income	3,798
General Revenues	20,492
Total	$33,923
Stipends, Training and Employment	
Government Grants and Contracts	14,217
Private Gifts and Grants	5,039
Endowment Income	180
General Revenues	8,215
Total	$27,651
Total Financial Assistance	$61,574

HOPKINS

3,660,784 needles and syringes are purchased in one year

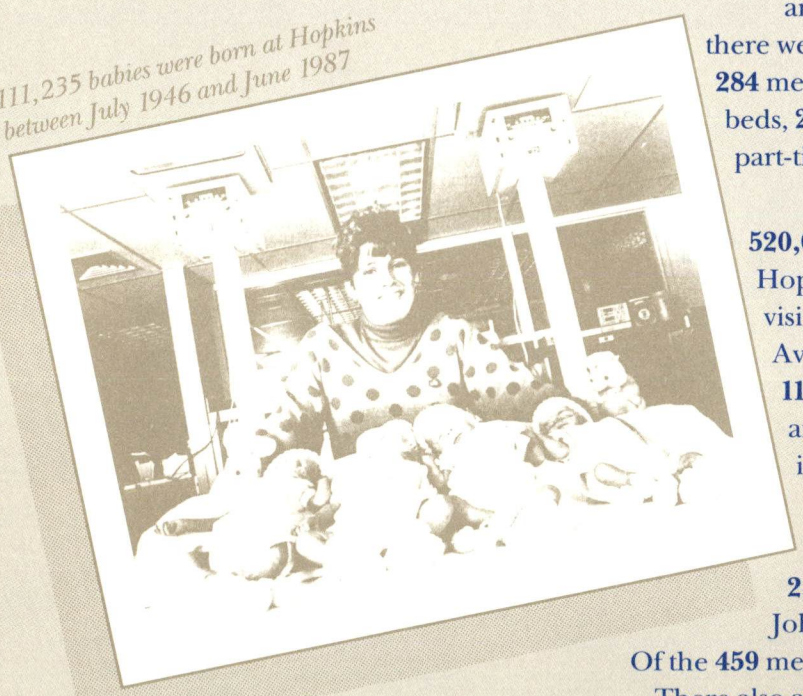




Then and Now:

When The Johns Hopkins Hospital and School of Medicine opened (1889 and 1893), there were **220** hospital beds, **18** medical faculty, and **18** medical students. In 1939, there were **954** hospital beds, **462** medical faculty, and **284** medical students. In 1989, there are **1,077** hospital beds, **2,440** medical faculty (**1,250** full-time and **1,190** part-time), and **459** medical students.

111,235 babies were born at Hopkins between July 1946 and June 1987



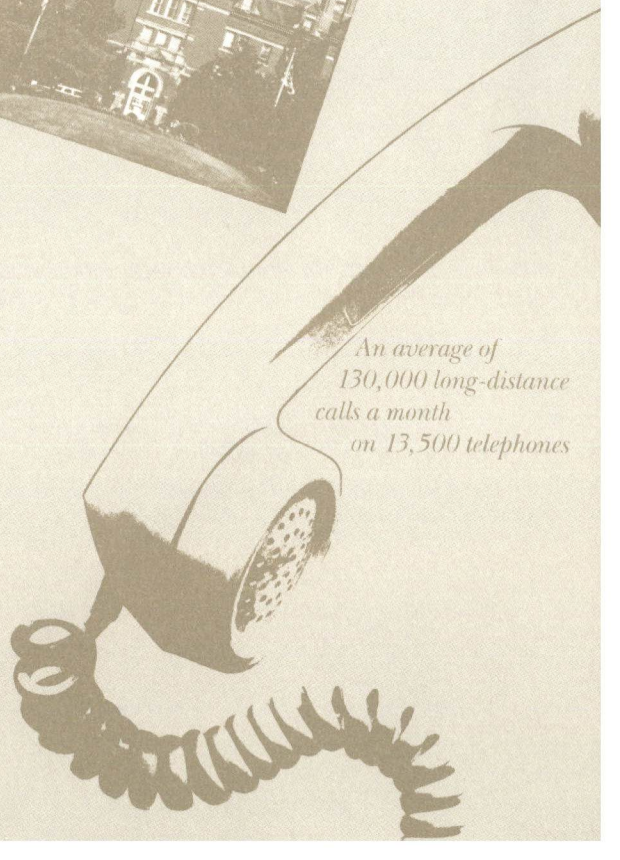
Patients:

520,047 total number of patient visits at The Johns Hopkins Hospital, including **485,052** outpatient visits, and **34,995** inpatient visits in fiscal 1987. Average length of inpatient stay was **8.3** days. **111,235** babies born at Hopkins between July 1946 and June 1987. Translators at Hopkins are trained in more than **36** languages, and patients come from more than **85** countries for treatment.

Schools

2,440 doctors on the faculty of the Johns Hopkins School of Medicine. Of the **459** medical students, **300** are men, **159** are women. There also are **220** graduate students (M.A. & Ph.D.) at the School of Medicine (131 men, 89 women); **6,173** living medical school alumni

An average of 130,000 long-distance calls a month on 13,500 telephones



500,000 pieces of mail are received at the Hospital each month

when the school opened in 1893, tuition was **$200.**
There are **357,414** books in the Welch Medical Library.
The **School of Public Health** has **1,002** students from **67** countries and **2,746** living alumni.
The **School of Nursing** has **50** students.
There are **3,091** nursing school alumni.

50,000 pieces of chicken are served in a year in the cafeteria

Employees

5,111 are employed at the Hospital.
4,751 work at the School of Medicine. And another **1,240** at the Schools of Nursing and Public Health.

Money

A patient bed costs **$326** a day. (It cost **$3** a day to be maintained on the wards when the Hospital opened, but the trustees set the maximum charge at **$2,** and made up the difference by charging private patients more than their rooms actually cost.) The Johns Hopkins Hospital spends **$248.8 million** a year; **$418.2 million** by the Johns Hopkins Health System. The Health System spent **$34.1 million** on unreimbursed patient care in fiscal year 1987. The School of Medicine attracted **$123 million** in 1987 in grants and contracts, the School of Public Health another **$53 million.** (The Johns Hopkins School of Medicine is second in the nation in the number of dollars it receives from the National Institutes of Health, with **$93.5 million** in fiscal 1987.)

20 heart transplants were done in 1987

There are 1,500 nurses at Hopkins Hospital

Translators at Hopkins are trained in more than 36 languages and patients come from more than 85 countries for treatment

Hospital

Hopkins is one of the largest, most diverse hospitals in the world. Altogether, there are more than **340** separate divisions and clinics in **21** Hospital buildings encompassing **2½ million** square feet of space—and more underway. Within those buildings, **74** elevators move people up and down. **23,000** people walk into the Hospital every weekday, **13,000** on a weekend day. (**127,000** people entered during a two-week study in November 1987). **49** escort messengers clock **17,000** trips a month inside the Hospital with patients and their specimens and charts. **3,153** people have been transported to the Hospital's helipad since 1982.

Statue

A **10½ foot** Carrara marble Christ statue greets visitors to the

William Wallace Spence, a Scottish immigrant and one of the wealthiest Baltimore businessmen, and is an exact replica of the Christus Consolator in Copenhagen, executed by Danish sculptor Bertel Thorwaldsen in 1821.

Transplants

Hopkins is **one** of only **eight** institutions nationwide with Medicare reimbursement approval for heart transplants. The number of transplants performed here in 1987: **20** heart, **3** heart-lung, **15** liver, and **43** kidney. Total to date: **95** heart, **12** heart-lung, (eleven patients-one patient had two), **31** liver and **248** kidney. Hopkins surgeons performed **1,010** open heart surgeries during 1987, an estimated total of **28,000** since 1954.

2,440 doctors on the faculty of the Johns Hopkins School of Medicine

Cars

7,500 cars are parked daily in the Institutions' parking garages in a total of **5,084** parking spaces including the Broadway garage with **2,131** spaces, the largest parking garage in Baltimore. New garages will open in fall, 1989 with **1,350** spaces, and an additional **1,080** in 1993. Total number of cars parked is **1,869,250** yearly. There are an additional **1,000** street parking spots within a three block radius of the institution.

7,500 cars are parked daily in the Institutions' parking garages

Housekeeping

More than **6,000** gallons of wax are used each year to polish the Hospital's floors. **7,438,418** pieces of linen are distributed within the Hospital in one year, or **4,751,284** pounds of clean wash at a cost of **$2,001,314.** Each month, the wash includes **48,444** bath towels, **55,877** wash cloths and **56,838** sheets.

There are 357,414 books in the Welch Medical Library

Communications

500,000 pieces of mail are received at the Hospital each month, as many as in a small U.S. postal station. Another **500,000** packages are delivered in a year. The annual bill for the Institutions' telecommunication's services is more than **$5 million** with **13,500** telephones and an average of **130,000** long-distance calls a month, **6 million** minutes of talk a year. **45** high-speed copiers produce more than **30 million** copies per year, and printing machines generate another **20 million** sheets of copy each year.

Medical Supplies

The largest quantity of medical supplies purchased are

syringes. We use **1,012,068** containers of IV solution each year, or **112,737** gallons each year.

are served in a year

Food

The Hospital serves more than **3 million** meals each year. Included are: **Eight** miles a year of Hoagies-by-the-inch in the cafeteria (sold at 50 cents an inch), **72,800** lbs. of coffee, **2,340,000** half pints of milk, **1,447,680** individual juices, **156,000** hamburger patties, **50,700** lbs. of roast beef, **31,200** lbs. of tomatoes, **4,160,000** packets of sugar. Also **280,000** slices of pizza, **16,120** lbs. of lettuce and **50,000** pieces of chicken a year in the cafeteria alone. And to wipe it all clean, we use **9,360,000** napkins.

Hopkins uses 1,012,068 containers of IV solution each year

1889 ~ 1989
JOHNS HOPKINS 100 YEARS
CENTENNIAL OF JOHNS HOPKINS MEDICINE

IN OUT

There were 485,052 outpatient visits and 34,995 inpatient visits in 1987

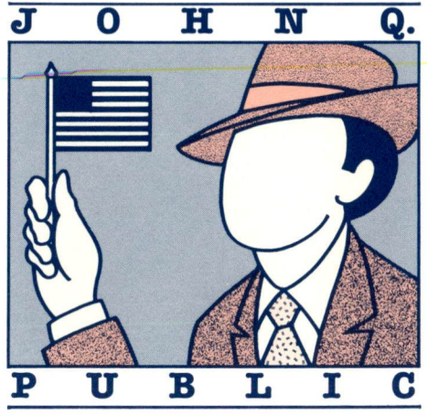
$123 million

The School of Medicine attracted $123 million in 1987 in grants and contracts

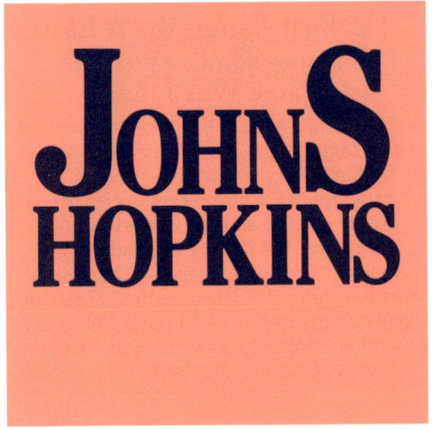
SNAPSHOT

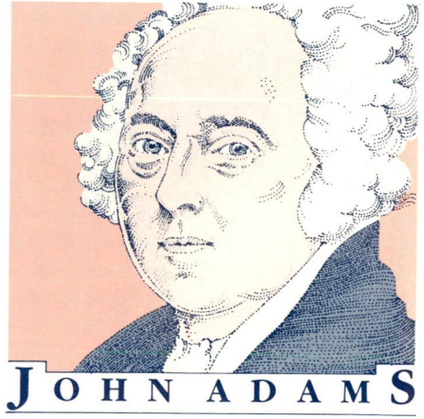
CENTENNIAL OF JOHNS HOPKINS MEDICINE OFFICE OF PUBLIC AFFAIRS 550 N. BROADWAY SUITE 1100 BALTIMORE, MD 301-955-6680

JOHN LENNON


JOHN Q.
PUBLIC

JOHN
WAYNE


JOHNS
HOPKINS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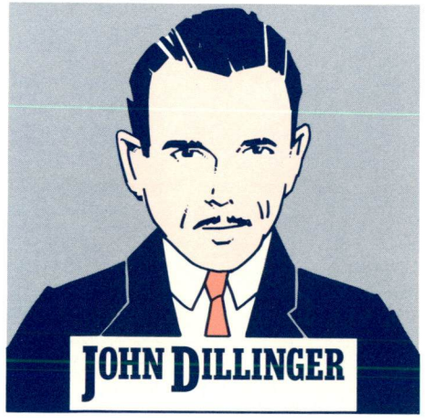
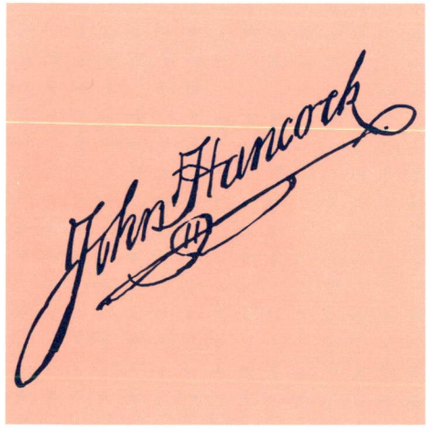
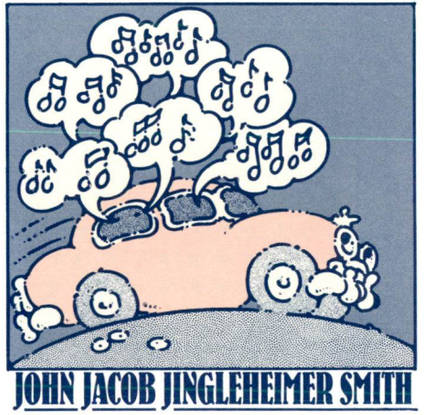

JOHN DILLINGER


John Hancock


JOHN JACOB JINGLEHEIMER SMITH

ALL ABOUT JOHNS

rst Name Was A Last ıe—That's Why His Name Was Johns

imple, really. Johns Hopkins was reat-grandmother's last name as ıame. She was Margaret Johns, r of Richard Johns, owner of an f 4,000 acres in Calvert County, ıd. In 1700 she married Gerard Their great-grandson amassed a ıd, in 1873, bequeathed $7 million sh The Johns Hopkins University : Johns Hopkins Hospital. We're ıur distinctive name. Please use it correctly and often.

The school sponsors the Law Program for Community Developers and Social Workers with the Cook County Legal Assistance Foundation. The Institute of Criminal Justice presents seminars to professional law enforcement officers and agencies. Student organizations include the Student Bar Association, three professional fraternities, and the Order of John Marshall local honorary society. Students publish the *Decisive Utterance* school paper and the *John Marshall Journal of Practice and Procedure*. The library has about 150,000 volumes. The school is accredited by the American Bar Association. Fred F. Herzog has been dean since 1975.

JOHNS HOPKINS UNIVERSITY. Thirty-fourth and Charles Streets, Baltimore, Maryland 21218 (301) 338-8000. In August 1867 twelve relatives, friends, and acquaintances of railroad millionaire Johns Hopkins formed the Johns Hopkins University corporation; a similar board was incorporated for the Johns Hopkins Hospital. On Hopkins' death on December 24, 1873, his will divided $7 million between the two institutions. In 1875 the trustees purchased land for the university on Howard Street in downtown Baltimore, Maryland. Daniel Coit Gilman (BDAE) became president on May 1, 1875; he traveled in Europe in the summer of 1875 and returned determined to found a university comparable to the best in Europe. The first faculty consisted of Basil L. Gildersleeve (BDAE), Henry N. Martin, Charles D. Morris, Ira Remsen (BDAE), Henry A. Towland, and James Sylvester. Twenty graduate fellows were selected in the summer of 1876, and the university was opened in October 1876. In November 1876, Sylvester began publication of the *American Journal of Mathematics,* the first scholarly journal in the country. Remsen began *American Chemical Journal* in 1877, and Gildersleeve founded *American Journal of Philology* in 1880. In June 1878, Henry C. Adams. Thomas Craig, Josiah Royce, and Ernest Sihler received the first doctor of philosophy degrees. Ira Remsen and Constantine Fahlberg, working in the university laboratory, discovered saccharin in 1878. The Johns Hopkins University Press was founded in 1878; it became the oldest continuing university press in the United States. The College of Arts and Sciences was established in 1882.

A medical faculty was organized in 1883 consisting of Remsen, Martin, John Billings, and William Welch (BDAE), who served as first dean of the medical school. The Johns Hopkins Hospital was opened in May 1889 as one of the first teaching hospitals in the United States; the Johns Hopkins Training School for nurses was established in 1889. The medical school was opened in October 1893 with fifteen men and three women students and a faculty of fifteen. The Anatomy Building was constructed in 1894. Fifteen students were graduated from the medical school in June 1897. Gilman retired in 1901; he was succeeded by Remsen (1901–1913). In March 1902 the university purchased the 140-acre site of Homewood House, built by John Carroll of Carrollton for his son; the first buildings, Gilman Hall and Maryland Hall, were constructed in 1915. The

School of Engineering was established in October 1912 with funds from the state. Frank Goodnow succeeded Remsen as president in 1913; he served to 1929. In 1917 the first school of hygiene and public health in the world was opened in east Baltimore as a division of the university. The Walter Hines Page School for the study of international problems was opened in 1930; it was closed in the 1950s.

In 1935 Isaiah Bowman (BDAE) became president; he served to 1948. Under Bowman the university assumed responsibility for the Applied Physics Laboratory in Silver Spring, Maryland, in 1942; it produced the first supersonic jet engine in 1945 and produced the first pictures taken from space in 1946. In 1967 the laboratory produced the first color pictures of the earth taken from a satellite. The Chesapeake Bay Institute was established in 1948. The "Johns Hopkins Science Review," the first weekly television series affiliated with a university, was produced in 1948. In 1950 the university assumed control of the School of Advanced International Studies in Washington, D.C.; the school had been established in 1943 by the United States Foreign Service Educational Foundation. A School of Advanced International Studies center was founded in Bologna, Italy, in 1955; it was the first American graduate school in Europe. Under Milton S. Eisenhower (BDAE), president from 1956 to 1967, the endowment was doubled, the School of Engineering became the School of Engineering Sciences in 1961, and departments of Social Relations (1959), Statistics (1962), and History of Science (1964) were established. The Center for Research in the Social Organization of Schools and Humanities Center were established in 1966, and the faculties of Engineering and Philosophy were combined into the Faculty of Arts and Sciences. The Center for Urban Affairs (renamed Center for Metropolitan Planning in 1972) was opened in 1969. The first women undergraduates were admitted to the university in 1970. The School of Health Services was initiated in 1971 and opened with a class of thirty-five students in 1973. In September 1972 Steven Muller, president of the university, also became president of the Johns Hopkins Hospital, placing the two institutions under a single leadership. On July 1, 1977, the Peabody Institute of Music became affiliated with the university. The G.W.C. Whiting School of Engineering was organized in 1977 to give a new emphasis to engineering.

On the 140-acre Homewood campus are located nearly forty buildings, including Remsen Hall chemistry building (1924), Levering Hall (1929), Rowland Hall physics building (1929), Mergenthaler Hall biology building (1941), Shriver Hall (1954), Ames Hall engineering building (1954), Nichols House president's home (1959), Milton S. Eisenhower Library (1964), Newton H. White, Jr., Athletic Center (1964), Garland Hall administration building (1971), Levering Hall Hopkins Union (1974), McCauley Hall, Seeley G. Mudd Hall, and student dormitories and apartments. The Johns Hopkins Medical Institutions are located in east Baltimore, consisting of the School of Medicine, School of Hygiene and Public Health, Welch Library, and Johns Hopkins Hospital. The School of

Medicine is located in W. Barry Wood Basic Science, Biophysics, Physiology, Traylor Research, and Turner Auditorium buildings. The Johns Hopkins Hospital facilities include the Brady Urological Institute, Marburg Building, Wilmer Ophthamological Institute, Henry Phipps Psychiatric Clinic, Radiology Building, Carnegie Dispensary, and Halsted, Osler, Alfred Blalock Clinical Science, and Edwards A. Park buildings. On the fourteen-acre medical campus are also the Regional Oncology Center (1977), Russell A. Nelson Patient Tower (1977), and A. McGehee Harvey Teaching Tower (1977). The hospital has a separate board of trustees and independent endowment from the university. The School of Hygiene and Public Health is located opposite the Welch Medical Library.

Among graduates of the university have been Nobel Prize winners in medicine: Joseph Erlanger, H. S. Gasser, H. K. Hartline, Peyton Rous, and G. H. Whipple. Many eminent individuals earned the doctor of philosophy degree at the university including President Woodrow Wilson (BDAE) and John Dewey (BDAE). Other graduates include John Henry Fischer (BDAE), Abraham Flexner (BDAE), Gonzalez Lodge (BDAE), George D. Strayer (BDAE), and Guy Everett Snavely (BDAE). Among graduates who also served on the faculty were Florence Rena Sabin (BDAE), first woman graduate and first woman faculty member, and Mary Adelaide Nutting (BDAE), member of the first nursing class to graduate. Other faculty members included Herbert Baxter Adams (BDAE), Alfred Blalock, Aaron Marshall Elliott (BDAE), Hiram Bentley Glass (BDAE), G. Stanley Hall (BDAE), William Stewart Halsted (BDAE), Howard Kelly, Adolph Meyer (BDAE), William Osler, and Isabel Adams Hampton Robb (BDAE).

Johns Hopkins University is a private, coeducational, residential university operating on the 4-1-4 academic calendar. In 1980 there were about 2,200 undergraduate and 850 graduate students, a full-time faculty of 257, and a part-time faculty of 37. The university is organized into the School of Arts and Sciences, G.W.C. Whiting School of Engineering, Evening College, Johns Hopkins Hospital, School of Medicine, School of Hygiene and Public Health, and School of Advanced International Studies. The School of Arts and Sciences offers the bachelor of arts degree in twenty-eight majors, master of arts degree, and doctor of philosophy degree. There are accelerated bachelor of arts and master of arts degrees programs. The McCollum-Pratt Institute is affiliated with the Department of Biology. The G.W.C. Whiting School of Engineering confers the bachelor of arts degree, bachelor of engineering science degree in eight majors, master of science in engineering degree, and doctor of philosophy degree. There are accelerated bachelor and master degrees programs.

The Evening College conducts courses on the main campus and at the Applied Physics Laboratory just south of Columbia, Maryland; Columbia Center in the Joseph Square Village Center; and Hagerstown Junior College in Hagerstown, Maryland. The college is organized into divisions of Administration and Business, Arts and Sciences, Education, Engineering and Physical Sciences, and

18,000 volumes. The university is accredited by the Middle States Association of Colleges and Schools. Steven Muller has been president since 1972.

REFERENCES: Robert Hewes, Johns Hopkins University; Bertram M. Bernheim, *The Story of the Johns Hopkins University* (New York: Whittlesey House, 1948); John C. French, *A History of the University Founded by Johns Hopkins* (Baltimore: Johns Hopkins University Press, 1946); Robert P. Sharkey, *Johns Hopkins: Centennial Portrait of a University* (Baltimore: Johns Hopkins University, 1975).

Peabody Institute of the Johns Hopkins University. One East Mount Vernon Place, Baltimore, Maryland 21202 (301) 659-8163. Philanthropist George Peabody founded the Peabody Institute in Baltimore, Maryland, in 1857; included in the plans was an academy of music. Construction began on the Peabody Conservatory building in 1861, the building was dedicated in 1866, and the first conservatory classes were conducted in 1868. First director was Lucien H. Southard (1868–1871); among others were Asgar Hamerik (1871–1898), Harold Randolph (1898–1927), Otto Ortmann (1928–1941), and Reginald Stewart (1941–1958). Located on a square block in downtown Baltimore, the physical plant is made up of the original Conservatory Building, Leakin Hall preparatory department building (1927), and Peabody Dormitory, consisting of two dormitory towers, a cafeteria and student center (1968). Also in the cluster of buildings is the Peabody Research and Reference Library, which has become a part of the Enoch Pratt Free Library System of the city of Baltimore. On July 1, 1977, the conservatory became affiliated with Johns Hopkins University.

Peabody Institute of the Johns Hopkins University conducts the Peabody Conservatory of Music, which is a private, coeducational, residential and commuter conservatory of music. It operates on the semester academic calendar with summer sessions. In 1980 there were about 500 students and a faculty of more than ninety. Degrees offered are the bachelor of music, master of music, and doctor of musical arts and the artist diploma. The conservatory is organized into the Undergraduate and Graduate departments. There are cross-registration arrangements with Johns Hopkins University, Loyola College,* and Maryland Institute College of Art.* Student organizations include the Dormitory Council, student government association, and professional fraternities and sororities. The school publishes the *Peabody News*. The Peabody Conservatory Library and Record Library includes more than 62,000 volumes. The conservatory is accredited by the National Association of Schools of Music and Middle States Association of Colleges and Schools. Elliott W. Galkin has been director of the conservatory since 1977.

REFERENCE: Pegi L. Jones, Peabody Institute of the Johns Hopkins University.

JOHNSON AND WALES COLLEGE. Abbott Park Place, Providence, Rhode Island 02903 (401) 456-1000. Johnson and Wales College was founded in 1914 in Providence, Rhode Island, as a school of business by Gertrude I. Johnson and Mary T. Wales with Johnson as president (1914–1947). In 1958 the school was

Astronomy's Educational Imperative

An Essay for the Policy Panel
of the
Astronomy Survey Committee

January 1990

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THERE WERE NO ASTRONOMICAL FACILITIES in the western hemisphere in 1825, when John Quincy Adams called for a United States national observatory in his first annual address to the nation:

> Connected with the establishment of a [national] university, or separate from it, might be undertaken the erection of an astronomical observatory, with provision for the support of an astronomer, to be in constant attendance of observation upon the phenomena of the heavens; and for the periodical publication of his observations. It is with no feeling of pride, as an American, that the remark may be made that, on the comparatively small territorial surface of Europe, there are existing upward of one hundred and thirty of these light-houses of the skies; while throughout the whole American hemisphere there is not one. If we reflect a moment upon the discoveries which, in the last four centuries, have been made in the physical constitution of the universe by the means of these buildings, and of observers stationed in them, shall we doubt of their usefulness to every nation? And while scarcely a year passes over our heads without bringing some new astronomical discovery to light, which we must fain receive at second-hand from Europe, are we not cutting ourselves off from the means of returning light for light, while we have neither observatory nor observer upon our half of the globe, and the earth revolves in perpetual darkness to our unsearching eyes?

By 1842, when Congress voted $25,000 for Adams' dream, five U. S. colleges and one high school had built observatories. By 1855, there were about twenty-five "light-houses of the skies" in the U. S. Seven were in private hands, fifteen were associated with educational institutions, and only three had been built with tax dollars. Private donors, large and small, paid for the rest. This pattern of private — not governmental — investment in astronomy persisted for the next century, until the advent of the NSF and NASA.

Ormsby MacKnight Mitchel was a professor at Cincinnati College until it was destroyed by fire in 1845. He garnered wide public support for astronomy through his great orations, and he raised the money from individual contributors to establish the Cincinnati Observatory. "The building of the Cincinnati Observatory," he said, "has forever settled the great question as to what a free people will do for pure science." It did not, at least not where tax dollars were involved. The U. S. did not fund basic scientific research until after the Second World War, when it was proposed, on the basis of the valuable role scientists had played in the war effort, that an expanded scientific establishment would produce abundant peacetime benefits to society. This hypothesis was accepted, but on what must be regarded as an experimental basis. Today's federally funded astronomy program is one consequence.

The question of proportionate return is a basic test for any federal program. Only by knowing the consequences of an action — in this case, allocating tax dollars to achieve expected benefits — can the action be assigned a priority and directed for best effect. The societal returns from federally funded science are to be measured in the national economy and in the nation's preparedness for political issues having scientific and technological bases.

The social indicators of the national science program's performance are cause for concern. The U. S. is losing its competitiveness in world markets. The strength of our technology base is declining. The skill level of the American worker is slipping. The average citizen has a poor appreciation of the *implications* of science and technology — in fact, the 1988 *Science Report Card* of the National Assessment of Educational Progress suggested the deficiencies threaten democracy itself. "The thinking skills and science knowledge possessed by these high-school students also seem to be inadequate for informed participation in the nation's civic affairs," it concluded.

If science has not been made explicitly accountable for its "bottom line," why bring it up here, in the context of the Astronomy Survey Committee? The answers are prudence and citizenship. Social problems related to science are increasingly prominent in the same public forum where the priority of science is also debated. The federal budget deficit is a chronic problem, and the costs of future astronomical projects are becoming conspicuous. If the forty-year social contract between the taxpayer and the scientist is re-opened, figuratively speaking, and serious debate ensues, our community should be prepared to engage the issues adroitly and with credibility. This may happen in the decade of the current Astronomy Survey Committee report. Therefore, an analysis of the social benefits of astronomy — and how they can be improved and increased — is timely.

It must also be said that scientists have a special responsibility to address social benefits exactly because science is *not* operated like a business accountable for profit. The science program is, in effect, run by scientists for the science community through peer review and solicited advice. Their position also puts scientists on the front line of such *meta*-scientific issues as: What disciplines should be funded at what level? What big projects should be started? Is the program coherent, productive, and efficient in terms of its expected benefits?

The fiduciary trust placed in scientists to run federal science is not immutable. It is an experimental feature of the government's sponsorship of pure science since the 1950's. If it is not widely perceived as a beneficial arrangement *for society*, it will change through *perestroika*.

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The question of the social benefits of science is complex, especially for science programs with conspicuous non-scientific attributes, such as the space sciences. The issue is perhaps most interesting for astronomy, which is commonly held the least "practical" yet most "accessible" field of science for the layman.

When the first observatories were built in this country, astronomers and their tools performed three services for the public: maintaining and distributing accurate time, improving ephemeris and almanac data useful for surveys and navigation, and, in broad and various ways, contributing to education and culture. Today, transportation and commerce no longer depend on the skies. After examining the present-day cultural possibilities of astronomy, along with other types of indirect benefits, we will focus on *education* as the primary avenue for astronomy to fulfill its social contract.

FY'90 Federal Budget	
National Endowment for the Arts	$171M
National Endowment for the Humanities	$157M
NASA Astrophysics	$530M
NSF Astronomy	$94M

Is cultural edification a valid justification for a big federal astronomy program? The public that follows astronomical research is minor as compared, for example, with the attentive audience for the arts and humanities, which receive much lower federal support than astronomy on both an absolute and a per-professional basis. Astronomers, artists, poets, and writers all work to create and extend human thought. However, the knowledge products of astronomy — new scientific results — are generally not understandable to the public that commissions them. This obviates the cultural impact of astronomical results, except perhaps in an entertainment or experiential sense. Those aspects are better viewed as enabling factors for astronomy's educational contributions, rather than as ends in themselves.

National prestige and international understanding are indirect benefits of astronomy. Historically, they constitute an intriguing and somewhat self-conflicting duality — competition and cooperation. Galileo's first discoveries with a telescope in 1610 brought honor to Tuscany. In 1835, Yale astronomers saved the U. S. from a minor humiliation in Adams' terms by finding Halley's comet weeks before word arrived from Europe of its sighting there. On the cooperation side, the first grand example of international science was the worldwide campaign of 150 groups at 110 sites to observe the 18th century transits of Venus to determine the true dimension of the solar system. Still today, astronomy provides opportunities to compete peacefully and to cooperate to mutual benefit on an international scale.

Technology — particularly optics — is an area that has benefitted from astronomy in the past. In principle, astronomy could contribute new products and processes to the economy by pushing the frontiers of technology. Increasingly, however, new projects must show that they are at low risk of extra costs or delays due to technical uncertainties. To the degree that this conservative approach discourages developmental technologies, the potential benefits are negated.

However great their potential value, the indirect benefits discussed above are not a useful basis for either justifying or managing the astronomy program. The concepts involved are elusive, and the effects are hard to measure. They are incidental to rather than allied with scientific purposes, and, for that reason, they cannot be independently optimized without interfering with scientific priorities. Furthermore, they do not make a case for any particular level of federal support to astronomy — except, perhaps, that the U. S. astronomy budget should be higher than those of other countries, simply to reduce the risk of being second best.

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The direct educational benefits of astronomy research are of two kinds: new knowledge and support to instruction. We will argue that, while astronomy's historical contributions to general knowledge were profoundly useful, the future results will necessarily be less so — from the public's standpoint. We will propose that the assets of astronomy other than its new facts — that is, its allure, human resources, and implementation — should be the basis of increasing the educational benefits from federally funded astronomy.

The sky has been a schoolroom from time immemorial. The challenge to explain the display of the sun, moon and planets moving against stars led directly to key advances in mathematics and physics, including — in modern time — the calculus, Newton's laws, and the law of gravitation. The scientific method itself arose to arbitrate between successful and failed theories of where the planets are, how they move, when and how they were formed, and what they are as separate worlds. When instruments became capable of analyzing stars

and nebulae, the windows opened into the universe on every scale and dimension ranging from the nucleus to the edge of light, from the beginning of time into the cosmic future. In many ways, the human history of the sky documents the history of the human mind.

Today, the physical principles of the directly-experienced world are understood, partly due to astronomy. This leaves little room for new knowledge from astronomy to materially affect human life. In any event, the educational impacts of the new knowledge cannot be planned and programmed, whereas those based on people and process *can*. Furthermore, the educational ramifications of *doing* astronomy are a natural subsidiary of the research program itself and could be managed as a coordinated sub-element. As such, the astronomical community would lead in defining the educational effort, just as it does currently in setting science objectives.

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We propose that the Astronomy Survey Committee adopt a people- and process-based educational initiative as a central element and theme of its report. We propose the following overarching goals for the initiative: that many more Americans should understand their location in the physical universe — their space-time place with respect to other places of significance; that they should believe the world has a physical basis that can be usefully understood through science; that they should appreciate the basic principles and beneficial applications of technology; and that they should come to view federally funded science as a proportionate contributor to national life.

Astronomy's special character is well adapted to these goals. Much in the fascinating history of astronomy is instructive about where we are and why we think so. Astronomy illustrates more attractively than other fields the basic principles and methods of science. The technologies required by astronomy — fine optics, spectral dividers, detectors, and computers — are advanced but perhaps more understandable than the special tools of physics, biology, and chemistry. The historical figures in astronomy are instructive on human genius, ingenuity, drive, and accomplishment. The people in the astronomy program today — scientists, engineers, managers, administrators and students — demonstrate an interesting variety of career paths for young people to consider. Our challenge is to fashion all these assets into an educational initiative.

We propose that the Astronomy Survey Committee recommend that NSF and NASA administer and manage their astronomy programs to produce educational products and services toward the goals of the suggested initiative. The astronomy infrastructure possesses only some of the necessary skills; others must be provided by coalitions with public and private, commercial and governmental entities peripheral to astronomy. In addition to new structures and alliances, new or reallocated resources will be required within the federal astronomy program. These resources will be devoted to public education objectives, including but not limited to: support for utilizing the products and personnel of astronomy for new educational materials; support for individual astronomy-based education sub-projects; and cooperative ventures in public education.

We propose that the Astronomy Survey Committee recommend that NASA and the NSF adopt special strategies to implement the education initiative, including but not limited to: motivating the astronomy community toward educational outreach activities with opportunities and resources; facilitating the development of curriculum materials for teachers based

on astronomy-related ideas, methods, and careers; encouraging the distribution of supplementary materials using advanced technologies, such as CD-ROM; participating in national programs that could benefit from or extend astronomy's education-related activities; conducting conferences and workshops for teachers and students; leveraging federal investments into commercially viable educational spin-offs; and, in appropriate but innovative ways, opening the definition, design, construction, and operation of new astronomy projects to the nation's classrooms and the public through advanced communication technologies.

In addition to these outward-looking activities, we propose that the way astronomical projects are implemented be examined and better adapted to the training of science and technology professionals. That is, astronomical research — particularly in space — can be done in such a way that a cadre of young scientists, engineers, and managers are educated in the process. This would contribute directly to U. S. technological preparedness. More small programs at universities might increase this benefit, to cite one example.

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Education provides the only distinctive argument for federal support of astronomy at a high level. It is a declared crisis in this country and national priority. Richard Darman, Director of the Office of Management and Budget, has called the educational impacts of the space program a key part of its justification. In his "thousand points of light" address, President Bush asked "all branches and all levels of government [to] join this great movement to extend national service into every corner of America." The top of NASA has promoted the same message. At the National Press Club recently, Administrator Richard Truly was asked facetiously: "Do you think we might find dinosaurs on Mars, or evidence of them?" Without missing a beat, Truly replied, "I don't know about that, but I hope we use dinosaurs and ghosts in space to educate our kids."

If, as we propose, the Astronomy Survey Committee adopts the educational initiative as a central focus of its report, it will respond to a national imperative and provide a model in citizenship for other disciplines supported by federal funds.

Under George Bush's leadership, Superfund will be a high profile program. He will protect appropriations for Superfund and vigorously enforce EPA regulations on toxic waste disposal.

- o George Bush will place even greater emphasis on getting those who have dumped toxic wastes to cooperate with expedited cleanups at priority sites. George Bush will instruct the EPA to vigorously pursue all responsible parties, so that no one has an incentive to drag out settlement negotiations.

- o George Bush will streamline and accelerate the priority cleanup process.

- o Building on the initiatives he has already made to rationalize federal regulation, George Bush will remove regulatory barriers to the introduction and implementation of new technology to reduce the production of toxic wastes and to dispose of these wastes more safely.

- o George Bush will ensure that federal facilities, including military bases, meet all environmental standards. There is no national security interest in contaminating groundwater.

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IOWA METHODIST HOSPITAL
Des Moines, Iowa
January 22, 1988

Undoubtedly, the three biggest challenges facing America's health care system as we prepare for the 21st century are affordability, availability, and quality. Here at Iowa Methodist I know you're working hard on all of these issues.

There is a cost problem -- anyone who's ever been hospitalized knows that -- and we need to address it. Our Administration has made a good start. The prospective payment system instituted in 1983 has finally permitted us to get a handle on hospital costs.

But the system is not perfect. For one, it's unfair to rural hospitals. When Congress decided to institute a differential scale for payment to rural and urban hospitals, it hurt rural hospitals. Rural hospitals do have more costs than Medicare assumes.

The rural hospital is the backbone of its community. When you lose the hospital, the community has a tough time keeping, let alone attracting, industry. As President, I will support efforts to correct this differential payment problem in a way that will not bankrupt the federal budget.

We need first-rate health care professionals to fill those hospitals and we have to attract and keep physicians in rural communities. One of the reasons for the decline in the number of doctors serving our farm communities is the terrible cost of malpractice insurance. And I was in the trauma unit just a minute ago. One of the doctors was helping me understand that more clearly -- he and his two assistants being right on the front line in that area. In December, the Iowa Medical Society polled the state's 500 doctors who performed obstetrics services. 150, half in rural counties, said that they had stopped delivering babies because the cost of malpractice coverage had doubled in just two years. Today, if you are pregnant in a rural county, you might have to travel a long way to have a baby delivered. The potential health risks to mother and child are alarming.

Now if we are going to stop this erosion of medical care in rural communities, we've got to restore common sense and fairness to the medical malpractice system. And one way to do that, and a way I strongly endorse, is tort reform. A lot of this is a state responsibility, but the federal government does have a role in it.

I think we ought to restore fault as a standard of recovery. We ought to eliminate this joint and several concept where somebody who is just peripherally there on the scene might have to do all the paying if the prime person to blame can't make it good. So we have to do something about that. And the Congress has been reluctant to move on it; there is some strong opposition to it in various quarters of the House and Senate. But one good thing that can come out of the election is getting a mandate to the Congress to take some action on questions that have just sat there dormant. And this is one of them, and I would like to have a hand in pushing to see that we can take some corrective action back there in Washington.

Another issue I want to mention is long-term care. This is a big concern of mine. The problems of affordability and availability are particularly acute when it comes to long-term care.

This issue takes on added importance here in Iowa because you have the second highest elderly population per capita in America. And the need for long-term care is not exclusive to seniors -- people of all ages can be struck by chronic illness.

Long-term care is very expensive. It costs an average of $22,000 a year to stay in a nursing home. Several weeks ago, I outlined a proposal to deal with the cost of long-term care -- by providing incentives for people to buy long-term care insurance, while ensuring that seniors who cannot afford this coverage do not have to exhaust their life's savings before their spouses are eligible for Medicaid assistance.

But the best solution to the high cost of long-term care will mean nothing if there are not enough professionals to care for the elderly. Currently, patients in more than 40 percent of all nursing homes get no more than 6 minutes of RN time apiece per day -- and almost a quarter of

all homes have no RNs at all. Those are startling statistics, but as all of you already know, we have a shortage of professional nurses in this country.

We've got to get more and more people interested in nursing, and that includes not just women but men, minorities, and people who want to re-enter the workforce in mid-career. There are great opportunities for nurses all across America -- and those opportunities are expected to grow and expand.

As our health care system diversifies, professional nurses will be needed in ever-growing numbers to work in HMOs, ambulatory surgery centers, and home health groups. Those patients who need to be hospitalized will require the sophisticated care that must come from professional nurses.

Since 1983 there has been a 25 percent drop in enrollment in nursing schools. By the year 2000, the American Hospital Association estimates that we will have only half of the nurses we need. Obviously, we need to do better than that.

We can begin by promoting a better awareness of what nurses actually do. I think the nursing profession suffers from a lot of misunderstanding.

You've got strong nursing activities here at Iowa Medthodist; it deserves to be emulated by other hospitals. I've always believed in deregulation and decentralization, and I like the idea of your head nurses being able to hire and fire and set their own budgets. I also believe in providing people with incentives. Your clinical ladder seems like a good way to reward excellence in nursing. We need other hospitals to follow your lead.

* * *

HEALTH CARE

The American health care system can provide the best health services in the world. People from all over the globe come to America for treatment by our doctors and hospitals. Our medical schools, medical research, and medical personnel are without parallel.

Most Americans have complete access to care, and for difficult problems where you really need a medical system, the American system is far better than any in the world. The answer is not to take giant steps backwards in quality of care to deal with access problems for the poor and the uninsured, but to continually improve the excellent American system and to give every American a plastic card and access to our health system.

Instead of taking untested, costly risks by requiring all employers, including schools, hospitals, and small non-profit organizations, to assume expensive new burdens, George Bush will work to address each segment of the problem. By taking these careful steps, he will protect those with sound

THE CLEVELAND CLINIC FOUNDATION
Cleveland, Ohio
April 18, 1988

I want to talk with you about the biggest challenge facing the United States in the years ahead -- how we're going to stay competitive in this increasingly aggressive world marketplace.

The steps we take to meet the competition will determine America's prosperity -- our standard of living -- long into the future. Some people would have us copy what our competitors are doing. Others would have us hide behind protectionist barriers.

But that's not competing, that's retreating.

We will succeed by doing what we do best -- by exploiting our comparative advantage. And our greatest single strength for the future is not mining or manufacturing or even agriculture -- it is our ability to expand the limits of our knowledge. From that will flow the scientific and technological advances that will enable us to compete and to raise the living standards of all the nations of the world.

The people working in places like this around the nation, pushing back the frontiers of human understanding, will have more of an impact on 21st century America than all of us down in Washington, D.C.

In the past year I have seen firsthand -- at the Monsanto Research Center in St. Louis and at Burroughs-Wellcome in North Carolina's Research Triangle Park, at Yale's new nuclear accelerator, from the Silicon Valley to Route 128 in Massachusetts -- the leading edge of science, and it is so impressive.

I have seen the future in these laboratories -- wheat that will withstand drought, strawberries that will repel frost, drugs that will combat AIDS.

Our Administration has recognized the importance of science to our national security and our economic health. Despite the extraordinary pressures on the budget, the President last year challenged all Americans to embark on "A Quest for Excellence," and he recommended that funding for the National Science Foundation be doubled over the next 5 years.

As the Foundation's director, Erich Bloch, put it, "Basic research and education are our key assets in the battle for international competitiveness. Where we have a clear lead, we must preserve it; where we are lagging, we must catch up."

"Investing in basic research and education will not immediately reduce the trade deficit, but it will provide the new knowledge and technically educated people that are prerequisites for anything we do in commerce, industry, defense, or health."

Sometimes the best thing the federal government can do is simply make less of a nuisance of itself. The task force that I head, the President's Task Force on Regulatory Relief, has been watching very closely an experiment at five Florida universities that dramatically reduces the red tape and paperwork requirements that accompany federal research grants.

We recently approved a substantial expansion of that experiment. We need researchers spending their time working in the laboratory, not filling out government forms.

The key to our success in the years ahead will be our people -- how well they're educated, how well they're trained and managed, how well they do their jobs. Of these, the most important is education, and that's why I've said throughout this campaign that I want to be the Education President.

Some say American workers can't compete any more, but I don't believe that. American workers are the best in the world. If we give them the tools, they can compete, and they will prevail.

Better education means better American workers, and better workers means better American products. And one thing we have learned from the Germans and Japanese is this: When it comes to competing in the world economy, quality sells itself.

You believe in treating the whole patient. This is the direction in which medicine must go.

You have been a bold pioneer in case management -- working with patients throughout their illness, not just when they are in the hospital. The result is better quality care, as well as reduced costs, because the patients don't get as sick.

You also have been a leader in the aggressive marketing of health care services, most recently with the opening of Cleveland Clinic Florida in Fort Lauderdale.

Because Cleveland Clinic physicians are salaried, you can offer innovative package rates to surgical patients, removing some of the financial uncertainty at a time of crisis.

Revenues in excess of salaries and operating expenses are used to fund clinical research, medical education, and technical innovation.

I understand that malpractice is not the problem here that it is in some other medical settings -- again, because of your quality patient care. But it is a problem elsewhere.

In Iowa, there was a survey done of 500 Iowa doctors who perform obstetric services. 150 of them said they had stopped delivering babies altogether because the cost of malpractice coverage had doubled in just two years. The implications of that trend for our great country are simply alarming.

Here in Ohio, I understand that physicians are exposed to malpractice claims for an unpredictable length of time. Medical liability claims and law suits have increased in this state, just as they have throughout most of the country.

What we must do in the years ahead is restore common sense and fairness to the medical malpractice system. One way to do that is with tort reform. One way not to do that is with intrusive and excessive government regulation.

In closing, let me say: No matter what we're doing, Americans always look for new and better ways of getting the job done. I could see that spirit as I toured your clinic today.

In your operating rooms, under you microscopes, with your own hands, dramatic medical breakthroughs are born. You haven't just sat back and waited for the future. You've made it happen.

That's the spirit, that's the American spirit we will need in the years ahead -- not just in health care, but in every field of endeavor -- if America is going to continue to lead the world.

With that spirit America can stand as tall in the 21st century as it does today -- the freest, the fairest, the most compassionate, the most prosperous nation on the face of the earth, and you all are doing far more than your share in making that happen.

* * *

THIRD INTERNATIONAL CONFERENCE ON AIDS
Washington, D.C.
June 1, 1987

Coming as you do from around the globe, united in purpose, what you accomplish is of vital imortance to every nation on earth. It is no exaggeration to say that the health and well-being of literally millions of men and women depend on you.

The cause that unites us, of course, is our battle against AIDS, a new and mysterious disease. The number of victims is almost doubling every year. As of a year ago the United States had a total of 16,000 cases of AIDS reported since 1981. Today that total is over 36,000. Over one-half of those victims have died of the disease. And the tragedy is that the rest may, too.

By this time next year we will have added more than 23,000 new cases of AIDS. And by the end of 1990, the U.S. Public Health Service predicts a quarter of a million Americans will have contracted AIDS.

When we in the United States first began to confront the AIDS epidemic six years ago, the victims were easily categorized. There were the homosexuals, the bisexual men, the I.V. drug users, and the recipients of blood and blood products. And these groups still account for 9 out of every 10 cases here in the United States.

But now we're receiving more and more reports of AIDS virus infecting heterosexual men and women who are not I.V. drug users. In fact, there heterosexual activity seems to be their only risk factor. Close to four percent of all reported AIDS cases in this country are reported to result from heterosexual contact.

On the face of it, four percent does not seem like much. But that number is expected to increase dramatically during the next five years.

It is projected that by 1991, most people in certain cities in America will know someone who died of AIDS.

So make no mistake about it. AIDS is spreading and killing, in every corner of the world. It does not discriminate. It is an equal opportunity merchant of death.

Cases of AIDS have been reported in 112 countries. The World Health Organization estimates that as many as 100 million people will become infected with AIDS during the next decade.

As if these figures are not appalling enough, there is more. A large number of individuals who do not knowingly practice high-risk behavior are also being infected by the AIDS virus -- people like the wives of bisexual men, the spouses of I.V. drug users, and the husbands and wives of promiscuous spouses, and, saddest of all, babies born to I.V. drug users or otherwise infected mothers. Tragically, some infants are being abandoned, left to die alone in hospital nurseries.

What can be done to help? Well, first and foremost we desperately need a cure or a vaccine. I chair the President's Task Force on Regulatory Relief and earlier this year we worked with the Food and Drug Administration to accelerate the availability of experimental drugs to AIDS patients. We did this to encourage more research and development on potential AIDS vaccines by the private sector.

Meanwhile, our government will spend $766 million this year and close to $1 billion next year on AIDS. And as we look into the 1990's we may have to spend even more.

But money alone won't stop AIDS.

Those at high risk must be educated on how to avoid contracting the disease. The only guaranteed way to halt the spread of AIDS, given what we know now, is a change of behavior. And those at risk will not change unless they know the terrible dangers they face.

As a world community, we have a tradition of taking a straight-forward approach to health warnings. When, through careful scientific research, a health hazard is identified, warnings are issued by health officials, and most people take steps to reduce their risk to disease or danger.

Research, warning, risk reduction -- three phases that have served us well in the past, and must continue to serve us well in combating the AIDS crisis.

If we know that dirty needles and certain kinds of sexual behavior can transmit AIDS, we have an obligation to make the public aware of the risks involved.

I am not a scientist or a research or a medical doctor. But as an elected official, I think an important role of the federal government is to provide timely, factual, and impartial information about this deadly, insidious disease.

I have spoken with the Secretary of Health and Human Services, Dr. Bowen, Surgeon General Koop, and many others about the possibilities of finding a cure or a vaccine as soon as possible. And I applaud the efforts they've made to educate the American people about AIDS.

In April, I toured the research facilities at the National Institutes of Health. I visited an AIDS patient, and talked to him about what he was going through. I saw firsthand what this disease can do. It is brutal. It is unforgiving.

We must wage an all-out war against the disease. Let me repeat: an all-out war against the disease -- not against the people. Not against the victims of AIDS, but an all-out war against the disease itself.

The most important thing we can do is to tell our people the facts about AIDS and what they can do to protect themselves from it and to prevent it from spreading any further.

We've got to put into the hands of parents and students and people throughout America essential facts about AIDS in a thoughtful, sensitive manner. I recognize some of the countries represented here have already successfully completed nationwide mailings. I hope we can learn from your experience and find creative ways to distribute some of the very good material that has been developed.

I believe that education is primarily a local matter. Parents and the community should control what goes on in their schools. That system has worked well for more than 200 years and I don't want to change it. I don't want the Federal government to mandate some insensitive educational program.

Most schools now offer some kind of sex education during the junior high or middle school years. Depending on local standards and after a meeting of the minds with parents and school officials, education about AIDS should be incorporated into the curriculum. If the curriculum is well-planned and thoughtfully carried out, we can teach children the facts about sexually transmitted diseases -- and AIDS in particular.

This kind of education can and should be non-threatening. It should teach traditional values. It should teach morality. It should help develop the child's own sense of personal responsibility. And it should strengthen the concept of the family.

When it comes to educating our young people about AIDS, we must all work together -- parents, educators, religious and community leaders, medical doctors and scientists.

As difficult or as awkward as it may seem, parents must assume much of the responsibility for educating their children about AIDS. They need to talk to their children in a way that only a parent can -- with a special love, compassion, respect, and understanding.

Not long ago, my wife Barbara and I received a telephone call from our second oldest son, Jeb. He was concerned about the threat of AIDS and how to explain to his children the dangers of this terrible disease. It seems that Jeb's 11-year-old son, Barbara's and my grandson, had come home from school one day asking about AIDS. That really brought home to me the absolute necessity of educating our young people.

Right now, education is our best weapon against this dreadful disease. In some respects, education is our only weapon.

And let me repeat again the crux of our battle. It is a battle against a disease and not against people. We must remember that the sick and the dying require our care and our compassion, no matter how the illness was contracted.

Which brings us to perhaps the most controversial subject in dealing with AIDS: testing. Who should be tested?

This issue raises some difficult and troublesome questions for me. It puts in conflict the need for more information and knowledge to benefit the majority versus our basic Constitutional right to privacy.

We have often had these questions where two of our basic rights or needs come into conflict. We use our political process and our government to resolve these conflicting interests.

Testing is an extremely complex issue for that very reason. But it is the responsibility of the political leadership to decide among competing principles. Ultimately, we must protect those who do not have the disease.

Thus, we have made the decision that there must be more testing. As the President said last night, the federal government will soon require testing for prisoners, immigrants and aliens seeking permanent residence. Tests are already being conducted in the military and in the foreign service. Additionally, we are encouraging the states to offer routine testing for those who seek marriage licenses and for those who visit sexually transmitted disease or drug abuse clinics. We are also encouraging states to require routine testing in state and local prisons.

Of course, any mention of testing must be hurriedly followed by the word, "confidentiality." If society feels compelled, in some circumstances, to test its citizens, then it is absolutely imperative that those records are kept appropriately confidential. It is also imperative that help be available to those who test positive.

In closing, let me say we need money for research and treatment. We need education. We need testing, but only accompanied by guarantees that everyone is treated fairly.

We all have a duty -- and I don't use that word loosely. Elected officials must use their position as a bully pulpit to get out our message about the dangers of AIDS. And the experts -- all of you -- the doctors and the researchers who deal with this disease on a daily basis must not let up until a cure is found.

Although our respective roles are different, we do share one common responsibility. And that is to remain understanding, caring and compassionate toward those afflicted with AIDS. We must not succumb to the demagoguery or the irrational ideas of some out there. The fight against AIDS is not a partisan fight. It is not a witch hunt.

It is our duty to do all we can not only to find a cure and a vaccine, but also to make sure we never create a climate in America, or in any other country, where friend turns against friend, where countryman turns against countryman.

The challenge is upon us. And it is a challenge we must meet.

* * *

STATEMENT ON THE AIDS COMMISSION REPORT

The Commission report is a landmark analysis of the problems facing our country due to the AIDS epidemic. There is little doubt that it will be the benchmark for future discussions.

Admiral Watkins and his colleagues have set the right tone for how we should approach AIDS in the months and years to come.

I am particularly pleased that the Commission recognizes the need for patient notification and wide-spread testing as a means to limit the spread of AIDS. Such programs will be ineffective without being coupled with strict confidentiality and anti-discrimination provisions.

I am also encouraged by their understanding that the AIDS crisis and the drug crisis are intertwined. We will be unable to stop the spread of AIDS if we do not stop the spread of drug abuse.

The Commission identified the problems confronting our scientific and medical communities in the search for a cure, vaccine and treatment of those with the disease. The Commission's recommendations to make these efforts more effective should be given the highest priority.

It is our duty to do all we can, not only to find a cure and a vaccine, but also to make sure we never create a climate in America where friend turns against friend, where countryman turns against countryman.

* * *

Driving Down Health Care Costs

Strategies & Solutions

1990

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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HEALTH COMMUNICATION ANALYST

OFFICE OF DISEASE PREVENTION AND HEALTH PROMOTION

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A Panel Publication

3

Health Promotion: The Only Long-Term Solution to Health Care Cost Management

Clark E. Kerr

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3.02 **Health Providers and Employers Falling Short**
3.03 **Ignorance Can Be Expensive**
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3.06 **Health Promotion: The *Only* Long-Term Solution**

Health care costs continue to rise extraordinarily in relation to the consumer price index. Predictions for 1989 are for a 22% overall increase, but actual individual company experience with health costs could be worse. In 1988 in California, some large private and public employers were faced with 30%, 40%, even as high as 60% increases in health insurance premiums.

The situation has become so serious that some large companies have actually made predictions as to the date that health care costs will entirely eliminate their corporate profits. As an example, one large, profitable Los Angeles business determined that if profit and health cost trends both continue without change, its profit, and thus its reason for existence, will evaporate in 1995.

3.01 U.S. COMPETITIVENESS HURT

As any U.S. computer or car company, bank, or appliance manufacturer realizes, its price competitiveness with Japanese companies is undercut by the fact that per-employee health care costs in Japan are less than half the U.S. rate. This differential translates to roughly $100 billion of additional costs that American companies must bear and this, in turn, hurts our world competitiveness. Equally disturbing is the fact that, even though our health care expenses are more than double, life expectancy in the United States is lower than it is in Japan, and infant mortality is twice as high.

Exhibit 1 shows that there is little relationship between health expenditures and the general health of a population. Although U.S. health costs will surpass $600 billion in 1989 and the increases seem to know no limits, there are very definite limits to the influence of health services on our health. According to many health experts, life style is the dominant factor affecting our health. This means that about half of the cost of employee health care is due directly to poor employee habits, including smoking, eating too much, exercising too little, drinking too much alcohol, not getting enough rest, being overstressed, not wearing seat belts when driving, lifting improperly, and so forth.

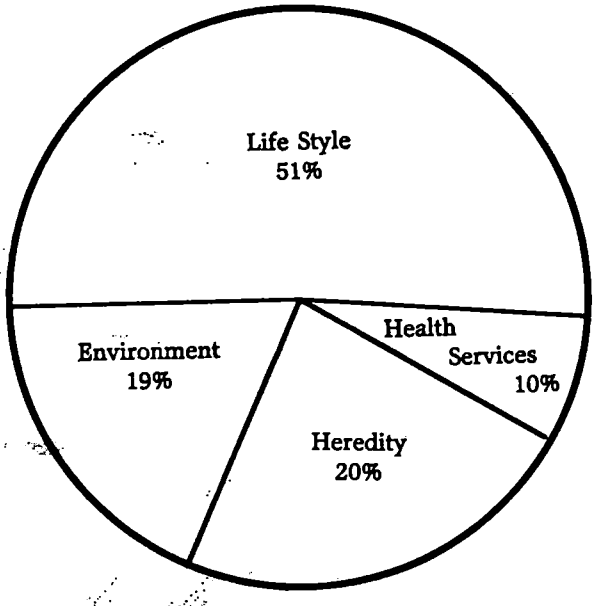
Because employees' unhealthy life styles are responsible for half of our health costs, effective health promotion is the single most powerful way to manage future health care costs. But how seriously is this potential being taken? And are the health plans that companies offer their employees helping to promote health?

3.02 HEALTH PROVIDERS AND EMPLOYERS FALLING SHORT

Last year, Bank of America surveyed a random sample of more than 3,000 of the employees in our fee-for-service plan and the 37 HMOs we offer. We wanted comparative

information on the plans in four primary areas: perceptions of quality of care, relative satisfaction, adverse selection, and health promotion.

Exhibit 1
Factors Influencing Health



Source: Based on statistics provided by the U.S. Department of Health.

We found that overall, there was no significant difference in perceptions of quality of care or relative satisfaction between the fee-for-service plan and the HMO "average" (although there were very substantial differences among the individual HMO plans themselves). The issue of adverse selection, that is, whether HMOs are attracting the best health risks into their plans, remains clouded. What we found was that although the fee-for-service members were older than their HMO counterparts by about six years, both groups had about the same percentage of ongoing medical problems and chronic disease. And the "average" HMO enrollee's life style was less healthy (more smoking, overweight, and stress, and less exercise) than that of their fee-for-service counterparts. In addition, the HMO par-

ticipants actually used medical services more often than the fee-for-service participants (8.5 medical encounters per year versus 7.9; 14.3% hospitalized per year versus 10.3%).

The bad, if not unexpected, news concerned health promotion. Although health plans tout their wellness programs in advertising, most are inadequate in this area in terms of actual outreach to their members. When we asked our employees if they had made use of health promotion programs offered by their health plans, only 12% of the HMO members responded that they had even "occasional" assistance in life-style enhancement. The fee-for-service response was 7%. Clearly more than 7% to 12% of health plan members are overweight, overstressed, exercise too little, or smoke or drink too much. Too many health care providers are simply not meeting their promise to help keep employees well.

And what about employers? Although there has been considerable talk about "wellness" for the past decade, a 1984 survey of Fortune 500 companies conducted by Market Pulse Management Systems indicated that these companies ranked wellness programs fifteenth in importance on a list of 15 health care cost-containment strategies. That health promotion came in dead last (even after "company representation on hospital boards") is not too surprising considering the lack, at that time, of corporate experience with and data on serious health promotion programs.

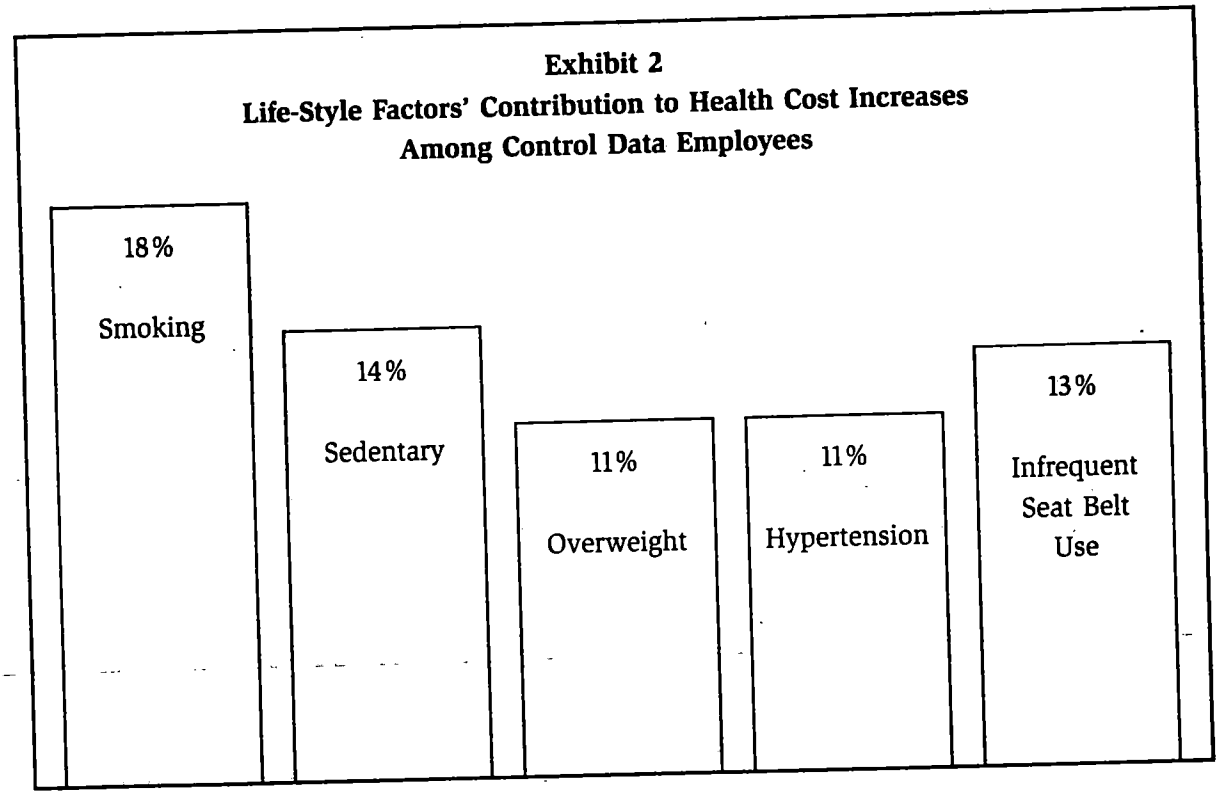
3.03 IGNORANCE CAN BE EXPENSIVE

Despite the fact that neither providers nor employers are doing much to address the issue of wellness, the evidence linking life style and health costs is compelling. In one study, Donald Vickery, MD, compared employees' responses on life style and age, and organizational size, with Blue Cross/Blue Shield rates for eight worksites in Ohio.[1] Life style was demonstrated to be the best predictor of health insurance rates. In fact, statisti-

cal analysis showed that 81% of the variation in insurance rates was explained by life style alone.

As further evidence, Control Data Corporation has been keeping track of both specific employee health habits and medical costs, and is one of the few corporations that has conclusively matched the two. Exhibit 2 summarizes Control Data's findings. As indicated, employees who smoke a pack of cigarettes a day generate 18% higher medical claims than nonsmokers; sedentary employees have claims 14% higher than individuals who exercise vigorously at least three times a week for a minimum of 20 minutes at a time; hypertensive and overweight (30% over ideal) employees have costs 11% higher for each group than healthy employees; and using seat belts less than 25% of the time while driving translates into 13% higher medical claims costs than when they are used frequently.

Exhibit 2
Life-Style Factors' Contribution to Health Cost Increases Among Control Data Employees



If there is no doubt about the link between life style and medical insurance costs, why are health promotion programs still a tough sell at many companies, and why are

they often among the first items cut in tough times? Few corporate executives would now dispute that changes in life style lead to improved employee mental and physical health. Nor do most question that a healthier employee translates into lower medical costs and less absenteeism. Instead, what executives question is whether health programs will actually result in significant improvements in employee health habits.

3.04 CHANGE IS POSSIBLE

A number of companies, including Bank of America, are finding that it is possible to change employees' health habits. This has sometimes dramatic payoffs in reduced costs (and enhanced employee morale), and can be accomplished relatively inexpensively and for a geographically dispersed employee population.

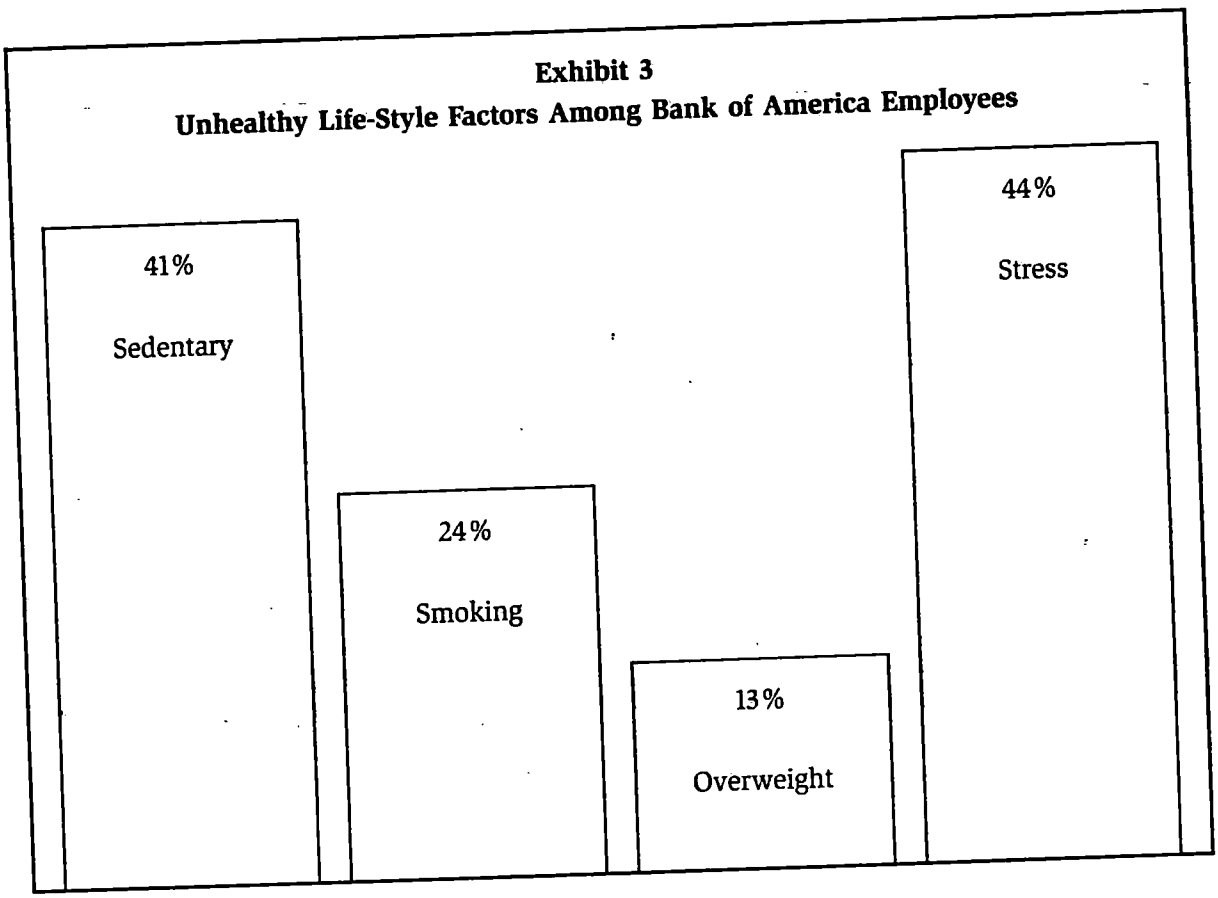
[1] "Be Your Best" Challenges

Bank of America is headquartered in San Francisco and has 53,000 employees in more than 1,000 locations throughout the United States. Our geographic spread, very limited funding due to difficult financial times, and philosophy that all units should have reasonably equal access to our programs required an innovative approach to employee health promotion. In 1987, we conducted a survey of employees that enabled us to identify health factors that were putting our workforce at risk. (The findings are summarized in Exhibit 3.) Much of our communication effort was directed at reducing these factors.

Bank of America's Corporate Health Programs launched its wellness promotion under the banner "Be Your Best." One of the most popular aspects of the program has become the monthly "Challenge" that is featured on the back page of our employee newsletter. These challenges have included the following: Take your children, spouse, or a friend out for a vigorous walk at least three times a week. Eat at least one generous serving of salad

or fresh fruit, drink two glasses of low-fat milk (or eat two servings of low-fat yogurt), and drink at least six glasses of water every day for a month. Complete a seven-minute "bankercise" stretching exercise routine every workday for a month. (We supplied the exercise guidelines.) Every workday for a month find one cartoon or joke that made you laugh and share it with someone else at work.

Exhibit 3
Unhealthy Life-Style Factors Among Bank of America Employees



Employees who meet that month's challenge clip a coupon from the newsletter and return it to us, certifying that they completed the challenge. We immediately reward them with a booklet or other information on a specific aspect of fitness, nutrition, stress management, or on another health-related subject. The coupons are also entered in a monthly drawing in which 50 prizes are given away. These prizes have included "Be Your Best" T-shirts, first-aid kits, low-fat cookbooks, giant rubber band exercise devices, and self-care

reduction and managing personal stress. We emphasize the first area through discussion of communication skills, time management, conducting productive meetings, motivation, handling conflict, and the importance of compliments and affirmation. We help managers reduce their own stress by encouraging them to exercise and eat properly and by teaching relaxation techniques (visualization and breathing). A variety of icebreaker exercises are used to help managers experience firsthand the importance of humor and open communication in relieving stress.

We also make available a video on stress management that managers who have completed training can show to their staffs, as well as stress management pamphlets that can be distributed to each employee, and posters on related health subjects that can be placed on bulletin boards.

[a] Stress Claims Slashed

We trained 250 managers from San Jose in our pilot program. The results of this initial attempt were gratifying. In the year before training, stress-related workers' compensation claims in that region were $124,000. Such claims dropped to $29,000 in the year following training.

We are now introducing a pilot program in our payroll processing units that involves staff as well as managers. Employees are trained to manage their own stress, and a Corporate Health Programs professional acts as consultant—performing quarterly stress "checkups." The consultant and unit managers first identify any new stresses in the workplace and establish an action plan to handle them. This is followed by a short meeting in which both manager and staff review stress management techniques. If any individuals are experiencing serious stress symptoms, the consultant will work one-on-one with them. The consultant then follows up by phone to be sure that all is going well. Although stress

is the workers' compensation claim that is rising most rapidly and is suspected as a major factor in many medical claims (it weakens the immune system, is implicated in accidents, and so forth), the good news is that companies can manage it successfully.

[4] Back Injury Prevention

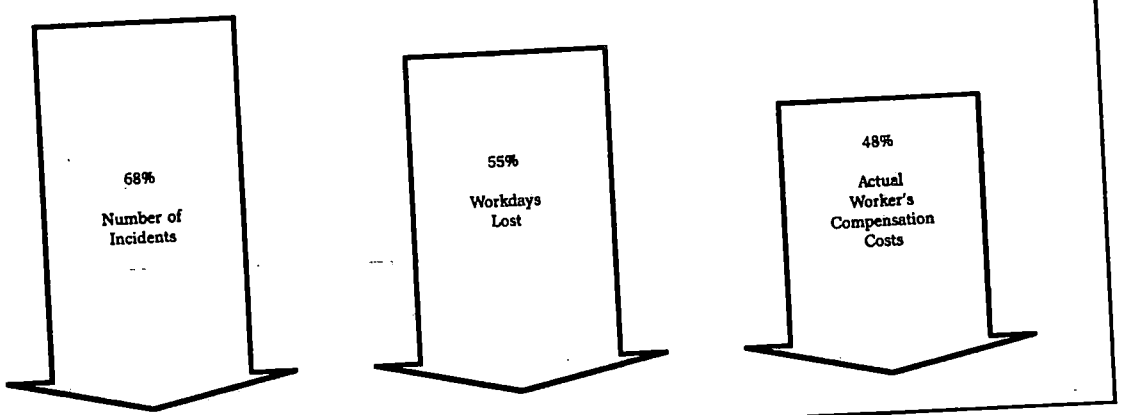
Our workers' compensation claims related to back injury surpass $1.3 million annually, and the claims are concentrated in a few departments. We targeted these departments for a program developed and implemented by a registered physical therapist on staff.

The therapist first works with managers, reviewing with them the workers' compensation costs related to lifting injuries in their units. Both the critical role of managers in preventing these injuries and the need to communicate concern for the individual rather than blame for an accident are emphasized. The body mechanics of safe lifting are covered, and an ergonomic evaluation of the workplace is made, with suggestions on modifications that would make the lifting environment safer.

Employees are shown a video that demonstrates safe lifting techniques. Anatomy and body mechanics are vividly illustrated. We feel that there is no reason to make health and safety boring, although too many presentations do. The physical therapist then ties in stress management, general fitness, and proper weight as keys to avoiding back pain. The therapist demonstrates correct lifting procedures, and then all of the employees take turns practicing and critiquing one another. Each employee also receives pamphlets on back-strengthening exercises and proper lifting techniques.

Results for the first six months since the program was introduced are summarized in Exhibit 4. As can be seen, there were substantial reductions not just in the number of injuries, but also in days lost and workers' compensation claims. If these trends continue, 245 fewer workdays will have been lost and $44,000 will have been saved in workers' compensation claims for the full year.

Exhibit 4
Reductions in Back Injuries and Associated Losses Among Bank of America Employees



[5] Smoking Cessation—Long-Distance Style

Our employee health survey indicated that 24% of our employees smoke (see Exhibit 3). (The national average is about 27%.) Studies have found that smokers, on average, cost their companies at least $400 more annually than do nonsmokers in terms of increased medical care, absenteeism, and so forth. Because an estimated 95% of people who stop smoking do so "cold turkey" on their own, we were already making free stop-smoking kits available to employees. But we wanted to offer additional support for those who needed it. We learned of a program developed at the University of California, San Francisco, medical school called "Quit for Life." The intervention program was designed for physicians to help their patients stop smoking.

Working with the university, we modified the program so that our company nurse could use the techniques to give employees assistance over the telephone. This solved our geographical diversity problem in that one person (our nurse) could easily "travel" the country by phone. But could phone contact alone work as effectively as personal contact? Physicians using this brief intervention and support program achieved quit rates of up to

15%. Our nurse, working with a pilot group of employees, was able to help 22% of them stop smoking, using only phone contact and support materials sent by mail.

[6] Hypertension Self-Care

Personal encouragement and support are essential in any successful health promotion program. With our stop-smoking program, phone contact was as effective as personal contact in helping employees improve health habits, and allowed a centralized health promotion staff to service a nationwide area. Our hypertension management program is another example of a long-distance program that works.

Units wishing to participate in the program are sent an information kit, a video on high blood pressure, and a digital blood pressure monitor. Employees have had no trouble understanding the directions for using the monitor and are soon taking their own blood pressures. All employees are encouraged to send their readings to the nurse along with a one-page form rating themselves on seven hypertension risk factors: weight, exercise, smoking, alcohol consumption, stress, and salt and cholesterol intake. In response, program participants receive a letter evaluating their status, along with a colorful package of relevant health materials. Those with high blood-pressure readings are contacted by phone and encouraged to report these findings to their personal physicians. The nurse also helps these employees develop a life-style action plan to help bring down their blood pressures. The nurse continues to send them helpful information and periodically calls to see how they are doing and to offer further advice and encouragement.

Employees ask questions such as "How can I keep on a regular exercise program when time is so limited?" or "How can I reduce my cholesterol intake during business lunches?" Our nurse offers suggestions to help overcome the obstacles unique to each person's situation, and this personal attention is the key to making the program a success.

Employees know that someone is concerned about them, so they are much more likely to change habits related to hypertension. The concern expressed over the phone seems as effective as personal attention. In fact, our employees were as successful in reducing their blood pressures as employees in organizations with on-site programs.

Among other successes, our nurse encouraged one group of employees to start exercise walks after work, helped another employee quit smoking after 30 years, and assisted yet another person in reducing his blood pressure by 20 mg.—into the low-risk range.

3.05 WHAT ABOUT RETIREE HEALTH CARE COSTS?

Because our health promotion programs were successful with employees, we wondered whether we could achieve the same results with retirees. Premiums for our retiree health plan have been soaring, with an average increase of more than 20% per year over the past three years. The real effect on most corporate bottom lines, however, will occur in 1994, when FASB requires us to move our unfunded retiree health care liabilities on to our balance sheets. This will affect most corporate earnings and will reduce stockholders' equity. According to some estimates, balance-sheet disclosure of these unfunded liabilities may add as much as $50 billion a year to corporate retiree health expenses. Rapidly escalating retiree health costs, plus the new accounting requirements, will necessitate action. We will have to significantly trim benefits, shift cost increases to retirees (adopting the defined-dollar approach in place of the defined-benefit plan), or find some way to significantly reduce the need for medical services by our retirees (make them more healthy).

[1] "Old Dogs" Don't Learn New Tricks, or Do They?

Myths die hard. In two pilot programs for our retirees, one to control high blood pressure and the other to teach low-impact aerobics, we discovered two important facts:

Retirees are very interested in health, and many are willing and able to make life-style changes that improve their health.

Bank of America recently undertook another large-scale pilot project with Blue Shield of California's Senior Healthtrac Program to see whether health promotion and self-care can significantly reduce overall retiree health costs. James Fries, MD, of Stanford University, believes that morbidity can be "compressed" so that less illness occurs in our later years, thereby reducing health costs. Because, unfortunately, health promotion does not materially extend average life spans, efforts aimed at promoting health will not increase pension costs.

3.06 HEALTH PROMOTION: THE *ONLY* LONG-TERM SOLUTION

We have not come close to taming the health cost monster with all the strategies employed to date: utilization review; case management; second surgical opinions; home care and hospices; HMOs and PPOs; and increased employee responsibility for premium costs, deductibles, and copayments. The one great remaining hope is health promotion. No other strategy has the potential of cutting current utilization of medical services.

At Bank of America, we found that employee health promotion programs need not cost a lot of money or require a large staff. Using advertising techniques to get the word out and generate interest, using the phone to "travel" to distant locations, using employee data to pinpoint health problems, and above all, showing concern, has saved us dollars while improving employee morale. Although we can never expect to motivate everyone to exercise vigorously, manage stress, limit intake of fats, and stop smoking, we must try, using all the creativity and ability we can muster.

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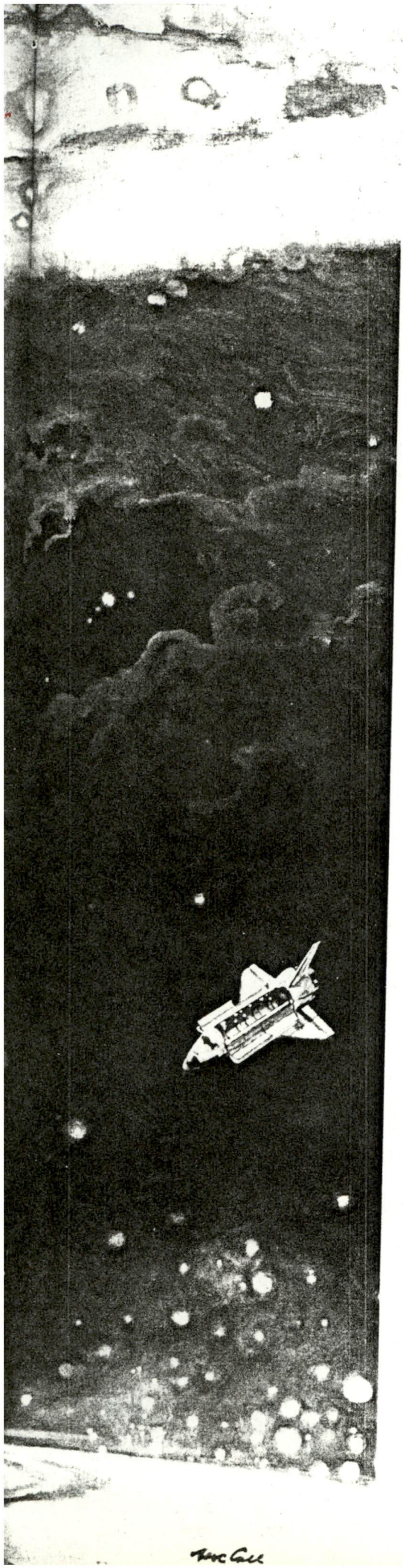
1. D. Vickery et al., *Journal of Occupational Medicine,* November 1986.



THE SEARCH FOR THE BEGINNING OF TIME

BY JOHN NOBLE WILFORD

ANY SPACECRAFT THAT inspires allusions to Alice of Wonderland cannot be meant for some ordinary excursion through the heavens. The Hubble Space Telescope is, indeed, not just any spacecraft. Scheduled for launching this spring, after five years of delays, the spacecraft and its exquisitely polished 94½-inch-wide telescopic mirror should enable astronomers to see farther and 10 times more clearly than they have before, out tantalizingly close to the edge of the universe and toward the very beginning of time. Excited astronomers can hardly believe their good fortune to be living at a moment so rich in the promise of revolutionary discovery. One of them likens the anticipated adventures in astronomy to Alice stepping into Wonderland.

Malcolm Longair, the Astronomer Royal of Scotland, has written, with respectful apologies to Lewis Carroll, a whimsical (though highly technical) book about the "world's most extraordinary looking glass" and titled it "Alice and the Space Telescope." His Alice encounters Humpty Dumpty, who has been put together again by the people at the National Aeronautics and Space Administration. She asks him why the telescope will revolutionize mankind's understanding of the universe. "The answer is very short," Humpty Dumpty replies. "Space Telescope will revolutionize mankind's understanding of the Universe because it cost a billion dollars."

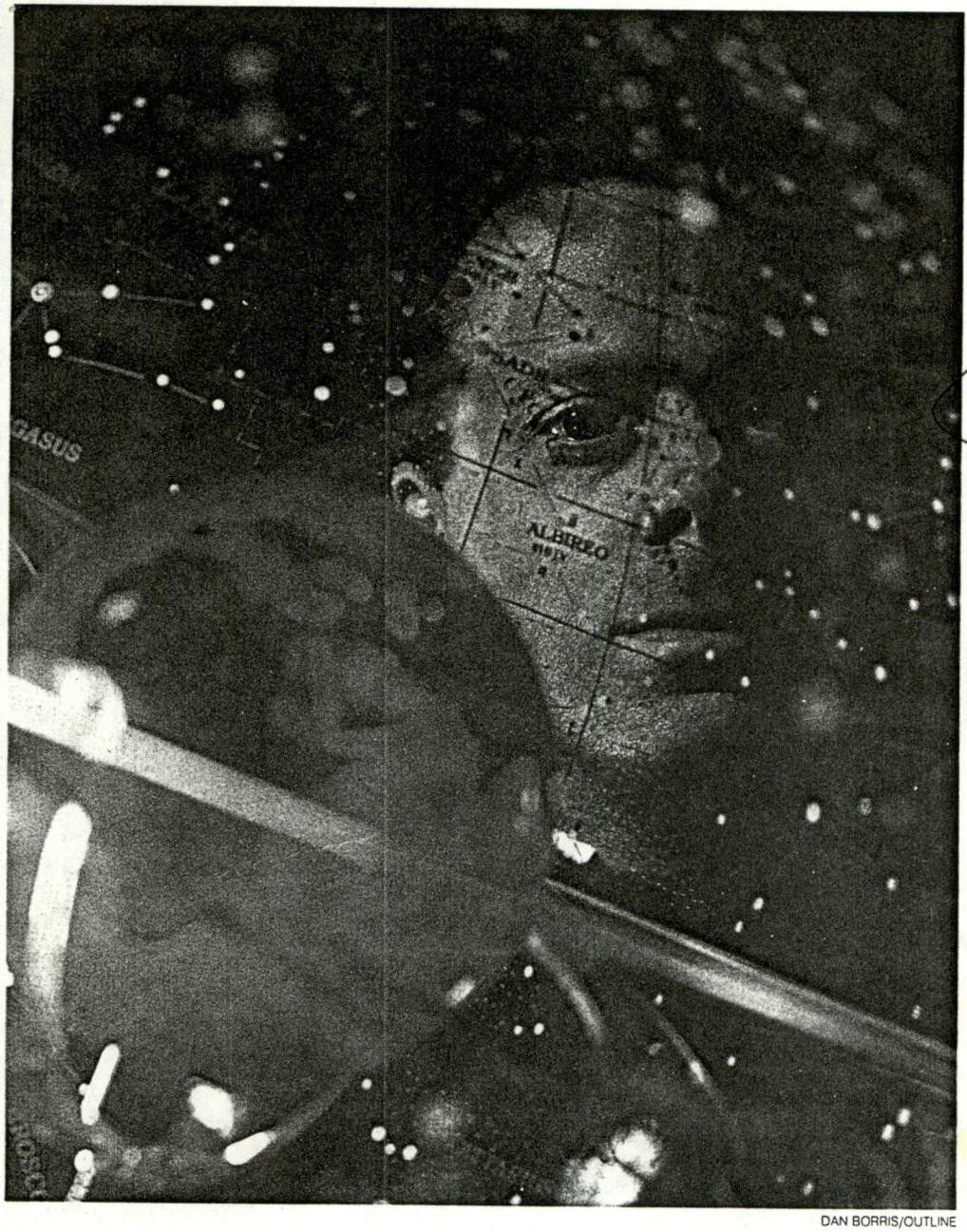
Actually, since construction began in 1977, one and a half billion have been spent on the space telescope, mostly by the United States, but with some critical help from the 13-nation European Space Agency. (By contrast, the bill for the Keck Telescope, the most powerful ground-based instrument, nearing completion in Hawaii, will come to $100 million.) Hubble's costs escalated, in large part, because of early development difficulties and the four-year launching delay necessitated by the explosion of the space shuttle Challenger in January 1986. Just operating the Hubble, once it gets into space, will run $200 million more a year.

But astronomers reckon the value of their expensive eye in the sky not by cost, the cynical Humpty Dumpty notwithstanding, but by their own vision of impending discovery. Over the next 15 years or more, the Hubble's designed lifetime, the

John Noble Wilford writes about science and space for The New York Times. His newest book, "Mars Beckons," will be published in May.

THE HUBBLE SPACE TELESCOPE, SCHEDULED FOR LAUNCH THIS SPRING, MAY PROVIDE CLUES TO HOW THE UNIVERSE BEGAN—AND HOW IT MAY END.

ROBERT McCALL



DAN BORRIS/OUTLINE

Rodger Doxsey of the Space Telescope Science Institute says the delays in launching, paradoxically, have been beneficial.

THE SPACE TELESCOPE WILL LET ASTRONOMERS SEE ALMOST TO THE END OF THE UNIVERSE.

breadth and depth of view from the telescope's 380-mile-high orbit should open their minds to realms of knowledge once denied mere mortals. With it they expect to learn the age and size of the universe, and to probe its origin, evolution and ultimate fate.

The telescope will search for planets around other stars, a key to the quest for extraterrestrial life, and examine interstellar dust and gases out of which stars are born. It will contribute to the heated dispute over the rate of the universe's expansion — and thus over its age — one of the most important measurements to be undertaken by astronomers operating the telescope. "In Wonderland, you get prizes for asking the questions, not for giving the answers," says Longair's Mad Hatter. "It's just like extragalactic astronomy."

With the spirit of Alice leading the way, I set out on my own wide-eyed adventure, which landed me in Baltimore. Now, astrophysicists applying Einstein's general theory of relativity to three-dimensional space believe that the universe is curved and has no center. But try telling that to the engineers and scientists established in a beige brick building on a wooded hillside on the campus of Johns Hopkins University. This is the Space Telescope Science Institute, financed by NASA and operated by the Association of Universities for Research in Astronomy, a consortium of 20 institutions that also runs major observatories at Kitt Peak in Arizona and Cerro Tololo in Chile. Here astronomers are putting the finishing touches on mission plans and will be directing, by remote control, what the telescope looks at. If this does not exactly make Baltimore the center of the universe, it insures that it will be a center of cosmic exploration well into the next century.

OVERSEEING THIS AMBITIOUS UNdertaking is Riccardo Giacconi, an Italian-born astronomer and the institute's director. He was a professor of astronomy at Harvard and led the international scientific teams that developed and successfully operated the Uhuru and Einstein X-ray astronomy satellites in the 1970's. For the last eight years he has been planning how to make the most of the Hubble telescope's abilities. He has also become an articulate and enthusiastic spokesman for modern astronomy.

The windows of his spacious office look out on the earthly delight of a brook flowing through Wyman Park, but in response to a question, he seems to see, from behind the thick lenses of his glasses, only the panorama of astronomy's history. Yes, he agrees, we have reached a point of mind-stretching revelation unlike anything since Galileo gazed through the first telescope in 1609 and, seeing the four moons orbiting Jupiter, glimpsed the truth of the Copernican concept of worlds circling the Sun. That was the beginning of the end of belief in an Earth-centered universe.

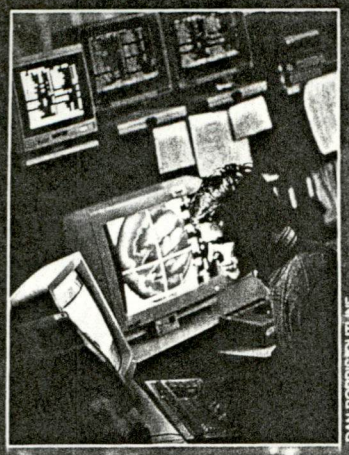
"We are in a period of revolution in astronomy," Giacconi says with a heavy Italian accent. "Anything you really want to know about the universe we've found out in the last 50 or so years. If you want to know how stars form, produce their energy and then die — that was unknown until the theory of general relativity and the discovery of nuclear fusion in this century. If you want to know how big the universe is, and how old — we started learning that in 1930."

It was the American astronomer Edwin P. Hubble who laid the groundwork for studying the age of the universe. In the 1920's, he made two startling discoveries — that the universe is organized into galaxies of many sizes and shapes, and that the galaxies are rushing away from one another. Moreover, the more distant galaxies are moving away from Earth faster than those closer by. This relationship between distance and recessional velocity became known as Hubble's law. The most distant objects, according to this law, represent conditions in the early universe, close to the beginning of time. It thus became conceivable that the age of the universe could be calculated.

It is altogether appropriate that the new telescope bears Hubble's name. His discovery of an expanding universe not only made sense in terms of Newton's theory of gravity and Einstein's relativity; it also proved to be the wellspring for the idea of the Big Bang, now the reigning theory of how the universe began.

The Hubble telescope alone will not bring a fuller knowledge of the birth and evolution of the universe, as Giacconi readily acknowledges. Visible light, which conventional optical telescopes magnify, tells only a small part of the cosmic story. Radio, infrared and ultraviolet waves, X-rays and gamma rays carry messages of an incredibly violent universe, which were unsuspected as long

NATIONAL OPTICAL ASTRONOMY OBSERVATORIES

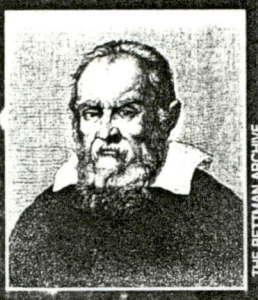


DAN BORRIS/OUTLINE

THE BIG QUESTIONS

Astronomers think that the Hubble telescope may deliver answers to three of the most challenging questions in cosmology:

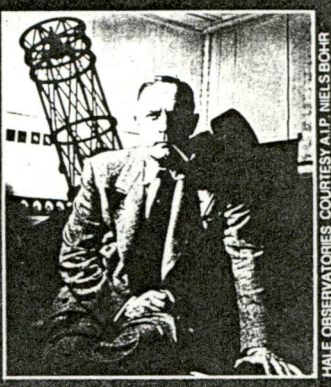
- How fast is the universe expanding? Observations of certain stars could determine the speed at which galaxies are receding and pin down the expansion rate to an accuracy of 10 percent.
- How old is the universe? Estimates range from 10 to 20 billion years. Examining extremely old and faint stars could yield a more precise answer.
- What is the fate of the universe? By learning the rate at which the universe is decelerating, scientists may be able to determine its mass, or density. These observations should give scientists important insights into whether the universe will continue to expand forever or collapse in on itself.



THE BETTMAN ARCHIVE

GALILEO

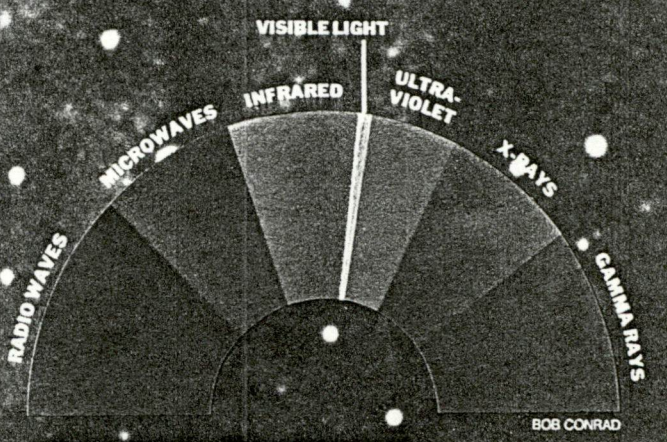
The Italian astronomer was the first to look at the heavens through a telescope, in 1609. His observation of four moons orbiting Jupiter supported Copernicus's belief that the Earth was not the center of the universe but was actually a satellite of the Sun.



HALE OBSERVATORIES COURTESY A.I.P. NIELS BOHR LIBRARY

EDWIN P. HUBBLE

The space telescope is named after an American who made two discoveries in the 1920's that transformed astronomy. He recognized that the universe is organized into galaxies, and that they are all hurtling away from one another. His discovery of an expanding universe led to the Big Bang theory of cosmic creation.



BOB CONRAD

THE ELECTROMAGNETIC SPECTRUM

The violent forces created by stars, galaxies and other cosmic objects result in electromagnetic vibrations that spread out into space like ripples in a pond where a pebble has been tossed. These electromagnetic waves come in different forms of radiation, varying in frequency and wavelength. Only a narrow band of the spectrum (visible light) is observable by the human eye. The Hubble telescope will not only see visible wavelengths more clearly but also penetrate more deeply into ultraviolet and some infrared wavelengths.

SCANNING THE GALAXIES

M83, 10 million light-years away, a spiral galaxy in the constellation Hydra.

Riccardo Giacconi, director of the Space Telescope Science Institute, holding a scale model of the Hubble telescope.

DAN BORRIS/OUTLINE

as human vision reached only as far as the apparent serenity of the night sky. Since Hubble's day, astronomy has developed an amazing variety of tools for observing wavelengths of radiation invisible to the eye.

In the 1960's, huge dish antennas first detected radio waves emitted by gases being sucked into enormous gravitational sinks in space known as black holes. In 1967, similar telescopes picked up radio waves emanating from neutron stars, or pulsars, which are stars that have collapsed into rapidly spinning dense objects. Two years earlier, radio antennas had detected the faint radiation left over from the Big Bang itself. Gamma and X-ray detectors borne by spacecraft have revealed the fantastically powerful forces at the core of galaxies and in quasars, those brilliant enigmatic starlike objects, each presumably associated with the core of a galaxy, billions of light-years away. Spacecraft with ultraviolet telescopes have defined much of the structure and composition of the vast regions between galaxies. And an infrared telescope, also operating from orbit, has detected stars in birth as well as disks of dust surrounding other stars, where planetary systems may be evolving.

One of the most liberating influences on astronomy has been the ability to rise above Earth's murky and turbulent atmosphere, which either blocks or attenuates radiation in all wavelengths, including visible light. The Hubble telescope's surpassing utility will derive from its orbital vantage point. Thus, though its mirror is less than half the size of that of the 200-inch Hale telescope on Mount Palomar in California, which has been astronomy's premier optical telescope since 1948, the Hubble should have 50 times the sensitivity.

NOTHING DEFINES THE HUBBLE'S potential for discovery better than the big questions that scientists, with an audacity bordering on hubris, are asking it to address. Colin A. Norman, a lanky Australian and former Rhodes Scholar, is a theoretical astrophysicist at the institute. He strides to the chalkboard in his office and poses the three big questions in the cryptic symbols of his profession.

H_0, he scratches on the board, pronouncing it H (for Hubble) naught. This stands for the present rate of the universe's expansion. The trouble is that no one can be sure what the rate is. Some estimates are twice that of others, resulting in uncertainty about what scale to apply in measuring cosmic distances and, hence, about whether the universe is as little as 10 or as many as 20 billion years old.

"This is one question we're really going after," Norman says. By observing stars of the Cepheid class, especially the luminous giants that serve as beacons for surveying astronomers, Hubble should accurately determine distances to remote galaxies, much farther away than any measured before. Analysis of these distances and of the speed at which the galaxies are receding, Norman predicts, should determine, once and for all, the rate of expansion of the universe to an accuracy of about 10 percent.

T_0 is the symbol for the second question, which has to do with the age of faraway globular clusters — dense accumulations of some of the oldest stars that can be observed. T stands for time. Current estimates range from 12 to 17 billion years old. Hubble's cameras and spectrographs, which spread out the light gathered by the telescope, dividing it into separate beams according to wavelength, should be able to resolve the colors and magnitude of these extremely old and faint stars and thereby fix an age for them and the distant clusters they inhabit.

"The first two questions I think we'll handle very well," Norman says, before writing the symbol for the third and more difficult question on the board: Ω_0. Omega naught, he explains, is the measure of the universe's density. (Omega, the last letter of the Greek alphabet, refers to the end of the universe.) Scientists believe the universe is still expanding but at an ever slower rate. If they learn the scale of distances and ages of the oldest stars, then they can, with other careful observations of galactic motion, determine the rate of deceleration of the expansion of the universe. That rate is a function of the mass, or density, of the universe.

Scientists may discover that the density is such that the universe should eventually cease expanding and collapse in on itself. Or they may discover that the universe will expand forever, growing more and more tenuous. A third possibility is that the universe *(Continued on Page 56)*

IN ASTRONOMY, A POINT OF MIND-STRETCHING REVELATION IS AT HAND.

TELESCOPE

Continued from Page 33

is closer to a state of equilibrium, expanding still, but in what scientists describe as a "coasting phase."

THE ADVANTAGES OF ORBITAL telescopes were prophesied in the 1920's by Hermann Oberth, an innovative thinker who influenced the German rocket team led by Wernher von Braun. Lyman Spitzer Jr., a professor of astronomy at Princeton University, began promoting the idea after World War II and, soon after space flight was inaugurated in 1957, gained an important ally in the National Academy of Sciences. The academy's strong recommendation moved NASA to begin designing the Hubble telescope in 1972.

But those were lean years for the space agency. Budget cuts and rising costs of building the reusable space shuttles left the cupboard bare. Only a herculean lobbying effort led by Spitzer and John N. Bahcall, an astrophysicist at the Institute for Advanced Study in Princeton, N.J., saved the project from extinction. In 1975, the astronomers finally struck a deal with NASA and Congress. The telescope would use the shuttle for launching and servicing, which meant it had to be reduced in size, down to a 94½-inch mirror from the originally planned 120-inch version. This compromise, and the promise from Europeans to assume 15 percent of the costs, cleared the way for work to begin in earnest.

Some 60 scientists from 38 institutions were selected by NASA to design and develop the telescope. Under the guidance of C. Robert O'Dell, the former director of the Yerkes Observatory in Williams Bay, Wis., who was chief project scientist, they decided on six instruments to be operated in conjunction with the telescope, each capable of making different but somewhat overlapping observations.

Two of these will be cameras, which will produce the mission's most tangible results. The wide-field-and-planetary camera developed at the California Institute of Technology and NASA's Jet Propulsion Laboratory, is actually two cameras in one. Operating in the wide-field mode, it will survey entire galaxies at a resolution about 10 times better than any ground-based telescope. In the planetary mode, the camera's field of view is narrower, but big enough to display the whole disk of Jupiter; it should be sensitive enough to see Uranus and Neptune better than ground-based telescopes do.

The faint-object camera, built by the European Space Agency, complements the other camera, but is specially designed to detect distant objects; it will see celestial bodies 50 times as faint as any so far seen from the ground, according to O'Dell.

Two spectrographs break up the light into the spectrum, allowing scientists to analyze the chemical composition, temperatures and magnetic fields of celestial objects.

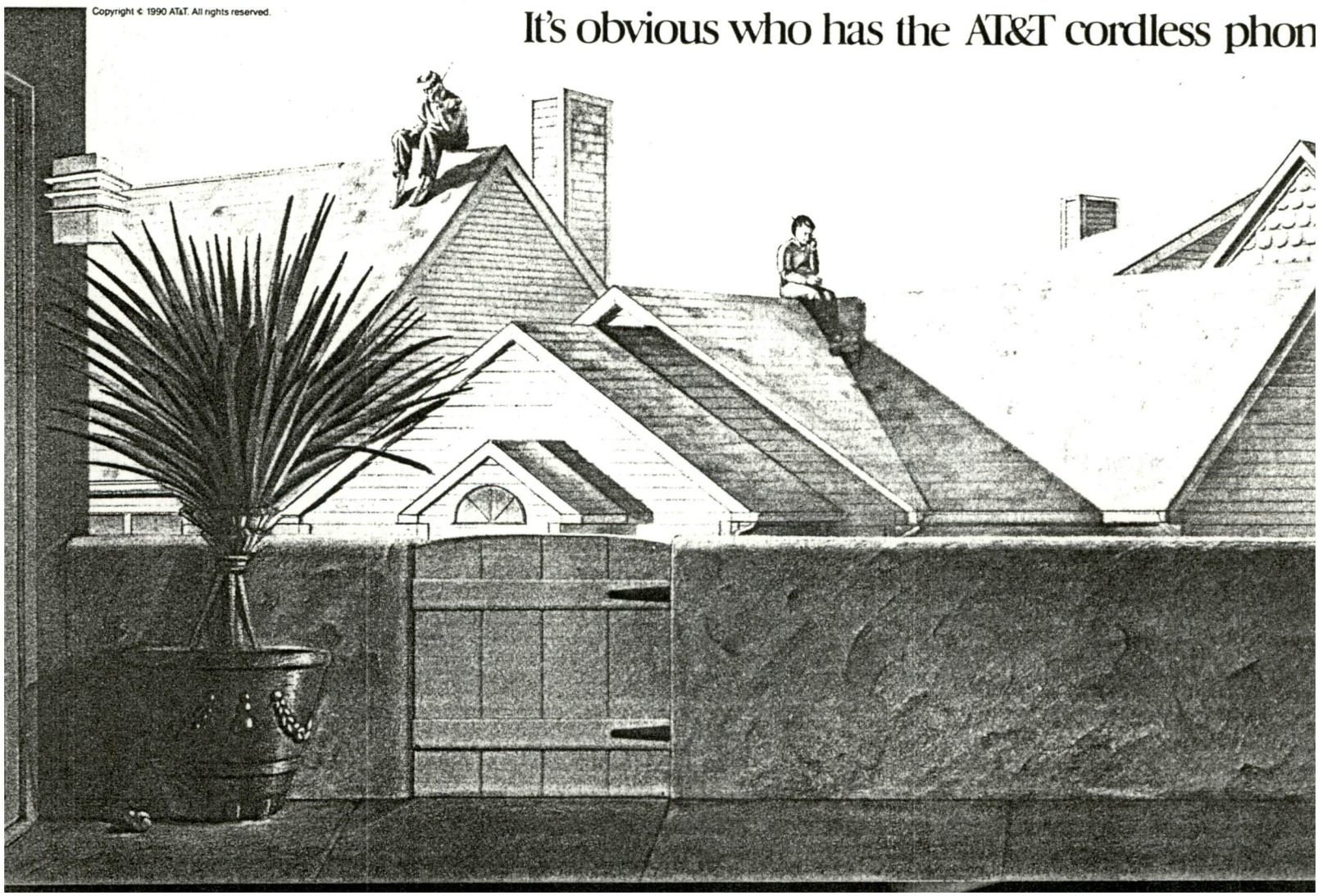
The simplest instrument on board will be the high-speed photometer, a very sensitive light meter that measures the intensity, wavelength and other properties of the light. The sixth of these instruments, a set of fine guidance sensors (which have three "pickle shaped" segments, according to Longair's description), points the telescope at its target. They will measure star positions 10 times more accurately than has been done, findings that should be invaluable in establishing distance scales in the universe. All of the instruments are sensitive to ultraviolet light, a part of the electromagnetic spectrum that is especially obscured by the atmosphere. The telescope itself is also sensitive to a portion of the infrared wavelength, which could be measured by instruments installed in the future.

Sitting in his Princeton office one morning recently, John Bahcall let his thoughts drift back to the early planning days and to one colleague in particular, Robert Danielson, a professor of planetary science at Princeton who did preliminary design studies for the telescope's cameras.

"Bob had a blood disease he knew to be terminal, and was in great pain," Bahcall says. "I carried his briefcase for him to meetings, and once, toward the end, I asked him why he kept on. He told me, because it was the most important thing he could do with the time left him. I think we all felt that way. We were excited, eager, absolutely hyper about the telescope. You know you have a chance to play a role in making history."

While the astronomers designed their instruments, engineers at Lockheed Missiles and Space Company in Sunnyvale, Calif., started on the spacecraft. The company was awarded the contract because of its experience building complex photographic surveillance satellites for the Air Force (although the Hubble's tracking system and light sensitivity preclude it from observing features on Earth). The spacecraft looks like a log wrapped in silvery insulating material, 43 feet long and 14 feet wide; with the telescope fitted inside, it weighs 12 tons. Once the telescope is released from the cargo bay of the space shuttle, the craft's antennas will be deployed, as will two wide solar panels, which will supply electric power for all operations.

The Perkin-Elmer Corporation in Danbury, Conn., a company knowl-



edgeable in military optics, won the contract to supply the electro-optical systems. Technicians started with a one-foot-thick circular "blank," a honeycomb structure sandwiched between glass plates, which had been prepared by the Corning Glass Works to specifications prepared by the Marshall Space Flight Center in Huntsville, Ala. Guided by laser blemish-spotting detectors, they polished the main surface 20 times and coated it with aluminum overlaid with magnesium fluoride, a covering one-thousandth the thickness of a human hair.

I remember a snowy January day in 1982 when the primary mirror was finished and ready for installation in the telescope. Visiting a "clean room" (free of dust and other pollutants), at the Perkin-Elmer plant, I found the mirror on loving display, like an objet d'art — or the elemental wheel in modern gloss. Up close, I could see myself as large as life. Stepping back, I saw my reflection explode larger than life, but without any funhouse distortion. The concave mirror is so smooth that no point on its surface deviates more than a millionth of an inch from an ideally perfect surface, Perkin-Elmer engineers say with understandable pride. (The division is now called Hughes Danbury Optical Systems.) The full telescope assembly includes two mirrors, which collect and condense the light detected and magnify it on the image plane, which has its own scientific instruments attached.

At that time, scientists were aiming for a 1985 launching, but because so much of the technology related to secret military systems, the Pentagon dictated that only 116 managers in the project could have access to the contractors' plans. "This lack of manpower came back to haunt us many times," Robert O'Dell, who now teaches at Rice University, wrote in Sky & Telescope magazine last July. "It kept NASA from closely following the contractors' work and made it very difficult for us to know what was happening at any given time."

Costs soared and deadlines were missed. The system that controls the telescope's directional pointing encountered difficulties, which made matters worse. Only after a management reshuffling at Marshall Space Center, and the addition of more overseers, did the project finally get back on track, but with launching delayed until late 1986.

Then the Challenger exploded and all shuttles were grounded indefinitely. The Hubble was put in storage, where maintenance and testing continued, at a cost of $7 million a month.

Linking the telescope to the shuttle has always seemed a mixed blessing to astronomers. "That's one of our sins for which we're paying now," Bahcall says. On the positive side was a promise that shuttle astronauts would service the Hubble every two years. The Hubble, unlike other, smaller telescopes to be put in orbit, is designed for such regular maintenance. Faulty components would be replaced, and new instruments could be added. The entire spacecraft would be returned to Earth every five years for a complete overhaul. (That idea was deemed impractical as early as 1984.) Now, with few illusions about shuttle reliability, project leaders plan for astronauts to visit the telescope only every five years, to replace instruments and nudge it back to an altitude safely above Earth's grasping atmosphere.

The telescope will be put in orbit 380 miles above the Earth, not the 22,300 miles that astronomers would have preferred.

From the beginning, astronomers complained that the shuttle could not put the Hubble in the orbit they would prefer, 22,300 miles above Earth's Equator, where it would give an almost unobstructed view of the heavens. At an orbit of only several hundred miles, the telescope's view of the sky will always be half blocked by the Earth — and a different part of the sky will be blocked out at any given moment in the spacecraft's 90-minute circuit of Earth. This has given mission planners a monumental scheduling headache.

Rodger Doxsey, chief of engineering support for the space telescope institute, concedes that the delay caused by the Challenger disaster was not all bad: "We were not ready to operate the telescope in 1986. There would have been a big scramble just to get it operating. But that's a route history didn't take."

The biggest problem was in developing the computer software to control the constantly orbiting telescope: slewing it into position, pointing it to targets and keeping them in the field of view, making adjustments dictated by the interference of Earth and the need to avoid looking at the Sun. (To prevent damaging glare to the optics, the telescope cannot point within 20 degrees of the bright limb of Earth or within 50 degrees of the Sun.) Computers also instruct the telescope about which cameras or sensors to operate for a particular observation, and which of the many camera filters it should use. The computer must then schedule a time when the resulting data can be radioed to Earth

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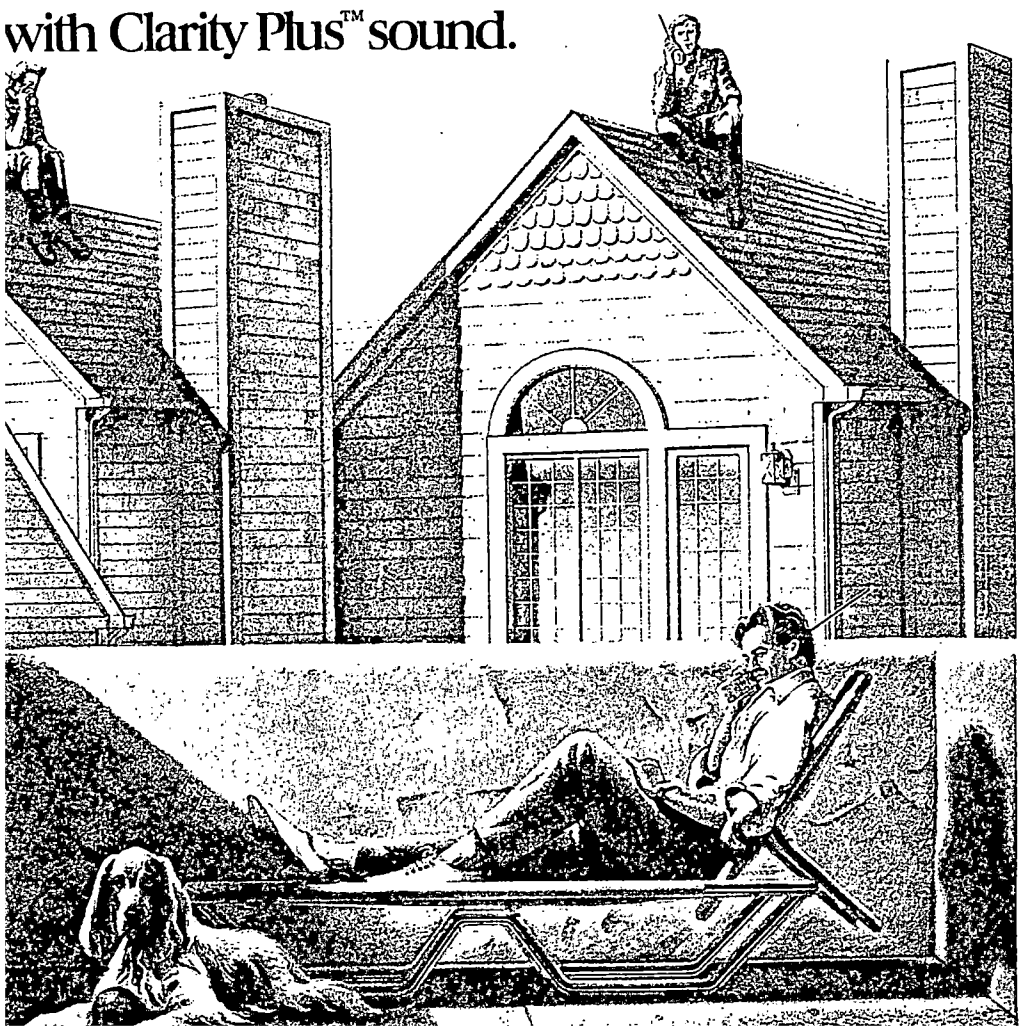

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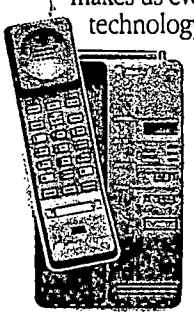

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through the two tracking and data relay satellites, which are not always available, because of commitments to shuttle missions and various spy satellites. Each observation, whether for a few hours or several days, must be meticulously planned down to the second. "The entire architecture for this software has had to be very much redefined in the last four years," Doxsey says.

The delays also have given astronomers time to complete a star catalogue and map giving the precise location and brightness of 18,819,291 celestial objects — everything from planets and stars to quasars, galaxies and clusters of galaxies. Previous catalogues inventoried a mere 250,000 objects. The Hubble will lock on targets by using nearby charted stars as landmarks, or skymarks.

Because all the operations are computerized and monitored by flight controllers, there is no necessity for the astronomers who planned an observation to be in the institute's control room. The data are recorded on tape, which can be viewed later. But, says Eric Chaisson, an astrophysicist who is director of educational programs for the institute, "If I were an observer, I would certainly be here." By monitoring the TV screen in the control room, "You're going to be looking at the universe in real time."

The Hubble is already booked up for observations in its initial year. F. Duccio Macchetto, an astronomer from the European Space Agency and chief of science programs at the institute, says more than 1,500 astronomers in 30 countries submitted a total of 600 proposals for observations — "10 times as many as we could accept and fit into operations the first year." An international committee of scientists makes recommendations to the institute for assigning telescope time.

Proposals fall into five categories: observations of planets in the solar system and the search for planetary systems around other stars, observations of stars and stellar systems, of the areas between stars, of galaxies, and of quasars, those distant energetic objects that may lie at the core of the universe's earliest galaxies. Every effort has been made to give equal observing time to each category. Six or seven projects can be fitted into each week's operations.

"The first science is tailored to things you know you want to investigate," Macchetto says. Astronomers will study dust storms on Mars and the atmosphere of Jupiter, two outstanding mysteries in astronomy. They will search for planetary systems, starting with Beta Pictoris, a star 53 light-years away, and four or five other likely candidates. They will try to confirm the existence of black holes, to observe stars being born, to look in the intergalactic medium for evidence of what scientists refer to as the universe's "missing mass" and to see if the powerful energies of quasars emanate from the heart of distant galaxies. Above all, they will be asking the instruments to answer the three big questions about the universe: its rate of expansion, its age and its destiny.

With abiding faith in nature's capacity for surprise, scientists believe the telescope will reward them with discoveries they never anticipated.

AT LAST, BOTH THE HUBBLE telescope and the space shuttle are ready. Launching at Cape Canaveral may be as early as the middle of April. Mission officials believe they have finally worked out the bugs in the computer software. So much money and hope have been invested in the telescope over the years. Will it be a disappointment? Will the images measure up to our fantasies of the promised cosmic discoveries?

Robert A. Brown, an astronomer at the institute, concedes that claims for the telescope may be impossible to fulfill entirely. The search for other planetary systems "is the Holy Grail of planetary astronomy," he says, noting that his generation of scientists has made this discovery its goal. He doubts the telescope will see objects even as large as Jupiter around other stars. "Hubble might very well identify young stars with surrounding disks of material, including young planets. But we do not really expect to pick out individual planets."

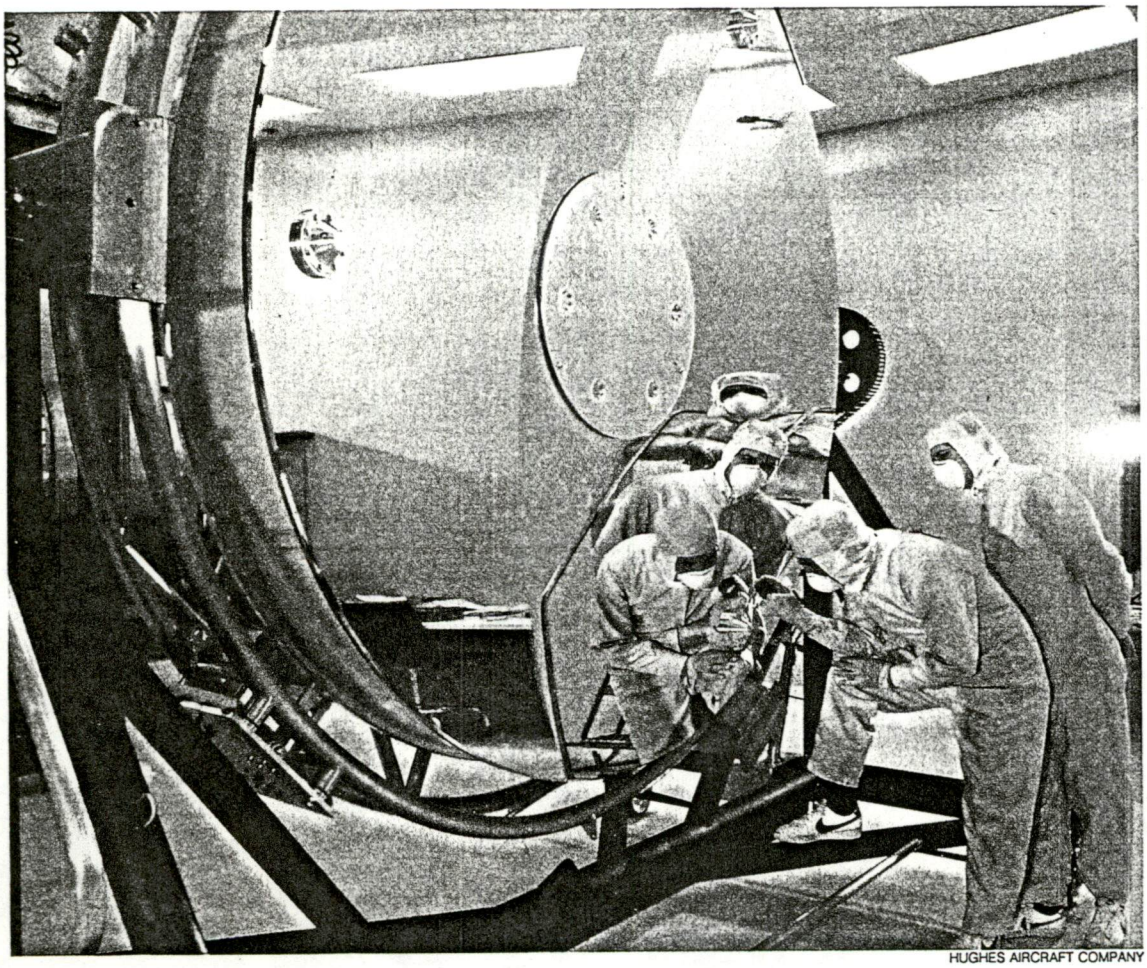
Astronomers also caution the public not to expect the same kind of spectacular vistas that the two Voyager spacecraft transmitted of the outer planets. Discovery is not likely to be as visually dramatic as the rings of Saturn or the volcanoes of Jupiter's moon Io or Neptune's icy Triton. Revelation will spring more slowly and only after bringing to bear the accumulated knowledge of Newton, Einstein, Hubble and today's architects of astrophysical theory.

Still, scientists are confident that they will succeed in getting the first accurate distance measurements to nearby galaxies and in determining the age of the universe. Even if that is all they accomplish, Duccio Macchetto says, he will not be disappointed. "If we can define the expansion velocity of the universe, that's enough, and I'm sure we'll do much more."

They also expect to confirm the existence of black holes. And, with their abiding faith in the telescope and in nature's capacity for surprise, they believe they will be rewarded with discoveries they never even anticipated, including insights into the beginning of time. Galileo, after all, did not know that his little telescope would give him a glimpse of those moons around Jupiter.

John Bahcall expects that the telescope will not fail to do its part. "If we are disappointed," he says, "it's not the telescope's fault or our fault. It will be because of a lack of imagination on the part of God. What we will see will depend on what nature has in store."

The Hubble telescope's most enduring and reassuring achievement may be nothing less than its affirmation of the spirit motivating our species to seek knowledge. Asking the big questions, the Mad Hatter would be pleased to hear, may well surpass in cultural significance any answers they elicit. "It's not how big the universe is that's impressive," Giacconi says. "It's the power of human reason. We can sit here with our little one kilogram of brain and figure out what this universe is all about." ■



HUGHES AIRCRAFT COMPANY

The telescope's 94½-inch concave mirror: its magnesium fluoride coating is a thousandth the thickness of a human hair.

Hot Shots

PHOTOGRAPHS BY CHRIS HARTLOVE

100 YEARS LATER

DYING THEN AND NOW

The diseases fought by Hopkins physicians have changed almost completely in a century. In 1889 the Baltimore Health Department reported the annual major causes of "Mortality From Certain Diseases" to be: Consumption, 1147; pneumonia, 592; cholera infantum, 507; measles, 248; cancer, 229; typhoid fever, 191; diphtheria and croup, 155; bronchitis, 133; whooping cough, 100; and scarlet fever, 71.

Today the health department reports the top ten causes of mortality in 1987 were: Heart disease, 3,197; malignant neoplasms (cancer), 2,043; cerebrovascular diseases (stroke), 549; pneumonia and influenza, 302; accidents, 288; chronic obstructive pulmonary diseases (COPD), 261; septicemia (blood poisoning), 247; homicide and legal intervention, 230; kidney conditions, 183; and diabetes mellitus, 179.

With the advent of antibiotics and the great rise in the general standard of living, most people today die of diseases associated with aging. Life expectancy has risen from 43.3 to 75 years. "You have to die eventually of something, so we die of heart disease or stroke or pneumonia," says Monroe Lerner, professor of health policy and management in the Hopkins School of Public Health.

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JING WU

Sharp Operator

Claim to Fame. Drug addiction is ripping up the city, so the DC government has pinpointed a cheap, promising method to unhook junkies; it's willing to let Wu, Washington's premier acupuncturist, stick needles in their ears. The treatment program isn't a cure, Wu notes, but it helps to ease the pain of withdrawal; and since it doesn't require hospitalization, it's also expected to cut down on the number of addicts who are waiting to get into detox centers. The city's endorsement of the program is the recognition that Wu has been searching for since 1983, when he opened the Green Cross clinic at 15th and U and tried to break habits for $35 a week—the price of the needles.

What He Says. "Modern medicine has done away with many diseases. We've killed all the wolves in the forest, and now the rats are eating us."

What They Say. "There isn't any real great data that proves the efficacy of acupuncture in the treatment of drug abuse," says Reed Tuckson, the city's public health commissioner, "but it interests me enough to do a study of it."

What We Say. Waiting for the results of Wu's treatment program has us on pins and needles.

MEDICINE

Watching the Babies Die

Romanian AIDS scandal

ROBERT WALLIS—SIPA

From cradle to grave: *Ceausescu's littlest victims at the Victor Babes Hospital*

At the Victor Babes Hospital in Bucharest, 15-month-old Nicoletta Buia lies in a too-small cot, eyes blank, hands swathed in bandages, her face covered with herpes sores. In the next bed, an 18-month-old slowly rocks his head back and forth, back and forth, keeping time to a dirge only he can hear. The room itself is eerily silent: its 15 inmates are too weak to cry. It reeks of dirty diapers and alcohol, but worst of all is the stench of death. There are five such rooms at Babes, some with as many as four little patients to a bed, a total of 70 children. All are dying of AIDS.

With the revelation last week of a pediatric AIDS epidemic in Romania, dictator Nicolae Ceausescu seemed to slip another rung in hell. Before the December revolution that led to his execution, AIDS did not officially exist in Romania—Ceausescu insisted only "decadent" countries were at risk. Now the awful truth has begun to emerge: because of antiquated medical procedures performed on newborns and inadequate medical supplies, AIDS has cut a deadly swath through Romania's pediatric wards and overcrowded orphanages. So far, out of 2,084 children in Bucharest and the port city of Constantsa, 706 tested positive for HIV, the virus that causes AIDS. Experts expect those numbers to increase dramatically. "Manifestly, this is an epidemic transmitted through medical acts," says Dr. Jacques Lebas, president of Doctors of the World, a French humanitarian organization assisting the Romanians. "That hurts especially."

Corrupt policies: The tragedy is a direct result of Ceausescu's corrupt policies. Unlike most AIDS babies in the West, who contract the disease in utero, the Romanian children were not born HIV positive. Instead, many are victims of microtransfusing—the long-discredited practice of injecting frail newborns with blood. Because of state-imposed food shortages, there were all too many who qualified—the low-weight offspring of malnourished mothers. Three years ago, the regime ordered hospitals to reuse needles to save money. Doctors were also reusing syringes to immunize youngsters against childhood diseases. "One HIV-positive blood donor could have infected 10, 12 or more children," says Dr. Jean-Gabriel Barbin, who led the Doctors of the World mission to Bucharest.

In an extraordinary piece of medical detective work, a few tenacious Romanian physicians finally brought the epidemic to light. Dr. Ion Patrascu, of Bucharest's Institute of Virology, was the first to suspect the disease's real dimensions. Last July he began randomly testing blood samples for viruses. The adult sera turned out HIV negative, but about a third of the children proved infected. The Ceausescu regime responded by banning all further tests. "They did nothing to help the children or inform any medical personnel," says Barbin. Patrascu and his colleagues canceled a clandestine meeting of pediatricians last November after Securitate agents threatened to throw them in jail.

Last month the new regime took the first steps toward controlling the epidemic. The Health Ministry banned microtransfusions and the reuse of needles, and finally began screening blood. But the efforts are haphazard and, despite international aid, materials, staff and expertise remain in short supply. For now, Ceausescu's grim legacy continues to take its toll. "At least one new child arrives every day," says Babes head nurse Leona Biris. "It's so horrible to watch them die."

ELOISE SALHOLZ *with* THERESA WALDROP *in Bucharest and* RUTH MARSHALL *in Paris*

TELEVISION

Andy Rooney Pays a Painful Price

Have you ever noticed that people who are paid for their opinions can't resist giving them away for free? Take Andy Rooney, who earns a reported $800,000 for speaking his mind on "60 Minutes." Rooney recently infuriated gay-rights groups by referring to "homosexual unions" as death-inducing "ills." Then, in an unreimbursed interview with a national gay magazine called The Advocate, Rooney angered black activists by allegedly proposing that "blacks have watered down their genes because the less intelligent ones are the ones that have the most children." That left Rooney accused of racism as well as homophobia—and last week CBS suspended him for three months without pay.

Rooney denied making the statements in The Advocate interview, which was not tape-recorded. But the magazine stood by its story. Why didn't CBS take Rooney's word? The explanation may lie in Rooney's letter of apology published in The Advocate along with the interview. After graphically describing sex between men, Rooney called homosexuality "morally wrong." For CBS, apparently, that clinched the case.

Another CBS employee received grim news. "CBS This Morning" coanchor Kathleen Sullivan, who once joked that the initials stood for "Cheap Broadcasting Service," was axed. The opinion that most weighed against Sullivan lay in the program's stagnant third-place ratings.

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over state laws. (10) Oliver Ellsworth (1745–1807), of Connecticut, served as chief justice 1796–1800. He was the principal architect of the Judiciary Act of 1789, creating the federal court system. In *United States* v. *La Vengeance* (1796), he spoke for the majority in extending federal authority to all inland rivers and lakes.

RANKING IN 1962 HISTORIANS POLL: Washington ranked second of 31 presidents and second of 5 "great" presidents. He ranked above Franklin Roosevelt and below Lincoln.

RETIREMENT: March 4, 1797–December 14, 1799. Washington, 65, returned to Mount Vernon to oversee much-needed repairs. He played host, often reluctantly, to an endless parade of visitors, many longtime friends, others perfect strangers there just to ogle the former president and his family. Briefed on affairs of state by War Secretary McHenry and others, he maintained a keen interest in the course of the country. With tensions between the United States and France threatening to erupt into war in the wake of the XYZ Affair (see "John Adams, 2d President," "Administration"), Washington was commissioned lieutenant general and commander in chief of American forces on July 4, 1798, the only former president to hold such a post. He accepted the commission on the condition that he would take to the field only in case of invasion and that he had approval rights over the composition of the general staff. He promised the cause "all the blood that remains in my veins." Fortunately the undeclared "Quasi-War" that followed was limited to naval encounters and Washington's services were not required. In his last year Washington faced a liquidity crisis: Money owed him from the sale or rental of real estate was past due at a time when his taxes and entertainment bills were climbing. As a result, at age 67 he was compelled for the first time in his life to borrow money from a bank.

DEATH: December 14, 1799, after 10 P.M., Mount Vernon, Virginia. On the morning of December 12, Washington set out on horseback around the plantation. With temperatures hovering around freezing, it began to snow; this turned to sleet, then rain, and back to snow by the time Washington returned indoors five hours later. Still in his cold, wet clothes, he tended to some correspondence and ate dinner. Next morning he awoke with a sore throat, and later in the day his voice grew hoarse. About 2 A.M. on December 14 he awoke suddenly with severe chills and was having trouble breathing and speaking. Three doctors attended him—his personal physician and longtime friend Dr. James Craik and consultants Drs. Gustavus Richard Brown and Elisha Cullen Dick. They diagnosed his condition as inflammatory quinsy. The patient was bled on four separate occasions, a standard practice of the period. Washington tried to swallow a concoction of molasses, vinegar, and butter to soothe his raw throat but could not get it down. He was able to take a little calomel and tartar emetic and to inhale vinegar vapor, but his pulse remained weak throughout the day. The physicians raised blisters on his throat and lower limbs as a counter-irritant and applied a poultice, but neither was effective. Finally, Washington told his doctors to give up and about 10 P.M. spoke weakly to Tobias Lear, his aide, "I am just going. Have me decently buried and do not let my body be put into a vault in less than two days after I am dead. Do you understand me?" "Yes, sir," replied Lear. "'Tis well,"[12] said Washington. These were his last words. Soon thereafter he died while taking his own pulse. After a lock of his hair was removed, his body was placed in a mahogany coffin bearing the Latin inscriptions *Surge Ad Judicium* and *Gloria Deo*. The funeral services, con-

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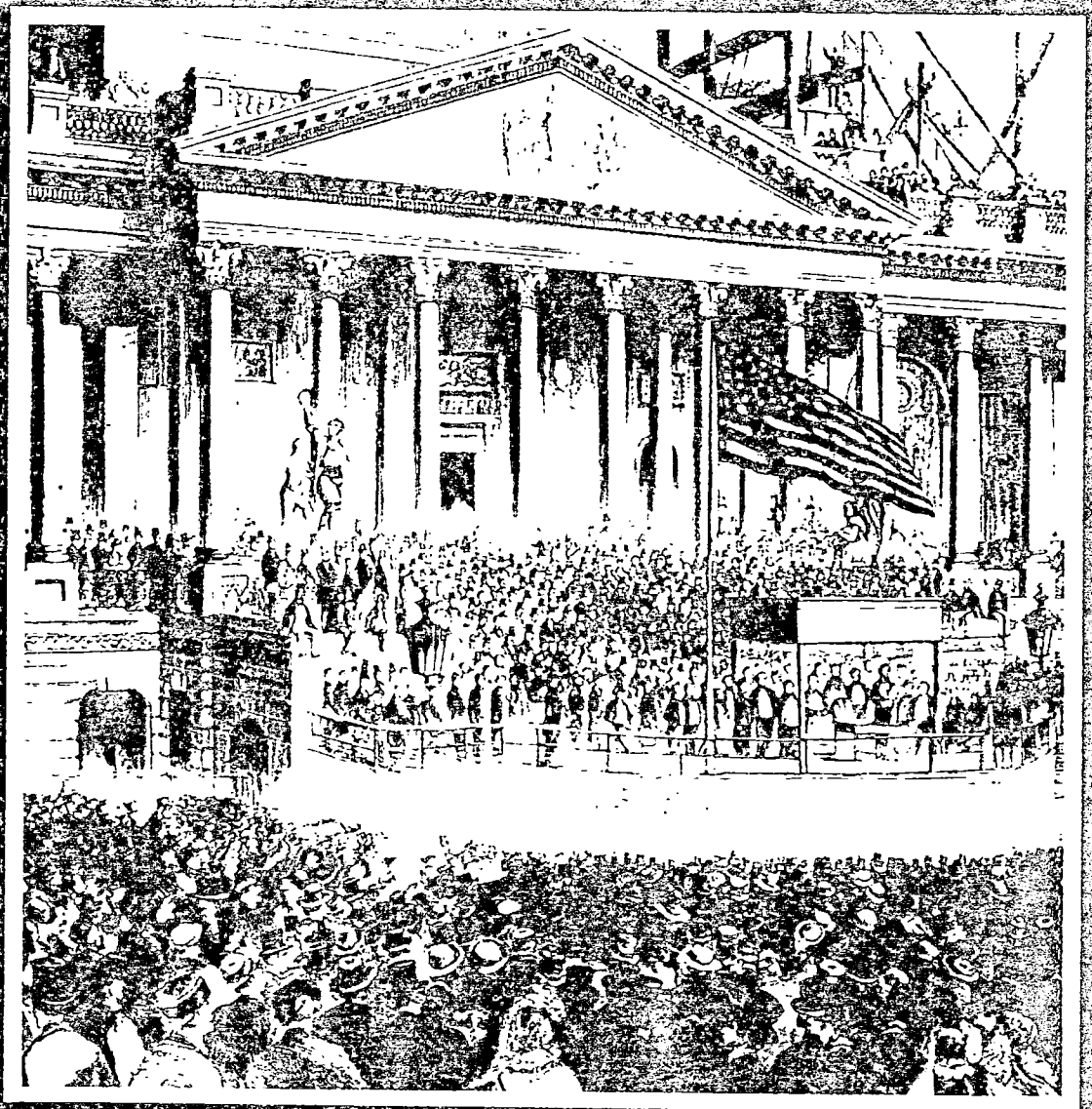

Ohio physician has the president's ear

By David Lore
Dispatch Special Projects Editor

Presidents — like the rest of us — like to talk about science as long as they don't have to listen.

What makes George Bush different, says Cleveland physician and White House science adviser Bernadine P. Healy, is that he's an eager student.

As deputy director of the Office of Science and Technology Policy in 1984-85, Healy rarely saw then-President Reagan.

"Science was just not as high on his agenda," she said.

Last month, however, Healy and other recently appointed members of the President's Council of Advisers on Science and Technology sat down together for four hours with Bush and his top aides at Camp David in Maryland.

"He was extremely interested," Healy said. "We invaded his weekend, and yet you could see not only his intellectual agility but the fact that he was enjoying it, having fun.

"The feeling was like a bunch of university people sitting around a table with sleeves rolled up, having a give and take. There was nothing stuffy or inhibited."

Healy, chairman of the Cleveland Clinic Foundation Research Institute, isn't one to be intoxicated easily by power. A former White House staffer, Healy has directed a half-dozen national science policy reviews and served as a member on many other such panels.

It didn't come as any surprise to Healy that — before ever appointing his science advisory panel — Bush reaffirmed his faith in Reagan's "Star Wars" space-based defense scheme, opposed federal support for fetal tissue research and committed himself to a budget-busting colonization of the moon and Mars.

Our system of checks and balances makes frustration "generic for anybody who works in Washington," she said last week.

"But I find it frustrating only in part; it's really a healthy frustration. Quite honestly, a lot of people in the science community would be very fearful of a science czar or somebody who might impose order on the science community at large."

Scientists working in Washington can hope only to influence policy, not control it, she said.

As head of a White House working group on biotechnology, and later as chairman of an Office of Technology Assessment panel on that topic, Healy said her contribution has been to help prevent hasty and short-sighted regulation of genetic research.

"We really did have an effect," she said.

Science advisers will compete with other voices in the Bush administration, but Healy said the office — under science adviser D. Allan Bromley — has been upgraded, with Bromley given more access, more money and more staff.

Healy, the only woman and only Ohioan on the science advisory council, said her interest is science education. A specific concern is that U.S. medical schools are getting fewer — and often less qualified — applicants, she said.

Dispatch photo

Bernadine P. Healy

"The physician-scientist pool is also likely to suffer from what appears to be a growing loss of interest in a medical career in general," she wrote in an October 1988 article in *The New England Journal of Medicine.*

"Young people today do not see a future in medicine as the good choice that their parents once did."

It was her father's enthusiasm for science that prodded Healy — and two of her three sisters — into technical careers.

Michael Healy was a small businessman in Long Island, N.Y., who didn't graduate from high school until much later in life.

Still, he was excited by learning and determined, even though the family didn't have much money, that his daughters have a microscope to play with, museums to visit and college opportunities.

A scholarship student, Healy graduated with honors from Vassar College and the Harvard Medical School and worked on the faculty at the Johns Hopkins School of Medicine before going to Washington.

Healy, a specialist in cardiovascular research, is a former president of the American Heart Association.

Today, Healy has two young daughters and hopes that, despite their more privileged background, they inherit this same hunger for education.

"In her book, *Blackberry Winter*, Margaret Mead makes the point that to do well, blackberries have to go through a frost," she said. "I think one of the things I'm concerned about is that they get a little bit of frost."

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Bush's Remarks at Hopkins

The President's Address to Doctors Strikes Some Off-Key Notes

By Abigail Trafford
Washington Post Staff Writer

The next time George Bush talks about medicine, he could do with a little help from a good speech doctor.

The President went to Johns Hopkins University in Baltimore on February 22 to get an honorary degree and address "some of the best health care professionals in the world."

By all accounts, the ceremony at Johns Hopkins was largely a successful occasion for the President. But it was not without controversy. A group of faculty and students held a press conference to protest the university's decision to award Bush an honorary degree, saying that the President has paid only lip service to the health problems of the country.

In fact, given some of the lip service he paid in his Johns Hopkins speech, he might have been better off having his speech writers hit the old research books a little harder.

VIEWPOINT

While much of his speech was serious, some of the President's prepared remarks read like bloopers from a Saturday Night Live script:

■ **The artificial heart miracle.** "We live in an age of miracles," he said. "Medical miracles as dramatic as the artificial heart."

What artificial heart? The mechanical device that kept 61-year-old Seattle dentist Barney Clark alive for 112 days? The so-called Jarvik-7 model heart, which caused blood clots and seizures—and more hype than help for people with heart disease?

Practically, the artificial heart no longer exists. It was George Bush's own administration that officially killed the Jarvik-7 artificial heart program earlier this year. Even before the Food and Drug Administration stopped further use of this permanent replacement heart, the scientific community recognized the media "miracle" as a dud and had already shifted to alternate devices. Now, research is under way on a variety of mechanical parts to take over functions of the heart.

■ **Kinder, gentler surgeon.** William Stewart Halsted of Johns Hopkins, in the President's words, "conceived and perfected a daring feat of surgery—the radical mastectomy—that to this day saves the lives of thousands of women afflicted with breast cancer." He called Halsted "a kinder, gentler surgeon, if you will."

Kinder, gentler surgery? Lopping off the breast and everything around it? If you say "Halsted radical mastectomy" to a group of women these days, their hands go protectively to their breasts. This surgical removal of the breast, lymph nodes under the arms and underlying muscle is considered one of the most mutilating of operations.

To be fair to Halsted, who was a leading physician at Hopkins from 1886 until his death in 1922, he was considered a fine—as they say, a tissue-sparing—surgeon in his day. (And he did introduce rubber gloves into the operating room—because his favorite nurse, who later became his wife, developed skin rashes that needed to be covered up. The fact that rubber gloves reduced the risk of infection was learned later.)

The President has paid only lip service to the health problems of the country, protesters at Hopkins claim.

But the Halsted radical is no longer the recommended treatment for most women with breast cancer. More and more surgeons are performing a modified version or a lumpectomy, where only the tumor and surrounding tissue are removed—and combining this really kinder, gentler operation with radiation and drug therapy. The Halsted radical is used less and less—and is hardly considered today a "kind" or "gentle" type of surgery.

■ **George Washington.** As Bush recalled the first President: "Diagnosed with a sore throat, the doctors bled him four times before he succumbed to its effects, thus depriving our young Nation of perhaps years of service from its most revered statesman."

Perhaps. And certainly medical care is much better today than it was. If Washington had a bacterial infection, treatment with an antibiotic could well have cured him. But he lived to be 67 years old in an era when life expectancy was less than 40. By 1980, life expectancy for men in the United States had climbed to 70. And Washington, who was given bleeding therapy, still had a longer life than Barney Clark, who got an artificial heart.

■ **Research dollars.** "Here at Hopkins, you are the leading recipient of federal research dollars—more than $500 million," the president said. Actually, Hopkins got $639.5 million in 1989. But most of it didn't go into medical research; the biggest chunk—$434 million—came from the Defense Department and went mainly to the Applied Physics Laboratory. The Hopkins medical institutions received about $175 million. That's still a hefty sum—on a par with Harvard University and the West Coast cluster of University of California at San Francisco and Berkeley—but obviously not on a par with more than a half billion.

■ **Finally—Let them play lacrosse.** Sports analogies have always been the stuff of political speeches and to be sure, the audience of Johns Hopkins alumni ranks among the best and brightest of the most elite in the country. But Bush showed himself again to be a Grand Old Preppie. As he said: ". . . the Johns Hopkins way—the American way—the same way your lacrosse team always makes the rankings: By being the best."

Certainly, Johns Hopkins is known for its lacrosse team, but it's not exactly a bases-loaded or hoop-over-the-back-door kind of Main Street sport. Lacrosse still has an image of blue blazers and private schools—a Yale "Boola-Boola" attitude toward winning in the Big Game of Life that has little relevance for, say, crack babies in the neonatal intensive care unit or the nursing home patient with Alzheimer's.

Besides, the Johns Hopkins lacrosse team lost the championship last year to Syracuse. ■

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Reasons to Choose Clinoril® First

TABLETS, 150 mg and 200 mg

(Sulindac|MSD)

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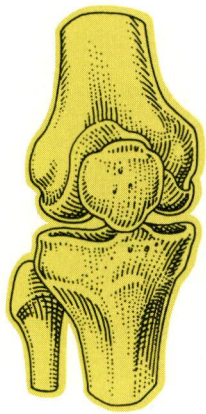
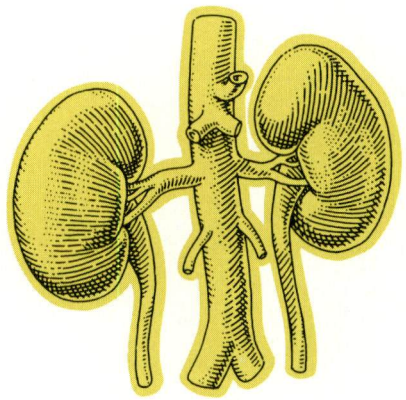


Prompt relief of the signs and symptoms of osteoarthritis. CLINORIL at 200 to 400 mg daily was comparable in effectiveness to aspirin 2400 to 4800 mg daily.

CLINORIL is contraindicated in patients who are hypersensitive to this product or in whom acute asthmatic attacks, urticaria, or rhinitis is precipitated by aspirin or other NSAIDs.

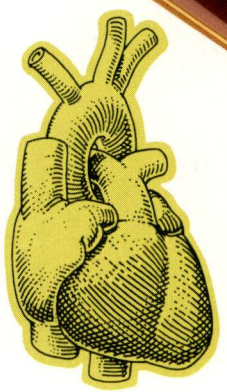
Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy.



CLINORIL may affect renal function to a lesser extent than other NSAIDs;* however, renal adverse effects have been reported.

Caution should be exercised when administering CLINORIL to patients with conditions associated with increased risk of the effects of NSAIDs on renal function, such as those with complications associated with advanced age.

*These observations need further clarification, and, in the interim, CLINORIL should be used with caution in patients whose renal function may be impaired or prostaglandin dependent or who have a history of renal lithiasis. Such patients should be closely monitored.



No reported blunting of certain antihypertensive agents.

Edema has been observed in some patients taking CLINORIL. Therefore, as with other NSAIDs, CLINORIL should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention.

For a Brief Summary of Prescribing Information, please see the following page.

For many osteoarthritic patients age 65 and older

Choose Clinoril® First

TABLETS. 150 mg and 200 mg

(Sulindac | MSD)

Contraindications: Hypersensitivity to this product; patients in whom acute asthmatic attacks, urticaria, or rhinitis is precipitated by aspirin or other nonsteroidal anti-inflammatory agents.

Warnings: ***Gastrointestinal Effects:*** Peptic ulceration and gastrointestinal bleeding have been reported. Fatalities have occurred. Gastrointestinal bleeding is associated with higher morbidity and mortality in patients acutely ill with other conditions, the elderly, and patients with hemorrhagic disorders. In patients with active gastrointestinal bleeding or an active peptic ulcer, an appropriate ulcer regimen should be instituted, benefits of therapy must be weighed against possible hazards, and the patient's progress carefully monitored; in patients with a history of either upper or lower gastrointestinal tract disease, CLINORIL® (Sulindac, MSD) should be given under close supervision and only after consulting the ADVERSE REACTIONS section.

Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Hypersensitivity: Rarely, fever and other evidence of hypersensitivity (see ADVERSE REACTIONS), including abnormalities in one or more liver function tests and severe skin reactions, have occurred; fatalities have occurred in these patients. Hepatitis, jaundice, or both, with or without fever, may occur usually within the first one to three months of therapy. Determinations of liver function should be considered whenever unexplained fever, rash or other dermatologic reactions, or constitutional symptoms develop; if unexplained fever or other evidence of hypersensitivity occurs, discontinue CLINORIL. Elevated temperature and abnormalities in liver function caused by CLINORIL characteristically have reverted to normal after discontinuation of therapy. CLINORIL should not be reinstituted in such patients.

Hepatic Effects: In addition to hypersensitivity reactions involving the liver, in some patients the findings are consistent with those of cholestatic hepatitis. As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests without any other signs and symptoms may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with CLINORIL. Although such reactions as described above are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), CLINORIL should be discontinued. In clinical trials, the use of 600 mg/day has been associated with increased incidence of mild liver test abnormalities (maximum recommended dosage is 400 mg per day).

Precautions: ***General:*** Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS: *Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy*). Although the effect on platelet function and bleeding time is less than with aspirin, CLINORIL is an inhibitor of platelet function; therefore, patients who may be adversely affected should be carefully observed when CLINORIL is administered. Pancreatitis has been reported (see ADVERSE REACTIONS); should pancreatitis be suspected, the drug should be discontinued and not restarted, supportive medical therapy instituted, and the patient monitored closely with appropriate laboratory studies (e.g., serum and urine amylase, amylase/creatinine clearance ratio, electrolytes, serum calcium, glucose, lipase, etc.); a search for other causes of pancreatitis as well as those conditions which mimic pancreatitis should be conducted. Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop eye complaints during treatment have ophthalmologic studies. In patients with poor liver function, delayed, elevated and prolonged circulating levels of the sulfide and sulfone metabolites may occur. Such patients should be monitored closely; a reduction of daily dosage may be required.

Edema has been observed in some patients taking CLINORIL. Therefore, as with other nonsteroidal anti-inflammatory drugs, CLINORIL should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention. CLINORIL may allow a reduction in dosage or the elimination of chronic corticosteroid therapy in some patients with rheumatoid arthritis. However, it is generally necessary to reduce corticosteroids gradually over several months in order to avoid an exacerbation of disease or signs and symptoms of adrenal insufficiency. Abrupt withdrawal of chronic corticosteroid treatment is generally not recommended even when patients have had a serious complication of chronic corticosteroid therapy.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of sulindac to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome. A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, the administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. CLINORIL may affect renal function less than other NSAIDs in patients with chronic glomerular renal disease (see CLINICAL PHARMACOLOGY section of Prescribing Information). Until these observations are better understood and clarified, however, and because renal adverse experiences have been reported with CLINORIL (see ADVERSE REACTIONS), caution should be exercised when administering the drug to patients with conditions associated with increased risk of the effects of nonsteroidal anti-inflammatory drugs on renal function, such as those with renal or hepatic dysfunction, diabetes mellitus, complications associated with advanced age, extracellular volume depletion from any cause, congestive heart failure, sepsis, or concomitant use of any nephrotoxic drug. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state. Since sulindac is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation. Since sulindac metabolites have been reported rarely as a component of renal stones, patients with a history of renal lithiasis should be given CLINORIL® (Sulindac, MSD) with caution and be kept well hydrated.

Information for Patients: CLINORIL, like other drugs of its class, is not free of side effects and can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are often essential agents in the management of arthritis but also may be commonly employed for less serious conditions. Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly in less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Use in Pregnancy: Not recommended for use in pregnant women, since safety for use has not been established and because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus) during the third trimester of pregnancy.

Nursing Mothers: Nursing should not be undertaken while a patient is on CLINORIL. It is not known whether sulindac is secreted in human milk; however, it is secreted in the milk of lactating rats.

Use in Children: Safety and effectiveness in children have not been established.

Drug Interactions: DMSO should not be used with sulindac; concomitant administration has been reported to reduce plasma levels of active sulfide metabolite and potentially reduce efficacy and to cause peripheral neuropathy. Although sulindac and its sulfide metabolite are highly bound to protein, studies with daily doses of 400 mg have shown no clinically significant interaction with oral anticoagulants or oral hypoglycemic agents; however, patients should be monitored carefully until it is certain that no change in their anticoagulant or hypoglycemic dosage is required. Special attention should be paid to patients taking higher doses than those recommended and to patients with renal impairment or other metabolic defects that might increase sulindac blood levels. Concomitant administration of aspirin significantly depressed the plasma levels of the active sulfide metabolite. Although addition of aspirin did not alter the types of clinical or laboratory adverse experiences, the combination showed an increase in the incidence of gastrointestinal adverse experiences; since addition of aspirin did not have a favorable therapeutic effect, the combination is not recommended. Concomitant administration of diflunisal in normal volunteers resulted in lowering of plasma levels of active sulindac sulfide metabolite by approximately one-third. Probenecid given concomitantly had only a slight effect on plasma sulfide levels, while plasma levels of sulindac and sulfone were increased; sulindac produced a modest reduction in the uricosuric action of probenecid, which probably is not significant under most circumstances. Neither propoxyphene hydrochloride nor acetaminophen had any effect on the plasma levels of sulindac or its sulfide metabolite.

Adverse Reactions: The following adverse reactions were reported in clinical trials or have been reported since the drug was marketed. The probability exists of a causal relationship between CLINORIL and these adverse reactions. The adverse reactions which have been observed in clinical trials encompass observations in 1,865 patients, including 232 observed for at least 48 weeks.

Incidence Greater than 1%: *Gastrointestinal*—Gastrointestinal pain (10%), dyspepsia,* nausea* with or without vomiting, diarrhea,* constipation,* flatulence, anorexia, gastrointestinal cramps. *Dermatologic*—Rash,* pruritus. *Central Nervous System*—Dizziness,* headache,* nervousness. *Special Senses*—Tinnitus. *Miscellaneous*—Edema (see PRECAUTIONS).

Incidence Less than 1%: *Gastrointestinal*—Gastritis, gastroenteritis, or colitis; peptic ulcer; gastrointestinal bleeding; GI perforation; liver function abnormalities; jaundice, sometimes with fever; cholestasis; hepatitis; pancreatitis (see PRECAUTIONS); ageusia; glossitis; a single report of sulindac metabolites in common bile duct "sludge" in a patient with symptoms of cholecystitis who underwent a cholecystectomy. *Dermatologic*—Stomatitis, sore or dry mucous membranes, alopecia, photosensitivity, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis. *Cardiovascular*—Congestive heart failure, especially in patients with marginal cardiac function; palpitation; hypertension. *Hematologic*—Thrombocytopenia; ecchymosis; purpura; leukopenia; agranulocytosis; neutropenia; bone marrow depression, including aplastic anemia; hemolytic anemia; increased prothrombin time in patients on oral anticoagulants (see PRECAUTIONS). *Genitourinary*—Urine discoloration; vaginal bleeding; hematuria; proteinuria; crystalluria; renal impairment, including renal failure; interstitial nephritis; nephrotic syndrome; renal calculi containing sulindac metabolites have been observed rarely. *Metabolic*—Hyperkalemia. *Psychiatric*—Depression; psychic disturbances, including acute psychosis. *Nervous System*—Vertigo, insomnia, somnolence, paresthesia, convulsions, syncope, aseptic meningitis. *Special Senses*—Blurred vision, visual disturbances, decreased hearing, metallic or bitter taste. *Respiratory*—Epistaxis. *Hypersensitivity Reactions*—Anaphylaxis, angioneurotic edema, bronchial spasm, dyspnea, hypersensitivity vasculitis. A potentially fatal apparent hypersensitivity syndrome has been reported; this syndrome may include constitutional symptoms (fever, chills), cutaneous findings (rash or other dermatologic reactions—see above), involvement of major organs (changes in liver function, jaundice, pancreatitis, pneumonitis with or without pleural effusion, leukopenia, eosinophilia, disseminated intravascular coagulation, anemia, renal impairment, including renal failure), and other less specific findings (adenitis, arthralgia, myalgia, fatigue, malaise, hypotension, chest pain, tachycardia).

Causal Relationship Unknown: Other reactions have been reported in clinical trials or since the drug was marketed but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians. *Cardiovascular*—Arrhythmia. *Metabolic*—Hyperglycemia. *Nervous System*—Neuritis. *Special Senses*—Disturbances of the retina and its vasculature. *Miscellaneous*—Gynecomastia.

Dosage and Administration: CLINORIL should be administered orally twice a day with food. The maximum dosage is 400 mg per day; dosages above 400 mg per day are not recommended. In osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, the recommended starting dosage is 150 mg twice a day; the dosage may be lowered or raised depending on the response. A prompt response (within one week) can be expected in about one half of patients with osteoarthritis, ankylosing spondylitis, and rheumatoid arthritis; others may require longer to respond. In acute painful shoulder (acute subacromial bursitis/supraspinatus tendinitis) and acute gouty arthritis, the recommended dosage is 200 mg twice a day; after a satisfactory response has been achieved, the dosage may be reduced according to the response. In acute painful shoulder, therapy for 7-14 days is usually adequate. In acute gouty arthritis, therapy for 7 days is usually adequate.

Management of Overdosage: Overdosage has been reported, and rarely deaths have occurred. In the event of overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Animal studies show that absorption is decreased by the prompt administration of activated charcoal and excretion is enhanced by alkalinization of the urine.

How Supplied: Tablets CLINORIL containing 150 mg or 200 mg sulindac, with cellulose, magnesium stearate, and starch as inactive ingredients, in unit-of-use bottles of 60 and 100, unit-dose packages of 100, and bottles of 100.

*Incidence between 3% and 9%. (Those reactions occurring in less than 3% of patients are unmarked.)

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486

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The Cover

When The Johns Hopkins Hospital opened on May 7, 1889, its "Famous Four"—William H. Welch in pathology, William S. Halsted in surgery, William Osler in medicine, and Howard A. Kelly in gynecology—were already in place, having been recruited as early as 1884 with the promise of similar faculty positions in the soon-to-be-opened medical school. However, financial reverses in the investment income from the endowment fund delayed ground breaking for the medical school for the foreseeable future. A sum of at least $500 000 was needed. The outlook remained bleak until, thanks to the Women's Fund Committee, a national effort organized by Miss Mary Garrett and several other daughters of the Hopkins trustees, the sum—of which $306 977 came from the personal funds of Miss Garrett—was raised and presented to the trustees on Christmas Eve, 1892. The women had only two requests: that the proposed medical school be a 4-year, rather than the planned 3-year, school with an AB degree or equivalent required for admission and that women be admitted on the same terms as men. Both conditions were met, although with one casualty: Welch's assistant, William Councilman, moved over to Harvard, which did not yet admit women, causing Osler to quip that while Harvard got the man, Hopkins got the money. The school opened in October 1893, with 15 men and 3 women in its first class.

But that was not to be Miss Garrett's only bequest to the medical school. Thirteen years later, in 1905, she commissioned John Singer Sargent (1856-1925), the most famous portrait painter of turn-of-the-century Europe and America, to paint the Famous Four. Presented by her to the university on January 19, 1907, *The Four Doctors* (cover) has been called "the acme of formal and official medical portraiture in American art" (William H. Gerdts. *The Art of Healing: Medicine and Science in American Art*. Birmingham [Ala] Museum of Art; 1981).

When Sargent came to paint *The Four Doctors*, he was no stranger to illness, death, or the medical profession. The second child of six, only he and two sisters lived beyond the age of 4 years. His father, Fitzwilliam Sargent, was a physician, although he was inactive by the time John was born. Prior to his marriage, Fitzwilliam had had a promising career in the United States. A graduate of the University of Pennsylvania, he was an attending physician at the Wills Eye Hospital in Philadelphia and a fellow of the College of Physicians of Philadelphia. He was the author of *On Bandaging and Other Operations of Minor Surgery*, a work that went into several editions, including Japanese, and was a standard work on the battlefields of the American Civil War. It was illustrated with his own drawings. Fitzwilliam had also edited two textbooks in the field of surgery. John's mother, Mary Newbold Singer, was a talented musician and watercolorist, who, however, for some reason was unable to live in the United States. For nearly 30 years after her marriage to Fitzwilliam, the family lived a nomadic existence in Europe traveling from spa to spa seeking the mother's and elder daughter's health and relief from the weather. John was born during one of the family's sojourns in Florence, Italy. He saw the United States for the first time in 1876, when he was 20.

When Welch, Halsted, Osler, and Kelly gathered in Sargent's Tite Street studio in London, England, for their initial portrait sittings, one of the immediate problems that faced Sargent was composition. He grouped and regrouped the four men until at last he had the desired effect. Thereafter he could work with each individually. Welch's face he got right away. Osler's was the most difficult and both Osler and Sargent had to go through several frustrating sittings. Another difficulty was color. Although Osler wanted to wear his red Oxford robes, Sargent would not permit it because, as he said, the red was simply too red. Welch, on the other hand, was permitted to wear his Yale robes. Finally, when the painting was nearing completion, Sargent grew discouraged. "It isn't a picture," he said. Then, recalling a large Venetian globe he had in his other studio, he had it brought over to Tite Street (even though it meant chopping away part of the studio door to get it in) and placed it in the background. "We have got our picture," he said. And indeed he had. The globe, besides unifying the composition in its echo of the arch above it, provides a contrast for the head of Osler and brings together the figure of Osler with that of Halsted, standing. Welch, seated at the left, and Kelly, seated at the right, balance the composition on either side. Or, looked at another way, the painting in the background, El Greco's *St Martin of Tours Dividing His Cloak With the Beggar*, besides providing an allegory, changes the number of figures in the painting from four to five, an easier number to deal with, and also forms the apex of a triangle with Welch, Halsted, the globe, and Osler as its sides. Kelly, asymmetrically placed off to the right, with the red of the drape above him contrasting with the green of the hood across his shoulders, provides an effective counterbalance, both in composition and in color. The books on the table (one of which, according to Welch, was an early edition of Petrarch, from Sargent's own library) symbolize the broad knowledge of the men, not only in science, but in the humanities. The quill in Osler's hand calls attention to his considerable literary output, and perhaps even to his textbook of medicine.

For his entire life, Sargent's joy was in working, and indefatigable he was. Usually recalled chiefly as a portraitist, he had done more than 600 by the time he died. But he did some 2500 other paintings as well, from watercolors to impressionist works, to World War I paintings, to murals for the city of Boston, Mass. He died in his sleep on April 15, 1925, at his London studio, aged 69, apparently of heart failure. The evening before, he had been guest of honor at a farewell party prior to his planned departure for the United States in 3 days' time. Lying open beside him was Voltaire's *Dictionnaire philosophique*.

The Four Doctors hangs today in the William H. Welch Medical Library at Hopkins. Next to it is another Sargent portrait, that of Miss Garrett, commissioned by the university.—M. Therese Southgate, MD

Although The Four Doctors *was reproduced as a* JAMA *cover on August 9, 1965, it is here repeated to commemorate the centennial for Johns Hopkins Medicine, June 7 through 11, 1989.*—ED.

John Singer Sargent (1856-1925), *The Four Doctors*, 1906, American. Oil on canvas. 327.7 × 276.9 cm. Courtesy of The Johns Hopkins Medical Institutions, Baltimore, Md.

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Most commonly reported side effects in clinical trials include edema, headache, dizziness, asthenia, sinus bradycardia, flushing, and 1° AV block

Please see brief summary of prescribing information on next page.

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BRIEF SUMMARY
CARDIZEM® SR
(diltiazem hydrochloride)
Sustained Release Capsules
CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

Adverse	Diltiazem N=315 # pts (%)	Placebo N=211 # pts (%)
headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
dizziness	22 (7%)	6 (2.8%)
edema	19 (6%)	2 (0.9%)
bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
asthenia	10 (3.2%)	1 (0.5%)
constipation	5 (1.6%)	2 (0.9%)
dyspepsia	4 (1.3%)	1 (0.5%)
nausea	4 (1.3%)	2 (0.9%)
palpitations	4 (1.3%)	2 (0.9%)
polyuria	4 (1.3%)	2 (0.9%)
somnolence	4 (1.3%)	—
alk phos increase	3 (1%)	1 (0.5%)
hypotension	3 (1%)	1 (0.5%)
insomnia	3 (1%)	1 (0.5%)
rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) or have been observed in angina trials. In many cases, the relation to drug is uncertain.

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope.
Nervous System: Amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tinnitus, tremor, abnormal dreams.
Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase, thirst.
Dermatological: Petechiae, pruritus, photosensitivity, urticaria.
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. Definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established.

Issued 1/89

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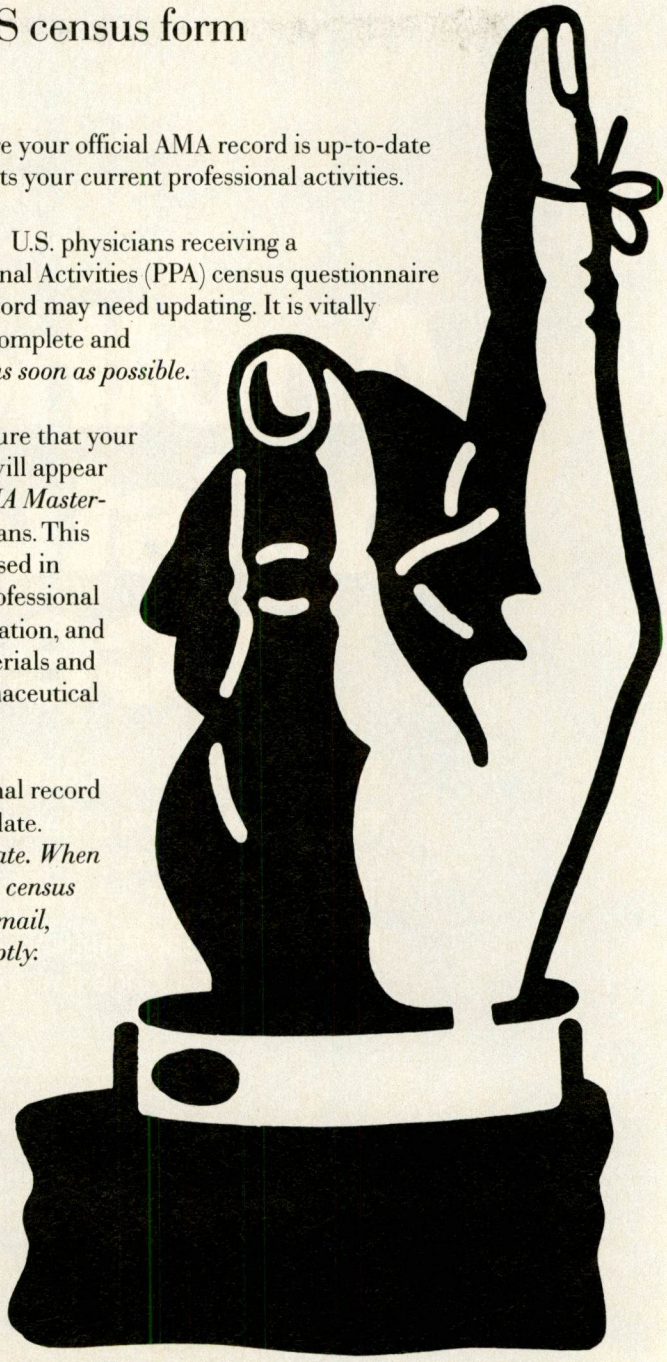


Hopkins Celebration This Month Prefaced by Science Writer Seminar

THE JOHNS HOPKINS Medical Institutions' centennial, major events of which will take place in the next few days, is reviving some fascinating questions of American medical history.

Would the university and hospital that bear his name ever have been founded if Baltimore banker Johns Hopkins had overcome family resistance and married the one woman he is said to have truly loved (instead of remaining a lifelong bachelor)? What would today's three-hospital system (55 000 inpatients and nearly 1 million outpatients annually) be like if physicians William H. Welch, William S. Halsted, William Osler, Howard Kelly, and John S. Billings had not served Hopkins in its early days?

While there are no precise answers to questions like those, the quality of work being done today at Hopkins—in the hospitals and schools of medicine, public health, and nursing—speaks for itself. It is apparent in the reports in this theme issue of *JAMA* that focuses on the centennial.

Those reports that constitute this week's Medical News & Perspectives section are based on interviews with Hopkins faculty members selected to participate in the Centennial Science Writers Seminar. That seminar set the stage for next Wednesday's opening convocation and the symposia, lectures, and other events scheduled for the June 7 through 11 centennial celebration in Baltimore.

Unless otherwise identified, the investigators named in the following stories are at the Hopkins institutions.

—by Phil Gunby

Evidence of New Physical, Genetic, Links in Autism

EMERGING EVIDENCE of genetic links to brain abnormalities and autistic behavior is establishing autism as an organic, rather than emotional, disorder.

To be classified as autistic, a patient must have 8 of 16 characteristics listed in the *Diagnostic and Statistical Manual of Mental Disorders*, revised third edition. Although the combination of characteristics displayed can vary widely among patients with autism, psychiatrist Allan Reiss, MD, and psychologist Lisa Freund, PhD, have found that one subgroup—males with fragile X syndrome—shows a consistent pattern of autistic symptoms and behaviors. This group has difficulty relating to peers, initiating conversations, making eye contact, and speaking normally. They also have motion disorders, such as hand-flapping, and abnormal sensory preoccupations, such as hypersensitivity to noise.

Men with the fragile X syndrome, which is characterized by as yet unknown chromosome abnormalities, are usually mentally retarded and usually have neuropsychiatric disorders that often include autistic behavior. Because females usually have only one fragile X chromosome, the degree of developmental disability in women and girls is less severe.

Reiss and colleagues have used magnetic resonance imaging (MRI) to examine the brains of 11 men and boys with the fragile X chromosome marker and varying degrees of autistic behavior. They found that among the study population, the cerebellar vermis, a region that is thought to be be involved in processing sensory information and in regulating motor function, is 13% smaller than among normal males.

Although Reiss notes that there is not a clear relationship between the amount of brain tissue present and the severity of autistic behaviors, he says that the abnormality may occur in a system that is involved in the development of autism. He suggests that because fragile X syndrome has a genetic basis, a physiologic, and thus genetic, basis for autism is also plausible.

Psychiatrist Susan Folstein, MD, is also exploring the genetics of autism. Folstein and colleagues are evaluating general mental ability, social skills, and language ability in a subgroup of normal family members of 100 autistic patients. They have found that among members of the 40 families evaluated, approximately 25% have deficits in reading and spelling ability and impaired social use of language, manifest in some adults in problems with spontaneous, conversational speech.

Because these deficits were not seen in controls—members of families of children with Down syndrome—Folstein thinks they cannot be attributed to the stress of dealing with an exceptional child. She sees the fact that these deficits are mild forms of disorders seen in patients with autism as further evidence of autism's genetic and possibly multifactorial nature.

To test this hypothesis, she is instituting genetic-linkage studies to identify a gene marker that is transmitted with the disease within families. She is also looking for physiologic markers, such as brain abnormalities or defects in the metabolism of neurotransmitters like serotonin, among these families.

Folstein, Reiss, and Freund are carrying on a line of research established at Hopkins in 1943 by psychiatrist Leo Kanner, MD, who coined the term "autism" to describe a particular syndrome that had theretofore been included in the nebulous category "childhood schizophrenia." Ironically, their work is providing strong evidence to refute Kanner's original (and later withdrawn) suggestion of a connection between autism and parents who were "intelligent, obsessive, perfectionistic, and humorless people who use set rules as a substitute for life's enjoyment."

—by Beverly Merz

Paleontologist Offers Lessons From Other Eons

WHY IS a paleontologist (whose credits include the first book on dinosaurs directed at scientists) teaching anatomy to first-year medical students?

The question is one frequently directed at David Weishampel, PhD, assistant professor of cell biology and anatomy. The answer is, "Because we are very good comparative anatomists."

Weishampel notes that, when it comes to extrapolating the anatomy of a hadrosaur or a parasaurolophus from a few bones, nothing is as valuable as experience in dissecting the composition of extant species. "One outlet is teaching human anatomy. The human structure has been very well studied, intensely scrutinized," he says.

Dividing his professional time between human anatomy and paleontology gives Weishampel a particular perspective on the human's role in today's world. His studies of extinction and speciation more than 75 million years ago can be used as a case study of population behavior in the face of environmental crises. "We have different kinds of models to assess the ways species fragment and how that's reflected in speciation and extinction rates," he says.

Weishampel speculates that humans, domesticated animals, and other large mammals may be approaching a fate similar to that of duck-billed dinosaurs. "With the way nature works and our fiddling with the environment, we may have increased our susceptibility to extinction," he says. "As an example, look at the destruction of the Amazon rain forests and its relation to increased global warming."

He suggests that, by disrupting other species, we may so alter the food chain that we eventually starve ourselves. "It's an ecological rule," he adds, "that when you take away habitat space, a population shrinks in size and reproductive continuity becomes disrupted."

Weishampel's long-range prognoses seem to have inspired his students. Five went with him on a field expedition to Cut Bank, Mont, last summer, where they unearthed 75 million-year-old hadrosaur nests (containing duck-billed dinosaur eggs). He expects to take 10 Hopkins students along this summer.

—by Beverly Merz

Seeking Scientific Acceptance of In Vitro Tests

MODERN-DAY TOXICOLOGY is going under glass.

Simultaneously with pressures from groups concerned about what they believe is unnecessary use of animals in tests, considerable scientific interest is developing in using in vitro techniques to evaluate the safety of commercial products, such as certain compounds or drugs. However, despite the fact that in recent years a number of in vitro tests have been developed to replace tests on animals, a broad science base using in vitro technologies has yet to be developed.

Alan M. Goldberg, PhD, of the School of Hygiene and Public Health says that, with an $800 000 research program spread among 12 to 15 institutions around the country as well as Hopkins itself, he and his associates are seeking to lay the groundwork for scientific acceptability of in vitro testing.

"There are those who think that the methodologies already exist to do this," he says. "But this is not true. We are just in the first stages of developing them."

These methodologies have become practicable as a result of advances in cell, tissue, and organ culturing, particularly the ability to maintain the functional capacities of these cells.

Methods are being developed to assay potentially hazardous compounds easily, speedily, and with a high degree of specificity in ways that avoid the limitations and uncertainties of animal testing, Goldberg says, adding: "With in vitro methods, we can get a much better handle on the nature of the chemical-biological interaction of a particular compound than we can with animal studies."

Goldberg cites a few examples of studies at Hopkins itself. Oerst Hurko, PhD, is working with a muscle cell line that can be turned into a tumor cell and replicate indefinitely or be turned back into a normal muscle cell using a zinc "switch." Add zinc and the malignant switch (a promoter of simian virus 40) is turned on; remove the zinc and the cells revert to normal.

"This is known as a 'reversible transformer,'" says Goldberg, who calls it a tremendous advance in terms of the ability to obtain large quantities of similar cells for study. These cells can be studied for the effects of compounds that may affect muscle. An investigator can put nerve cells into the culture and observe interactions between muscle and nerves cells as, for example, a screen for drugs that might affect the neuromuscular junction.

In the Department of Ophthalmology, Ruben Adler, MD, is cultivating retinal cells. His purpose is to study the processes associated with vision loss, but the same cells can be used to look at the toxic effects of specific chemicals on the cells, says Goldberg.

"Then," Goldberg says, "in our own laboratory we have been studying liver cells. John Frazier, PhD, is looking at hepatocyte cultures, studying the metabolism and detoxification of chemicals as well as their direct effect on the cells. As the cells break down the agent being studied, one can look at the metabolites and see what effect they have on the cells and whether the breakdown products are toxic or not."

A recent example is the now universal adoption of the limulus test for pyrogenicity, which used to involve a battery of rabbits. The test originated in Hopkins out of the need to develop a fast screening test for the pyrogenicity of short-lived isotopes.

Goldberg says: "It took almost 8 years from the time this test was developed and accepted by the Food and Drug Administration to the time it was fully implemented as an acceptable and desirable test to the toxicology community."

This was a reflection of the fact that the scientific community had to be comfortable about the validity of the test, he says, adding: "People will adopt a test when they become comfortable with the way to interpret the data."

As in vitro testing methods are developed and adopted, Goldberg believes that they will permit toxicology testing to be put on a much more rational basis than it is at the moment. "In our standard toxicological protocols we have a checklist mentality," he says.

He offers as an example the 14-day requirement for acute testing, contending that this period is not based on any evidence. "It's not unreasonable, but we may be being overly conservative and so paying an unrealistic price," he says.

Before any new compound is tested there should be a thorough search of the scientific literature to uncover what is

known about the compound, he says. This can be followed by a series of in vitro tests that would show what happens in individual organ systems.

Then, he says, the investigator is in a position to design small-animal studies that would provide accurate and detailed information about the compound in question. In fact, Goldberg says, this is already happening at the commercial level.

Ultimately, he predicts, it will affect the regulatory bodies. "As academics," he says, "we have both the obligation and the necessity to ask if we can't do better. Not that we're doing badly—we aren't—but we might well be able to do better."—by Charles Marwick

Promising Drug Combination for Sickle Cell Anemia

TEAMWORK between an anticancer agent and a hematopoietic growth factor may provide the first effective treatment for sickle cell anemia.

Promising data from a small study in which the drug hydroxyurea was used to treat patients with sickle cell anemia have prompted the expansion of trials to six centers. Pediatrician George J. Dover, MD, and internist Samuel Charache, MD, who have been using hydroxyurea to treat 2 patients since 1983, have expanded treatment to 38 patients in the enlarged study.

In a pilot study involving six patients, three of whom were treated at Johns Hopkins, three patients demonstrated marked clinical improvement. However, it was pathological rather than clinical findings that stimulated enthusiasm for hydroxyurea. The drug appeared to turn on the gene responsible for the production of the gamma protein chain, which in turn can combine with the alpha protein chain to form the fetal hemoglobin molecule.

The gene for the gamma chain is normally partially inactivated shortly before birth when a gene for the beta chain is turned on. However, if both beta genes code for defective beta chains, the resultant hemoglobin molecule, sickle hemoglobin, gives rise to the curved, elongated erythrocyte characteristic of sickle cell disease.

For some time hematologists have theorized that reactivation of the dormant gamma gene and the resultant resumption of fetal hemoglobin production might provide enough normal hemoglobin to restore the erythrocyte to its original state. Hydroxyurea, administered in small daily doses, appears to do just that, although no one is certain exactly how it does so.

In a separate study sponsored by the National Institutes of Health, Bethesda, Md, and conducted at Johns Hopkins and Harvard Medical School, Boston, Mass, investigators are adding another agent, erythropoietin, to the protocol. The protein, a hormone manufactured by the kidneys in minute amounts, is now available in large quantities through genetic engineering.

The recombinant version, like the natural protein, stimulates erythrocyte production. It may amplify the effect of hydroxyurea in two ways—by multiplying erythrocytes containing the reactivated gamma-chain gene and by directly stimulating the production of fetal hemoglobin. In doing so, it may enable the use of even lower doses of hydroxyurea, which has been associated with some adverse effects, including anemia, in cancer therapy.

The treatment is an attractive alternative to traditional therapy with antibiotics, analgesics, and multiple transfusions. By reducing the number of transfusions required, it is also expected to reduce the risk of viral infection, as well as the incidence of vessels blocked with sickled cells and iron toxicity.

In Dover's view, the treatment is a form of gene therapy. "Other efforts are being made to insert a new gene to replace the defective gene in sickle cell anemia. The Hopkins research is directed toward drugs [like hydroxyurea and erythropoietin] that guide regulatory genes to supply a needed product," he says.—by Beverly Merz

Exploring Causes of Paralysis in Spina Bifida

AN UNUSUAL CASE of spina bifida has set two neurosurgeons on a road that may eventually lead to a better understanding of events that cause the paralysis in this condition.

About 3 years ago, pediatric neurosurgeon Dan S. Heffez, MD, repaired a myelomeningocele in a 6-month-old infant. "In this particular case the typical malformed spinal cord seen in classic spina bifida was present but the cord, instead of being exposed, was covered by a full thickness of skin," he says.

"This is very unusual," Heffez points out. "It's only been reported once or twice before."

"But what was most important about this case was that there was no paralysis. So here was a patient with half the characteristics of a myelomeningocele; that is, the cord was structurally malformed and was outside the spinal column but—since it was fully covered by skin—it had not been exposed to the intrauterine environment."

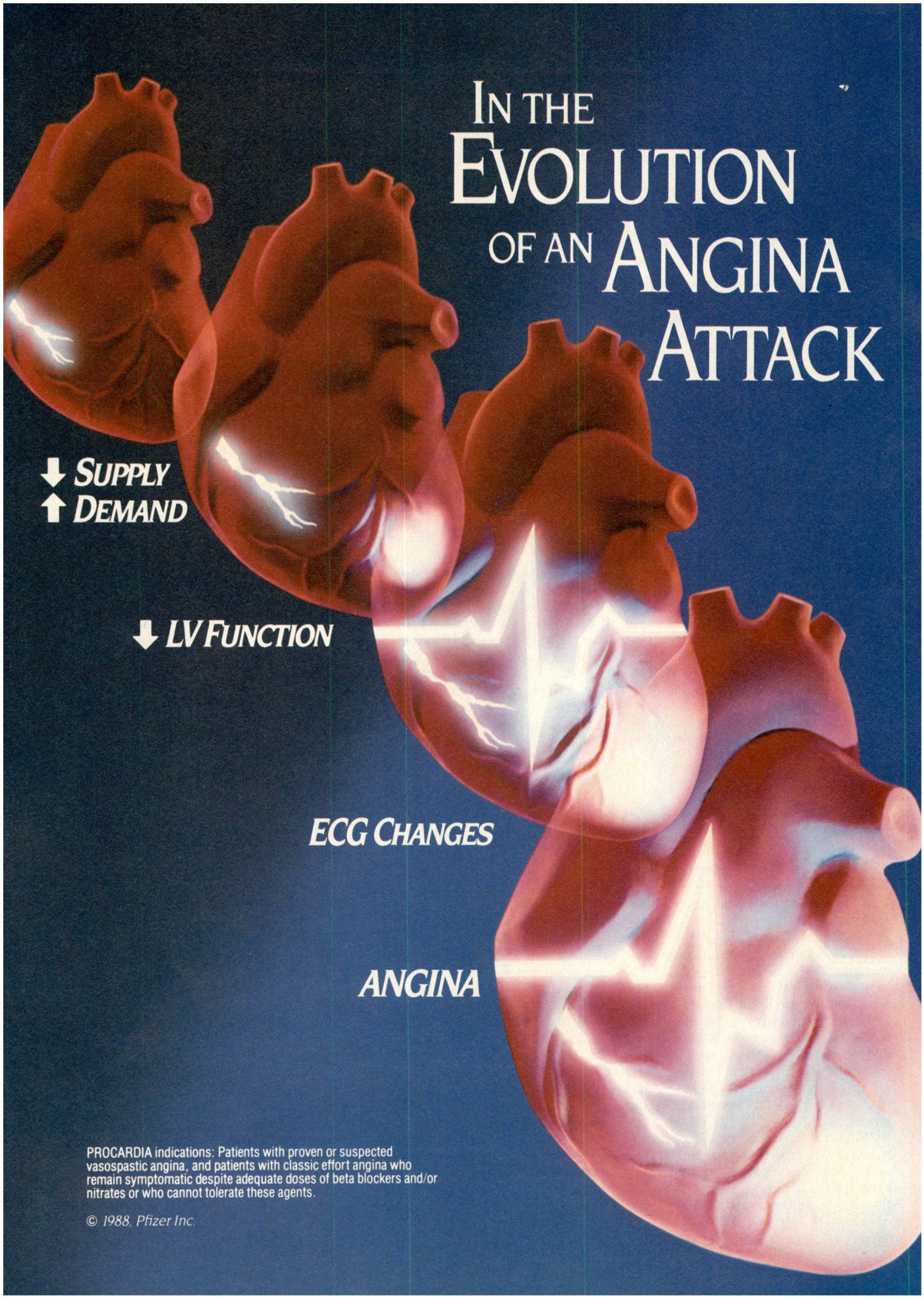
Spina bifida is the most common congenital malformation. The incidence is 1 per 1000 live births. Although Heffez has no firm numbers, he suspects that the number of spina bifida cases has been decreasing in recent years.

"Put it this way," he says, "it probably occurs just as frequently. But the number of live-born children with spina bifida is certainly decreasing as a result of prenatal diagnosis and the option of pregancy termination."

The case 3 years ago set Heffez to thinking about a conversation he had been having with John Freeman, MD, professor of pediatric neurology. "We had been discussing the possibility that, in part, the paralysis seen in children with myelomeningocele might be related to an injury to the spinal cord. Our experience with this patient seemed to provide strong, if circumstantial, evidence for this. It prompted me into doing something more than just having an interesting discussion about the subject," he says.

Heffez and his associate John Aryanpur, MD, devised an experiment in which they surgically exposed the spinal cords of fetal rats. In one group of fetuses the cord was left exposed to the intrauterine environment; in another group the wound was covered up. "The only difference between the two groups of animals was that the spinal cord in one group, the experimental group, was exposed to the intrauterine environ-

(Continued on p 3074.)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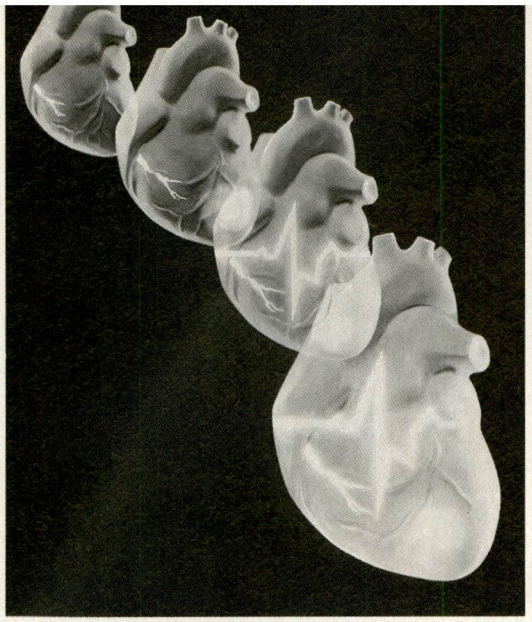

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...With an Excellent Side-Effects Profile

PROCARDIA side effects are usually mild and include dizziness, peripheral edema, nausea, weakness, headache and flushing (each in about 10% of patients); transient hypotension (about 5%); exacerbation of angina occurs rarely.

Brief Summary
PROCARDIA® (nifedipine) Capsules For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See WARNINGS.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting PROCARDIA or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Laboratory tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. The relationship to PROCARDIA therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms, however, cholestasis with or without jaundice has been reported. Rare instances of allergic hepatitis have been reported.

Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some PROCARDIA (nifedipine) patients. No clinical significance for these findings has been demonstrated. Positive direct Coombs test with/without hemolytic anemia has been reported.

Although PROCARDIA has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare, reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to PROCARDIA therapy is uncertain in most cases but probable in some.

Drug interactions: Beta-adrenergic blocking agents: (See INDICATIONS and WARNINGS.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Coumarin anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom PROCARDIA was administered.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%) after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, mutagenesis, impairment of fertility: Nifedipine was administered orally to rats for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats and embryotoxic in rats, mice and rabbits. There are no adequate and well controlled studies in pregnant women. PROCARDIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS: The most common adverse events include dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, shortness of breath, diarrhea, constipation, gastrointestinal cramps, flatulence, inflammation, joint stiffness, shakiness, jitteriness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, sexual difficulties, thrombocytopenia, anemia, leukopenia, purpura, allergic hepatitis, gingival hyperplasia, depression, paranoid syndrome, transient blindness at the peak of plasma level, erythromelalgia, and arthritis with ANA (+). Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

HOW SUPPLIED: PROCARDIA soft gelatin capsules are supplied in:
Bottles of 100: 10 mg (NDC 0069-2600-66) orange #260; 20 mg (NDC 0069-2610-66) orange and light brown #261. Bottles of 300: 10 mg (NDC 0069-2600-72) orange #260; 20 mg (NDC 0069-2610-72) orange and light brown #261. Unit dose packages of 100: 10 mg (NDC 0069-2600-41) orange #260; 20 mg (NDC 0069-2610-41) orange and light brown #261.

The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request.

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J-8275
October 1988

(Continued from p 3069.)
ment; in the other, the control group, it was not," Heffez says.

"Out of a total of 23 live-born rat pups, we found that every one of the 14 pups in the experimental group had some degree of paralysis in the hind legs. But in the 9 control animals, where the wound had been covered over, only 1 or 2 had signs of paralysis.

"Even in those cases we found that the wounds exposing the spinal cord had not really healed well in utero. So, effectively the cord was exposed. Indeed, we could actually see the spinal cord through the wound."

The simple conclusion from the study is that the amniotic fluid caused the paralysis. But Heffez is cautious. "Maybe the fluid does have a deleterious effect on the cord, but it's perfectly possible that there's something else present that we don't even recognize," he says.

Heffez looked at the structure of the spinal cords in the rats. "But remember," he emphasizes, "the clinical condition is much more complicated than this small aspect of it that we are studying. It may go far beyond simply exposing the spinal cord to the intrauterine environment. Just how relevant these experiments are to humans is something that cannot be accurately estimated at this point."

For example, in clinical spina bifida, spinal cord malformation is present. Heffez points out that the rat model he has been working with has no relation to this aspect of spina bifida.

The question, he says, is: Is it this that causes the paralysis, or does it also require the addition of a damaging exposure to amniotic fluid or the intrauterine environment? This is what the investigators are trying to determine now.

Nevertheless, Heffez says, "there's a strong possibility that there are other factors at work here than just the malformation of the cord."

Heffez says that if an interuterine or environmental factor can be demonstrated, and if "we can do something about it in animals, then many years down the road there may be some application to human spina bifida. But not at this stage of the game."

—by Charles Marwick

Investigators Add Pieces to Insulin Puzzle

THE IDENTIFICATION of two key molecules in a chain of insulin-initiated reactions is increasing understanding of a multi-step cascade that is initiated when insulin binds to membrane receptors and that terminates with glucose transportation into the cell.

The elucidation of that metabolic pathway is expected to do for diabetes research what the description of cholesterol metabolism has done for atherosclerosis investigation—identify several stages at which defects may occur and thus provide several opportunities for therapy.

M. Daniel Lane, PhD, director, Department of Biological Chemistry, has been pursuing that investigational avenue for almost a decade. Recently he and his colleagues have been approaching the problem by blocking the chain of metabolic reactions that have occurred at a certain point after insulin binding, then analyzing the products that have accumulated.

When they undertook their recent experiments, Lane and his colleagues already knew a few things about the reaction. They knew that when the insulin molecule binds to the receptor's membrane domain, it activates the domain that extends into the cytoplasm—a tyrosine-specific protein kinase. They also knew that there is evidence that the kinase is involved in transmitting a signal to mobilize the glucose-transport system in the cytoplasm and that the signal involves phosphorylating intermediate molecules in the chain.

The team incubated adipocytes with radioactive phosphate as a tracer and with an inhibitory agent (an organic arsenic-containing compound) that prevents the signal from being transmitted, then exposed the cells to insulin. They found that the signal halted after the phosphorylation of a small soluble protein, which they named "pp15."

The group has also compared the glucose transporter proteins of immature adipocytes, which have little response to insulin, with those of mature cells, which dramatically increase glucose uptake after insulin binding. They found and cloned the gene for one protein that was present in very high levels in mature cells and in very low levels in immature cells, a characteristic they had expected to find in a glucose transporter molecule. The molecule, GT2, has been found to be present in cardiac and skeletal muscle as well.

Lane and colleagues speculate that a defect in either molecule may play a role in the etiology of type II diabetes. "People with type II still produce insulin, but their cells become resistant to it. Their receptors may bind insulin, but something downstream is defective. It may be one of the intermediates, such as pp15 or GT2," he says.

—by Beverly Merz

Studying Color Blindness and Other Visions

RESEARCH that has identified the genes responsible for color vision has revealed a strong connection among the myriad sensory genes, including those involved in transmitting the sense of smell, regulation of heart rate, processing memory, and thinking.

Jeremy Nathans, MD, PhD, assistant professor of molecular biology, embarked on this sensory trail at Stanford (Calif) University, where he and colleagues isolated the genes for three pigment proteins that function as receptors on the cone cells of the retina. The pigment proteins respond to light of different wavelengths to register the colors red, green, and blue.

In doing so, they took advantage of a previously isolated gene for bovine rhodopsin, the pigment in rod cells responsible for black-and-white vision. They theorized that the rhodopsin and the three color pigment genes had evolved from a common precursor and that there would be a relatively high degree of homology among the four genes. Thus, they reasoned that a probe might bind to the human pigment genes as well.

Nathans and his colleagues found that the probe formed a strong bond with one human gene and weak bonds with three others. They identified the first as the rhodopsin and the others as the red-pigment, green-pigment, and blue-pigment genes. They traced the red-pigment and green-pigment genes to the X chromosome, and the blue-pigment gene to chromosome 7. The dis-

(Continued on p 3077.)

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Please see brief summary of prescribing information on adjacent page.

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BRIEF SUMMARY

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate.

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration..

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be non-systemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

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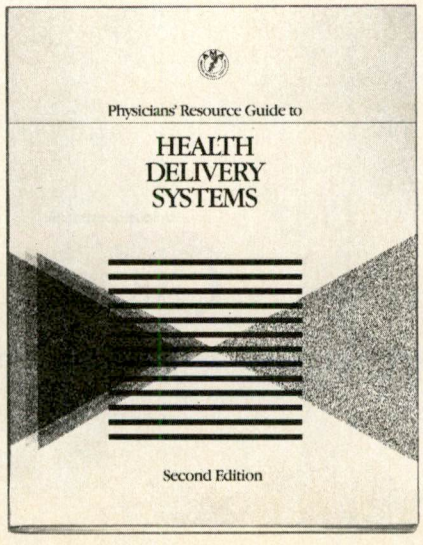

(Continued from p 3074.)
covery fit neatly with the observation that red-green color blindness occurs in 8% of men but in only 0.5% of women.

The team then began to look at the arrangement of the genes in men with normal color vision and in those who are color-blind. They found that men with normal vision appear to have only one copy of the red-pigment gene, but may have as many as three copies of the green-pigment gene.

Nathans reasons that this disparity could be a result of homologous recombination during meiosis. Because the red-pigment and green-pigment genes are in tandem arrangement on the chromosome, the exchange of genetic material between homologous chromosomes could result in the duplication or loss of either the red-pigment or green-pigment gene or the creation of hybrid genes composed of DNA from both pigment genes.

He suggests the green-pigment gene is altered more frequently than the red because it is positioned in the middle of the pigment gene cluster. Although the amplification of a pigment gene alone appears to have no effect, the deletion or hybridization of a gene can result in alterations in color vision.

Elsewhere, other investigators have used a similar approach to unveil connections among other receptors that process sensory stimuli. They have detected 20% to 30% homology among the pigment-containing molecules and other molecules that are the receptors for G-proteins, a class that includes most small-molecule drugs, hormones, and neurotransmitters.

The identical sequences of amino acids occur in patches throughout the receptor proteins, indicating that they may have had a common ancestor, and that they contain regions that were conserved because they performed a vital function. Nathans speculates that the individual proteins might be variations on an original theme and that each might have evolved in response to stimulation by a different substance.

Nathans' current work is, in a sense, an effort to reproduce these evolutionary steps. He is manipulating the rhodopsin gene to create changes in structure of the protein and observing the alterations in receptor function that result. —by Beverly Merz

Information Accumulating on How Brain 'Hears'

NEW INFORMATION about the way the brain "hears," that is, how it processes the signals it receives from the inner ear, is accumulating from research at the Center for Hearing Sciences. Learning how the auditory nerves process the information they receive from the external auditory system has important implications for understanding brain function as well as hearing.

"When you talk about hearing, you're really talking about the brain, and expanding our knowledge of this process has broad implications for treating sensory disorders," says Murray B. Sachs, PhD, the center's director.

Humans' ability to hear allows them to detect the slightest sound in a hushed forest yet also to converse in a noisy subway. "We can process sounds over a range of intensities of about 100 million million (trillion) to 1, yet virtually over this entire range, speech is perfectly intelligible. We can detect frequency changes as small as 0.01%. Indeed, our capacity to communicate with sound depends on this ability to discriminate between frequencies," Sachs notes.

The auditory system has two parts, peripheral and central (the brain). In the peripheral system, sound vibrates the tympanic membrane. The vibration is transferred to the cochlea via the malleus, incus, and stapes. This in turn causes motion of the fluid in the sensory organ for hearing, the organ of Corti, which is contained in the cochlea and supported by the basilar membrane.

The organ of Corti contains hair cells, the sensory cells of the auditory system. When the hair cells move in response to the mechanical vibrations transmitted to them from the outer and middle ear, the movement is converted into electrical signals that are then transferred to the auditory neurons, which carry the signal to the brain, where they are "encoded" and interpreted.

"Our goal is to break this code and understand how the brain processes sounds as complicated as speech," says Sachs. "Already we have found what the code is in the auditory nerve and how some of auditory neurons in the brain process speech."

About 30 000 such auditory nerve fibers innervate one human cochlea. These cells convey acoustic signals in the form of bioelectrical "spike trains," or sequences of nerve signals in a specific time frame. All the spikes have the same size and shape. The information these acoustic signals transmit to the brain is carried by the variations in time between the spikes. "It is these temporal sequences that carry the information; the features of sound are encoded or represented in these temporal patterns of spike trains," Sachs says.

Two aspects of the spike train are important in defining the response of an auditory nerve fiber to a sound stimulus—rate and time. The rate at which the spike discharges fire in response to a sound can increase, and the temporal pattern of the spike trains can change in response to sound. However, there are limits to the capacity of these auditory nerve fibers.

Auditory nerve fibers, like other sensory neurons, have a limited dynamic range. Their firing rate increases as the intensity of the sound increases, but it can go only to some maximum value—about 200 spikes per second.

"Given this limitation, how is it that we can communicate with sound over a range of 100 million million to 1?" Sachs asks. Sachs notes that there are two types of cells in the cochlear nucleus of the brain that handle auditory information. Each type of cell recognizes the information it receives in a different but complementary way.

Recently one of Sachs' associates, Carol Blackburn, PhD, studied one group of these cells, stellate cells. She has found evidence suggesting that they process the rate at which spike discharges are recorded.

And, notes Sachs, there is another group of cells also present in the cochlear nucleus, bushy cells, that deals with the temporal pattern of the spike trains' response to a sound stimulus. "These bushy cells have structural features that allow them to pass on precise timing information," he says.

"We speculate that these two groups of cells process different aspects of the auditory nerve code," he says. "The bushy cells deal with the temporal-place component while stellate cells process the rate-place component."

Sachs' success in describing the way the auditory system functions at the low levels of the system is encouraging him to investigate what has been called the "higher auditory function," eg, to auditory areas in the cerebral cortex. "We are now in a position to begin to understand the complex signal processing that goes on in our brains every time we perceive a sound."

—by Charles Marwick

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This fixed-dose combination is not indicated for initial therapy. Patients already receiving a diuretic when enalapril is initiated or given a diuretic and enalapril simultaneously can develop symptomatic hypotension. In the initial titration of the individual entities, it is important, if possible, to stop the diuretic for several days before starting enalapril or, if this is not possible, to begin enalapril at a low initial dose (2.5 mg; see DOSAGE AND ADMINISTRATION). This fixed-dose combination is not suitable for titration but may be substituted for the individual components if the titrated doses are the same as those in the combination.

VASERETIC, containing 10 mg enalapril maleate and 25 mg hydrochlorothiazide, is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

Evaluation of the hypertensive patient should always include assessment of renal function.

For a Brief Summary of Prescribing Information, please see last page of this advertisement.

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CONTRAINDICATIONS: VASERETIC is contraindicated in patients who are hypersensitive to any component of this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor. Because of the hydrochlorothiazide (HCTZ) component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS: ***Hypotension:*** Excessive hypotension was rarely seen in uncomplicated hypertensive patients but is a possible consequence of enalapril use in severely salt/volume-depleted persons, such as those treated vigorously with diuretics or patients on dialysis. Syncope has been reported in 1.3% of patients receiving VASERETIC and in 0.5% of patients receiving enalapril alone. The overall incidence of syncope may be reduced by proper titration of the individual components (see PRECAUTIONS, *Drug Interactions*; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION in complete Prescribing Information). In patients with severe congestive heart failure, with or without associated renal insufficiency, excessive hypotension has been observed and may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Because of the potential fall in blood pressure in these patients, therapy should be started under very close medical supervision. Such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, should receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including enalapril. In such cases, VASERETIC should be promptly discontinued and the patient should be carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered** (see ADVERSE REACTIONS).

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with thiazides (see PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*).

PRECAUTIONS: General: ***Enalapril Maleate:*** *Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including enalapril, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in BUN and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy. Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in BUN and serum creatinine, usually minor and transient, especially when enalapril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of enalapril and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function.**

Hyperkalemia: Elevated serum potassium (>5.7 mEq/L) was observed in approximately 1% of hypertensive patients treated with enalapril alone in clinical trials. In most cases these were isolated values which resolved despite continued therapy, although hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. Hyperkalemia was less frequent (approximately 0.1%) in patients treated with enalapril plus HCTZ. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with enalapril (see *Drug Interactions*).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because enalapril reduces the production of aldosterone, concomitant therapy with enalapril attenuates the diuretic-induced potassium loss (see *Drug Interactions: Agents Increasing Serum Potassium*).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients, dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus, latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, may occur, especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue and/or difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness, especially during the first few days of therapy. If actual syncope occurs, patients should be told to discontinue the drug until they have consulted with the prescribing physician. All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion, such as vomiting or diarrhea, may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with VASERETIC is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Enalapril Maleate:*** *Hypotension—Patients on Diuretic Therapy:* Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to enalapril treatment. If it is necessary to continue the diuretic, provide medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (see WARNINGS and DOSAGE AND ADMINISTRATION). *Agents Causing Renin Release:* The antihypertensive effect of enalapril is augmented by antihypertensive agents that cause renin release (e.g., diuretics). *Other Cardiovascular Agents:* Enalapril has been used concomitantly with beta-adrenergic-blocking agents, methyldopa, nitrates, calcium-blocking agents, hydralazine, and prazosin without evidence of clinically significant adverse interactions. *Agents Increasing Serum Potassium:* Enalapril attenuates diuretic-induced potassium loss. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. *Lithium:* See WARNINGS, *Hydrochlorothiazide*; and PRECAUTIONS, *Drug Interactions: Hydrochlorothiazide*.

Hydrochlorothiazide: When administered concurrently, the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—dosage adjustment of the antidiabetic drug may be required. *Other antihypertensive drugs*—additive effect or potentiation. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with VASERETIC. *Nonsteroidal anti-inflammatory drugs*—In some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when VASERETIC and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Pregnancy: ***Enalapril Maleate-Hydrochlorothiazide:*** *Pregnancy Category C.* There was no teratogenicity in rats given up to 90 mg/kg/day of enalapril (150 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose) or in mice given up to 30 mg/kg/day of enalapril (50 times the maximum human dose) in combination with 10 mg/kg/day of HCTZ (2-1/2 times the maximum human dose). At these doses, fetotoxicity expressed as a decrease in average fetal weight occurred in both species. No fetotoxicity occurred at lower doses: 30/10 mg/kg/day of enalapril-HCTZ in rats and 10/10 mg/kg/day of enalapril-HCTZ in mice.

There are no adequate and well-controlled studies of VASERETIC in pregnant women. VASERETIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Enalapril Maleate: Post-marketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity, such as patent ductus arteriosus, have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Hydrochlorothiazide: Thiazides cross the placental barrier and appear in cord blood. *Nonteratogenic Effects:* These may include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: It is not known whether enalapril is secreted in human milk; however, thiazides do appear in human milk. Milk of lactating rats contains radioactivity following administration of ^{14}C enalapril maleate. Because of the potential for serious reactions from HCTZ in nursing infants, a decision should be made whether to discontinue nursing or to discontinue VASERETIC, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: VASERETIC has been evaluated for safety in more than 1,500 patients, including more than 300 patients treated for one year or more. In clinical trials with VASERETIC, no adverse experiences peculiar to this combination drug have been observed. Adverse experiences that have occurred have been limited to those that have been previously reported with enalapril or HCTZ.

The most frequent clinical adverse experiences in controlled trials were dizziness (8.6%), headache (5.5%), fatigue (3.9%), and cough (3.5%). Generally, adverse experiences were mild and transient in nature. Other adverse experiences occurring in >2% of patients treated with VASERETIC in controlled clinical trials were muscle cramps (2.7%), nausea (2.5%), asthenia (2.4%), orthostatic effects (2.3%), impotence (2.2%), and diarrhea (2.1%).

Clinical adverse experiences occurring in 0.5% to 2.0% of patients in controlled trials included: *Body as a Whole:* Syncope, chest pain, abdominal pain. *Cardiovascular:* Orthostatic hypotension, palpitation, tachycardia. *Digestive:* Vomiting, dyspepsia, constipation, flatulence, dry mouth. *Nervous/Psychiatric:* Insomnia, nervousness, paresthesia, somnolence, vertigo. *Skin:* Pruritus, rash. *Other:* Dyspnea, gout, back pain, arthralgia, hyperhidrosis, decreased libido, tinnitus, urinary tract infection. *Angioedema:* Angioedema has been reported in patients receiving VASERETIC (0.6%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASERETIC should be discontinued and appropriate therapy should be instituted immediately (see WARNINGS). *Hypotension:* In clinical trials, adverse effects relating to hypotension occurred as follows: hypotension (0.9%), orthostatic hypotension (1.5%), other orthostatic effects (2.3%). In addition, syncope occurred in 1.3% of patients (see WARNINGS).

Clinical Laboratory Test Findings: *Serum Electrolytes:* See PRECAUTIONS. *Creatinine, BUN:* In controlled clinical trials, minor increases in BUN and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.6% of patients with essential hypertension treated with VASERETIC. More marked increases have been reported in other enalapril experience. Increases are more likely to occur in patients with renal artery stenosis (see PRECAUTIONS). *Serum Uric Acid, Glucose, Magnesium, and Calcium:* See PRECAUTIONS. *Hemoglobin and Hematocrit:* Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in hypertensive patients treated with VASERETIC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia. *Other (Causal Relationship Unknown):* Rarely, elevations of liver enzymes and/or serum bilirubin have occurred.

Other adverse reactions that have been reported with the individual components are listed below and, within each category, are in order of decreasing severity. *Enalapril Maleate*—Enalapril has been evaluated for safety in more than 10,000 patients. In clinical trials, adverse reactions which occurred with enalapril were also seen with VASERETIC. However, since enalapril has been marketed, the following adverse reactions have been reported: *Cardiovascular:* Cardiac arrest; myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high risk patients (see WARNINGS, *Hypotension*); pulmonary embolism and infarction; rhythm disturbances, atrial fibrillation; hypotension; angina pectoris. *Digestive:* Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, glossitis. *Hematologic:* Rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported in which a causal relationship to enalapril cannot be excluded. *Nervous System/Psychiatric:* Depression, confusion, ataxia. *Renal:* Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). *Respiratory:* Bronchospasm, pneumonia, bronchitis, rhinorrhea, asthma, upper respiratory infection. *Skin:* Herpes zoster, alopecia, flushing, photosensitivity. *Other:* Vasculitis, blurred vision, taste alteration. A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy. *Hydrochlorothiazide—Body as a Whole:* Weakness. *Digestive:* Pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation, anorexia. *Hematologic:* Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia. *Hypersensitivity:* Purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions. *Musculoskeletal:* Muscle spasm. *Nervous System/Psychiatric:* Restlessness. *Renal:* Renal failure, renal dysfunction, interstitial nephritis (see WARNINGS). *Special Senses:* Transient blurred vision, xanthopsia.

HOW SUPPLIED: No. 3418—Tablets VASERETIC 10-25 are rust, squared capsule-shaped, compressed tablets, coded MSD 720 on one side and VASERETIC on the other. Each tablet contains 10 mg enalapril maleate and 25 mg hydrochlorothiazide. They are supplied as follows: NDC 0006-0720-68 bottles of 100 (with desiccant).

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Questions and Answers

Diarrhea Associated With Nonsteroidal Anti-inflammatory Drugs

Q I have seen three patients over the last several years who have developed diarrhea in association with the use of several chemically unrelated nonsteroidal anti-inflammatory agents. In the most recent case the patient developed uncontrollable diarrhea while using ibuprofen (Motrin), naproxen (Naprosyn), piroxicam (Feldene), and indomethacin (Indocin).

Has this adverse effect been described? What is the mechanism thought to be? Are there specific agents with which this would be less likely to occur, such as nonacetylated salicylates?

Lawrence S. Schiffman, MD
Florence, Mass

A The major organ system affected by adverse reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) is the gastrointestinal (GI) tract. Although we primarily focus on the side effects produced in the upper GI tract by these agents, lower GI tract side effects, including diarrhea and lower GI tract bleeding, have been reported with the use of these agents.[1-4] Diarrhea is most commonly seen with the use of meclofenamate sodium (Meclomen), occurring with a frequency of up to 30% in clinical trials. The incidence of diarrhea with use of other NSAIDs is probably no greater than 1% and not significantly different from what occurs in patients receiving placebo in controlled clinical trials. The mechanism of action underlying this toxic reaction is likely related to inhibition of prostaglandin biosynthesis in the colonic mucosa. The explanation for the increased toxicity associated with use of meclofenamate is most likely the enterohepatic recirculation of the active drug, which leads to an increased concentration in the lower GI tract.

Recently, Kaufmann and Taubin[1] reported eight cases in which flare-ups of inflammatory bowel disease were associated with the use of NSAIDs. In light of this report, it is interesting to note that one of the three patients reported on by Schwartz[2] had ankylosing spondylitis and Crohn's disease; the latter was diagnosed only after the patient developed diarrhea and lower GI tract bleeding in the setting of ibuprofen therapy. Therefore, it seems prudent that patients who develop severe diarrhea, especially if it is complicated by lower GI tract bleeding, during therapy with NSAIDs should be evaluated for occult inflammatory bowel disease. Furthermore, we have recently seen two patients with the entity collagenous colitis develop severe diarrhea while taking indomethacin.

I am unaware of any data concerning the relative relationship of nonacetylated salicylates compared with other NSAIDs in causing diarrhea. However, if prostaglandin inhibition is an important mechanism explaining the side effect, it seems reasonable that nonacetylated salicylates may be less likely to produce severe diarrhea; the nonacetylated salicylates are less potent prostaglandin inhibitors than either aspirin or nonsalicylated NSAIDs.

Marc C. Hochberg, MD, MPH
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Traumatic Injury of the Brachial Plexus: Should Radiotherapy Be Postponed?

Q During a radical neck dissection for an epidermoid carcinoma of a cervical lymph node, the brachial plexus was traumatized. Both sensory and motor loss ensued involving the deltoid, biceps brachii, and the external rotators of the shoulder of the left arm. There is also sensory dysthesia of the left hand and forearm. Originally, it was planned to follow surgery with a course of radiation therapy. My question is whether exposure of the damaged brachial plexus to radiation would be contraindicated until the involved nerves have recovered. What is the risk that radiation will cause further, possibly irreversible, injury to the nerves?

Genevieve A. Arneson, MD
Gretna, La

This inquiry was answered by a radiation oncologist (Dr Lee) and an otolaryngologist–head and neck surgeon (Dr Mattox).

A Brachial plexus injury is a rare complication of radical neck dissections. Traumatic injury of the brachial plexus during surgery can cause both sensory and motor dysfunction. Since the incidence is extremely rare, the information on the effect of postoperative radiotherapy on the recovery of the traumatized brachial plexus is scant; however, some inferences can be drawn from the literature.

A course of postoperative radiotherapy for metastatic carcinoma in the neck does not injure the normal brachial plexus.[1] In our experience, none of 550 patients with head and neck carcinomas treated with postoperative radiotherapy developed brachial plexus injury. It should be noted that radiotherapy for breast carcinoma (with the treatment portal covering the axilla) can induce brachial plexus neuropathy, although the incidence is low, usually less than 3%.[2]

We also know that recovery of the facial nerve after elective resection and grafting is probably mildly impaired by postoperative radiation therapy. However, it is unclear whether this is a direct effect on the regenerating axons or results from an increase of scarring and fibrosis of the surrounding tissues and facial musculature.[3,4]

The most important consideration for this patient is adequate and complete treatment of the carcinoma. It will take 3 to 18 months for the brachial plexus to recover, and it would be unwise to postpone the radiation based on the theoretical possibility of better nerve regeneration. After this delay, the radiation will be much less effective and the tumor may have recurred. In summary, if radiation therapy is indicated for management of the patient's tumor, we recommend it be started as soon as possible regardless of postoperative nerve injuries.

Ding-Jen Lee, MD, PhD
Douglas Mattox, MD
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Edited by Helene M. Cole, MD, Senior Editor.
Every letter must contain the writer's name and address, but these will be omitted on request. Questions are submitted to consultants at the discretion of the editor and published as space permits.

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Cholesterol Elevation in the Elderly

Q A 75-year-old woman has been in good health with no significant medical problems encountered during my annual examinations over the last several years. She has taken conjugated estrogens for a number of years since a partial hysterectomy at 66 years of age. The dosage has been steadily reduced. There are no signs or symptoms of atherosclerotic disease in any organ system. One sister died at the age of 76 years of a stroke, and an older sister is alive and well at 80 years, having had at least one myocardial infarction. Another sister is well at the age of 85 years. My patient's cholesterol level was 7.40 mmol/L in 1985 and had risen to 8.50 mmol/L in 1987. The high-density lipoprotein (HDL) level was 1.90 mmol/L. Her triglyceride level was 2.28 mmol/L. Over the past year the patient has followed a low-cholesterol diet and has reduced her weight by a few pounds. She appears to be at a normal body weight. With this "therapy" her cholesterol level has gone to 8.10 mmol/L with a triglyceride level of 2.36 mmol/L and an HDL cholesterol level of 1.75 mmol/L. Should this woman undergo pharmacologic therapy to reduce her cholesterol level?

Jeffrey B. Gluckman, MD
Newport News, Va

A Whether and how to treat cholesterol elevations in the elderly are probably the most common questions addressed to physicians specializing in preventive cardiology. The need to resolve the issue is magnified by two factors. One is the greater frequency in the elderly of cholesterol levels that exceed the desirable values in the National Cholesterol Education Program Adult Treatment Guidelines. Second, the extensive media coverage of cholesterol has encouraged large numbers of people to participate in mass screening programs that use devices for rapid cholesterol measurement.

There is no easy answer to the general question; decisions must be based on the specific medical situation and the attitudes of each individual patient. Even then opinions vary widely. Two colleagues proposed diametrically opposite answers to the question raised about this patient.

On the one hand, because angiographic studies have shown that a significant reduction in cholesterol levels slows the progression of coronary artery disease, how can a physician conclude that a patient is too old to benefit from lowering cholesterol levels? On the other hand, good levels of HDL cholesterol appear to be more important than bad levels of low-density lipoprotein (LDL) cholesterol in the elderly, and does their relatively short remaining life span justify severely restricted diets or the possible side effects of medications?

In the case of this particular patient, in addition to her age, arguments against the use of medications include her evident lack of cardiovascular disease, longevity in her sisters, an HDL level well above average, and a "good" LDL/HDL ratio of 3.0. Yet, her calculated LDL cholesterol level of 5.33 mmol/L is clearly above the recommended cut point (4.91 mmol/L) for pharmacologic treatment, even for patients at low risk.

One factor that could influence your decision regarding more aggressive treatment is the presence or absence of other risk factors: hypertension, cigarette smoking, diabetes, and obesity. Her level of concern about the high cholesterol level should also affect your decision. Before considering the use of pharmacological agents, you should stress further weight loss if she is obese (because weight control also has benefits unrelated to blood lipid levels) and have her see an experienced dietitian to be sure that the patient understands and is following a moderate cholesterol-lowering diet.

Should LDL cholesterol levels be elevated despite further dietary instruction, I would be willing to initiate treatment with medication after explaining its pros and cons (including possible side effects) *if it is the patient's desire*. One rationale for trying to lower low-density lipoprotein levels is that men with higher HDL levels in the Coronary Primary Prevention Trial had the greatest benefit from reducing their low-density lipoprotein. In addition, drug treatment is likely to be more effective and less disruptive of this woman's life than a more rigorous diet.

My choice of medications would be Metamucil, 5 mL three times daily, and/or lovastatin, 10 mg or 20 mg each night. Both are well tolerated by most patients, and the major concern about lovastatin, the possibility of as yet unrecognized complications with its long-term use, is less alarming in this woman with a relatively limited life span.

Simeon Margolis, MD, PhD
The Johns Hopkins
School of Medicine
Baltimore, Md

Potency of Expired Ophthalmologic Preparations

Q I am part of a group of physicians who have supplied ophthalmologic medications to the Third World. It has come to our attention that many of these medications are disposed of when received because the expiration date has been passed. We believe it would be better to have a drug that may be slightly out of date and free than no medication at all. Our perusal of the literature on the relationship between stability of the preparation and the expiration date has not been helpful. Would you be able to supply information as to the effectiveness of drugs after the expiration date, particularly for ophthalmologic preparations?

Davis G. Durham, MD
Wilmington, Del

A Most pharmaceutical manufacturing firms can provide you with information concerning the termination of expiration dates on their medications. As a general rule, the Food and Drug Administration demands an expiration date that corresponds with a 10% loss in potency, so that most of the ophthalmic solutions still have a good bit of potent agent remaining in the carrier, whether it be a bottle, a tube, or other container. Of course, there will be a breakdown of products. In some cases the breakdown products will continue to be potent compounds, sometimes as potent as the original. Further breakdown after the initial expiration date will vary with each drug. Some drugs will continue to deteriorate slowly and others more rapidly. Proof of a drug's potency depends on its action on the condition for which it is being employed. There may be some variation in toxicity of the so-called expired preparations with further passage of time.

Pharmaceutical companies destroy expired medication so that preparations that are available for purchase will meet all specifications. Then a lack of response can be attributed to ineffectiveness of the drug, not to a lack of active drug. Although a manufacturer might determine the breakdown curve of each agent, it would be difficult to be certain of the quantity of active drug present as well as any potentially toxic breakdown products at any one time in a particular product.

In summary, the answer to your question is yes, many so-called expired drugs still have activity, but there are many variables that make their use an unreliable approach.

Irving H. Leopold, MD
Allergan, Inc
Irvine, Calif

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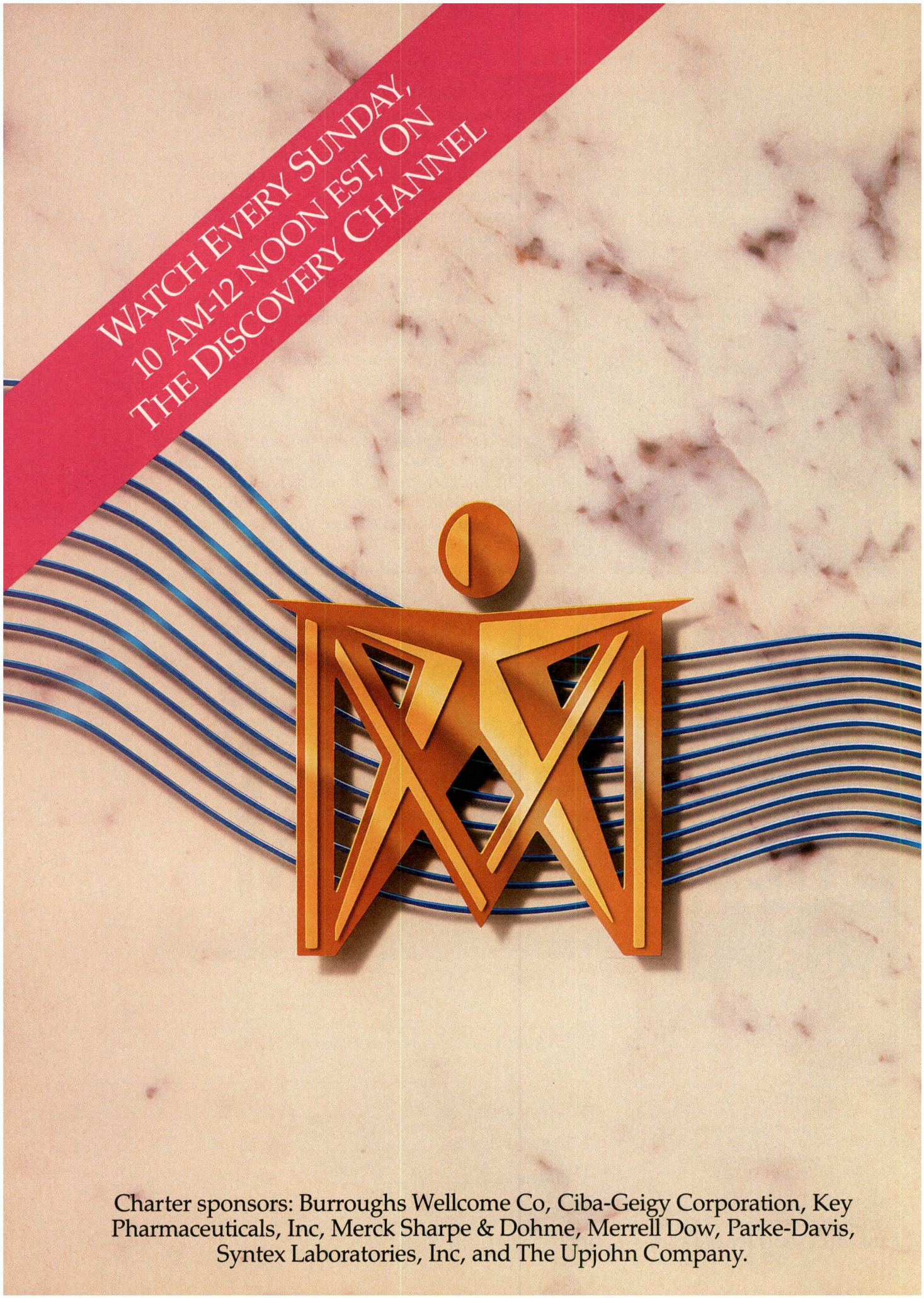

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Abstracts

N ENGL J MED Boston, Mass

Urinary-Bladder Management After Total Joint-Replacement Surgery

We conducted a randomized study of 100 patients to examine the efficacy and risks of two methods of urinary-bladder management after total joint-replacement surgery. Patients who had hip or knee replacement were randomly assigned either to group I, in which indwelling catheters were placed during the operation and removed the next morning, or to group II, in which urinary retention was managed by intermittent catheterization as needed. After the removal of the indwelling catheter, the patients in group I had a lower incidence of urinary retention than those in group II (27% vs 52%; $P<.01$). Bladder distention (volume, >700 mL) was more common in group II (45% compared with 7% in group I; $P<.01$) and was associated with an increased need for subsequent long-term catheterization. There was no significant difference between the groups in the rates of urinary tract infection (11% vs 15%). We could not identify patients at high risk for retention or infection on the basis of preoperative urinary symptoms, previous urinary tract surgery, previous urinary tract infection or urinary retention, high-risk medical conditions, sex, type of anesthesia, or age (in the absence of prophylactic management). We conclude that the short-term use of an indwelling catheter after extended surgery, such as joint replacement, reduces the incidence of urinary retention and bladder overdistention without increasing the rate of urinary tract infection.

(1988;319:321-326) James D. Michelson, MD, et al, Department of Orthopaedic Surgery, The Johns Hopkins Hospital, Harvey 611, 600 N Wolfe St, Baltimore, MD 21205.

N ENGL J MED Boston, Mass

Calcium-Antagonist Receptors in the Atrial Tissue of Patients With Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is characterized by a nondilated, hypertrophied left ventricle in the absence of any overt cause. A possible role of adrenergic innervation or of cellular calcium regulation is suggested by the presence of hyperdynamic left ventricular function and by the clinical and symptomatic improvement seen in patients treated with β-receptor antagonists or calcium antagonists. Therefore, we measured the density of calcium-antagonist receptors and β-adrenoceptors in the atrial myocardium of 16 patients with hypertrophic cardiomyopathy and 19 patients with various other cardiac disorders. For comparison, we also measured the number of voltage-sensitive sodium channels. Calcium-antagonist binding sites, measured as the amount of dihydropyridine bound to atrial tissue, were increased by 33% in patients with hypertrophic cardiomyopathy (mean [± SD], 397 ± 104 fmol/mg of protein in patients with hypertrophic cardiomyopathy, compared with 299 ± 108 fmol/mg in patients with other cardiac disorders; $P<.01$). The densities of saxitoxin-binding sites on voltage-sensitive sodium channels and β-adrenoceptors were the same in the two groups, although the density of β-adrenoceptors was higher in atrial samples from patients receiving β-receptor antagonists (165 ± 86 fmol/mg of protein [patients receiving β-blockers] vs 85 ± 60 fmol/mg [patients not receiving β-blockers]; $P<.04$). The increase in the number of calcium-antagonist receptors in hypertrophic cardiomyopathy suggests that abnormal calcium fluxes through voltage-sensitive calcium channels may play a pathophysiological part in the disease.

(1989;320:755-761) John A. Wagner, PhD, et al. Reprint requests to Solomon H. Snyder, MD, The Johns Hopkins University School of Medicine, Department of Neuroscience, 725 N Wolfe St, Baltimore, MD 21205.

AM J EPIDEMIOL Baltimore, Md

Outbreaks of Smallpox due to Variolation in China, 1962-1965

In 1985, previously unknown outbreaks of smallpox were uncovered that had occurred in Shanxi Province and Nei Monggol Autonomous Region in northern China during 1962 to 1965, several years after smallpox transmission was thought to have been interrupted. During field investigation, we learned that most of the cases were known to local health officials but had not been officially reported to national authorities. All were among persons who had been variolated or were their close contacts. Variolation is an ancient method of protection against naturally acquired smallpox that was officially proscribed in the early 1950s but was renewed in remote areas when smallpox vaccination activities were interrupted during the three-year famine of 1959 to 1962, following the "great leap forward" program of 1958. It was found that the variolators in Shanxi Province and Nei Monggol Autonomous Region inoculated persons with the use of powdered smallpox scabs mixed with human milk, and that they obtained fresh supplies of scabs every 6 to 12 months by variolating relatives and friends. The health authorities responded by capturing the variolators, confiscating their variolation material and equipment, and vaccinating the population. The last known cases occurred in 1965, and the practice of variolation is now believed to be extinct.

(1988;128:39-45) Yutu Jiang et al. Reprint requests to D. A. Henderson, The Johns Hopkins School of Hygiene and Public Health, 615 N Wolfe St, Baltimore, MD 21205.

AM J EPIDEMIOL Baltimore, Md

Epidemiologic Evidence on Cocaine Use and Panic Attacks

Experienced drug takers and clinicians report that cocaine causes panic attacks. This claim is supported by laboratory evidence on the pharmacologic activity of the drug. In this article, we have used an epidemiologic strategy to examine the suspected cocaine-panic association, with interview data from 5896 adult household residents sampled in the early 1980s and followed prospectively for a collaborative multisite study of mental disorders in five US metropolitan areas as follows: New Haven, Conn; Baltimore, Md; St Louis, Mo; Durham, NC; and Los Angeles, Calif. The risk of panic attacks was observed to be greater for identified cocaine users in this sample compared with subjects who did not use cocaine during the follow-up interval. The

(Continued on p 3090.)

Edited by Jody W. Zylke, MD, Contributing Editor.

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BRIEF SUMMARY

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Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

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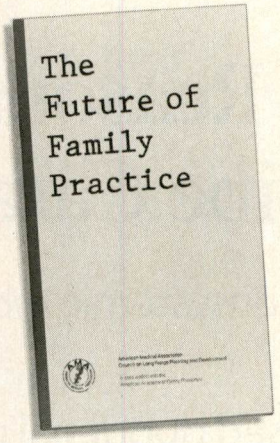

The AMA's Council on Long Range Planning and Development introduces the latest report in a series of environmental analyses of individual specialties. Each report analyzes the factors influencing changes in the profession. And each features data describing manpower and economics, key issues and pertinent trends affecting the specialty.

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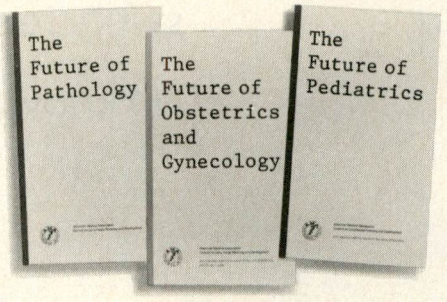

These reports were all originally printed in 1987/88 issues of JAMA.

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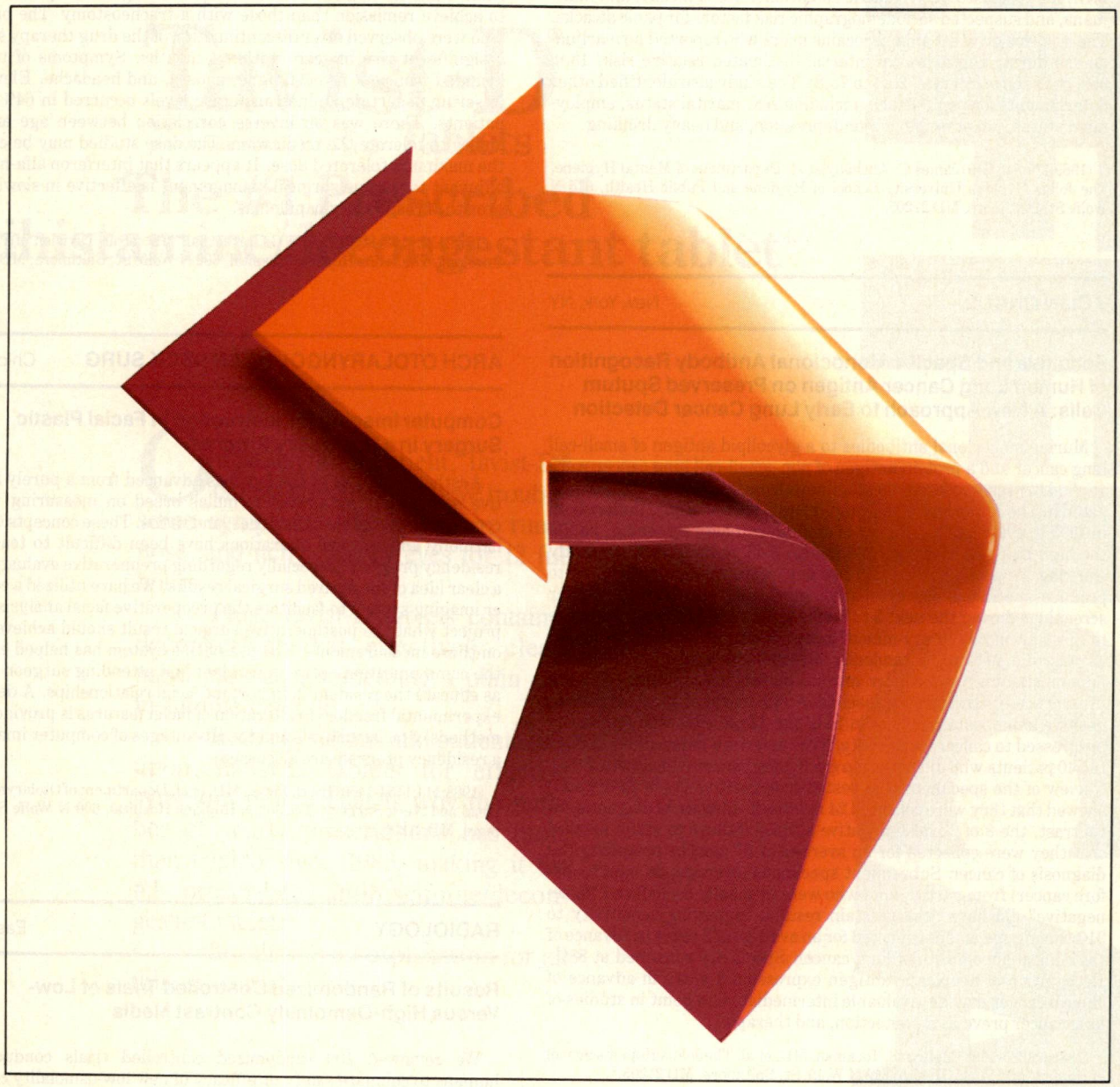

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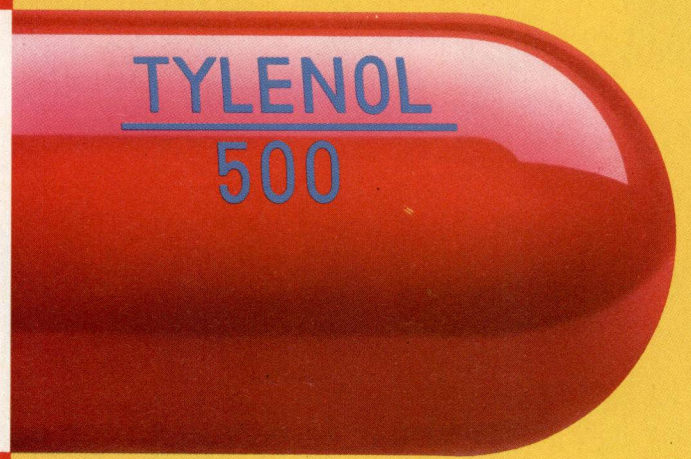

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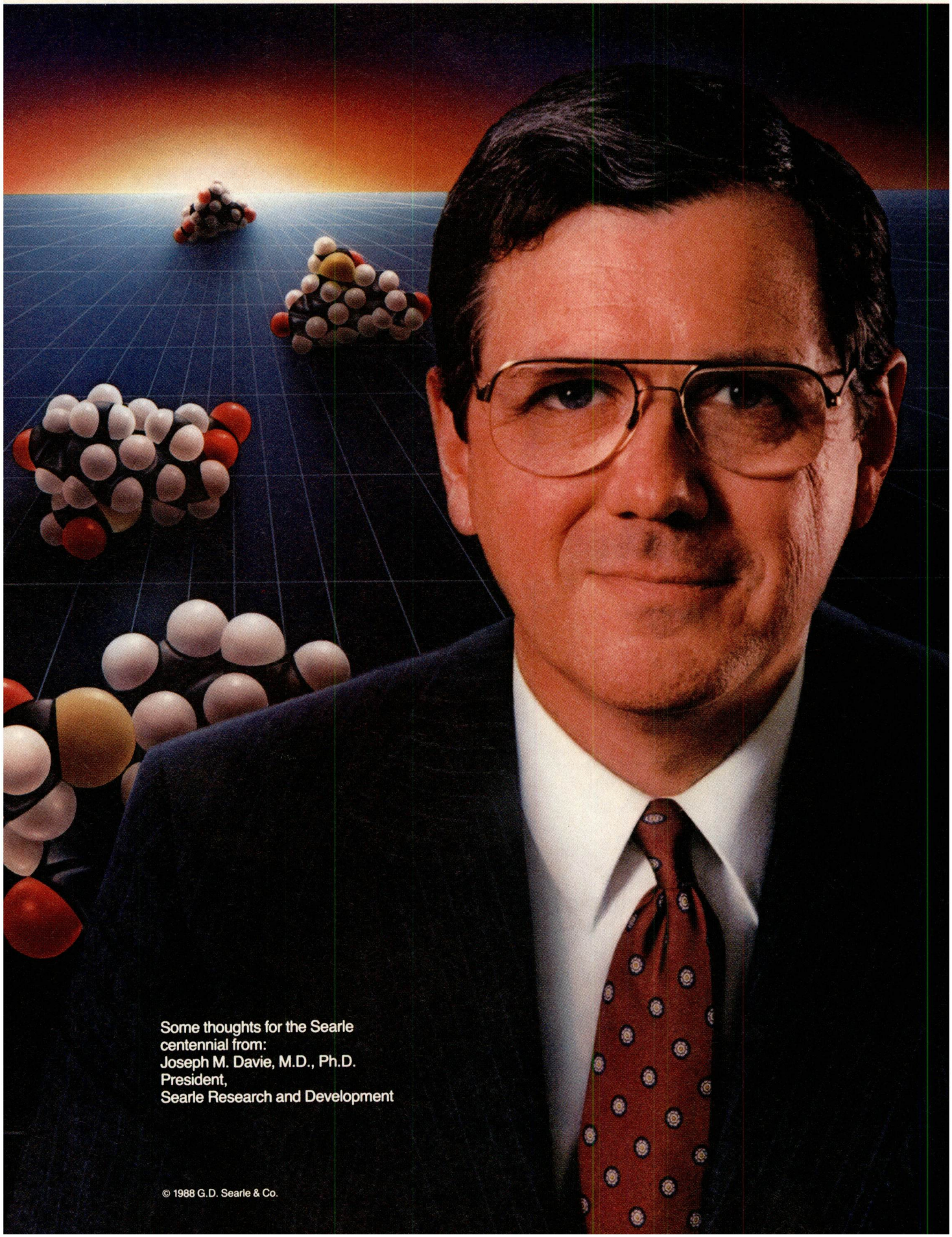

Some thoughts for the Searle
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Joseph M. Davie, M.D., Ph.D.
President,
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SEARLE

(Continued from p 3090.)

RADIOLOGY

Easton, Pa

Congenital Arteriovenous Malformations: Tailored Embolotherapy

Congenital arteriovenous malformations involving the pelvis or an extremity were occluded in 16 symptomatic patients who subsequently underwent tailored embolotherapy. An additional 11 patients did not undergo embolization due to unfavorable vascular anatomy or lack of significant symptoms. Permanent occlusive agents including isobutyl cyanoacrylate, particles of polyvinyl alcohol foam, and coils were used to embolize the multiple feeding vessels and, when possible, the nidus of the arteriovenous malformation. All patients experienced dramatic reduction in pain and resolution of ulceration and bleeding, with a mean follow-up period of 41 months. Symptoms recurred in 4 patients but again resolved with repeated embolization. We conclude that selective and repetitive embolization is highly effective in palliation of symptomatic congenital arteriovenous malformations.

(1988;169:511-516) David M. Widlus, MD, et al, Department of Radiology, The Johns Hopkins Medical Institutions, 600 N Wolfe St, Baltimore, MD 21205-2191.

STROKE

Dallas, Tex

Decline in US Stroke Mortality: Demographic Trends and Antihypertensive Treatment

Stroke mortality has been falling rapidly in this country since 1973. To investigate age-race-sex effects on stroke mortality, we studied US vital statistics during 1950 to 1972 and 1973 to 1981 in 55- to 64-, 65- to 74-, and 75- to 84-year-old race-sex groups. The accelerated rate of decline in stroke mortality since 1973 has had a substantial public health impact, with more than 200 000 fewer stroke deaths than would otherwise have occurred. For all groups, stroke mortality declined at a greater rate ($P<.05$) in 1973 to 1981 than during 1950 to 1972. The rates of decline during 1973 to 1981 were greater with increasing age ($P<.05$) and were more substantial for younger blacks. There were no consistent differences in the rate of decline by sex. The greater rate of decline in absolute stroke mortality in the older age groups and blacks was explained by higher baseline mortality in these groups. Overall, stroke mortality decreased by approximately 2% per year in 1950 to 1972 and by approximately 7% per year after 1973. Rank order of average annual percent decline after 1973 by age-race-sex groups did not correspond to rates of change in management or control of hypertension obtained from three national surveys. The accelerated rate of decline after 1973 may have resulted from improved antihypertensive therapy, but our findings fail to confirm this hypothesis and suggest that management of hypertension may not be the principal reason for the decline in stroke mortality.

(1989;20:14-21) Michael J. Klag, MD, et al, Department of Medicine, The Johns Hopkins Medical Institutions, Room 8034, 1830 E Monument St, Baltimore, MD 21205.

AM J CLIN PATHOL

Philadelphia, Pa

A Survey of Epstein-Barr Virus DNA in Lymphoid Tissue: Frequent Detection in Hodgkin's Disease

A total of 151 unselected malignant and nonmalignant lymphoid-tissue samples were surveyed by Southern blotting for the presence of Epstein-Barr virus (EBV) DNA. Eight of 28 samples with Hodgkin's disease (29%) had detectable EBV DNA. Both nodular sclerosis and mixed cellularity histological results were positive. The tumor type with the next highest frequency (8%) was diffuse large-cell lymphoma. The presence of EBV DNA in some Hodgkin's disease biopsy samples suggests that EBV may be a factor in the pathogenesis of this disease. Alternatively, its presence may be secondary to the immune deficiency characteristic of Hodgkin's disease. The clonal B-lymphocyte expansions reported in some cases of Hodgkin's disease may result from EBV infection.

(1989;91:1-5) Stephen P. Staal, MD, et al, Room 1-109, The Johns Hopkins Oncology Center, 600 N Wolfe St, Baltimore, MD 21205.

AM J PUBLIC HEALTH

Washington, DC

Childhood Injury Deaths: National Analysis and Geographic Variations

Twenty-three causes of injury mortality in children aged 0 to 14 years in the United States were analyzed by age, race, sex, and state of residence for the years 1980 to 1985. Motor vehicles caused 37% of all injury-related deaths and were the leading cause of injury mortality in every group except children younger than 1 year of age, for whom homicide was the leading cause. Male death rates were at least four times female rates for suicide, unintentional firearm injury, and injuries related to farm machinery or motorcycles. The drowning rate among whites was almost twice that of blacks for ages 1 to 4, but in the 10- to 14-year-old age group the drowning rate for blacks was more than three times that of whites. In general, the highest injury death rates were in the mountain states and the south. Between 1980 and 1985, the suicide rate in the 10- to 14-year-old age group more than doubled.

(1989;79:310-315) Anna E. Waller et al, Injury Prevention Center, School of Hygiene and Public Health, The Johns Hopkins University, 624 N Broadway, Baltimore, MD 21205.

ARCH OPHTHALMOL

Chicago, Ill

Ultraviolet Light Exposure and Risk of Posterior Subcapsular Cataracts

Posterior subcapsular (PSC) cataracts are a visually disabling form of cataract and account for 40% of surgical cases. Although PSC opacities may occur following intraocular inflammation, trauma, or use of steroids, the cause is often unknown. A case-control study was undertaken to investigate the role of exposure to ultraviolet light in the B range and other potential risk factors for the development of PSC cataracts. Surgical PSC cataract cases from a large rural ophthalmic practice on the lower eastern shore of Maryland were matched with phakic controls without PSC cataract changes from the same geographic area by age, sex, and referral pattern. All patients with PSC opacities who underwent cataract surgery in a 12-month period were chosen. One hundred sixty-eight cases and 168 controls were interviewed regarding sunlight exposure, drug use, occupational history, history of diabetes, hypertension, and other diseases. Matched-pairs analyses indicated that a history of relatively high exposure to ultraviolet light in the B range was associated with increased risk of PSC cataracts. The association of PSC cataracts with steroid use and diabetes was reconfirmed. Subjects with blue eyes and less than high school education were also at increased risk for PSC cataracts. Smoking and hypertension were not found to be PSC cataract risk factors. These data suggest that exposure to ultraviolet light in the B range may be an important risk factor for PSC cataracts.

(1989;107:369-372) Tom W. Bochow, MD, et al. Reprint requests to Sheila K. West, PhD, 116 Wilmer Bldg, The Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21205.

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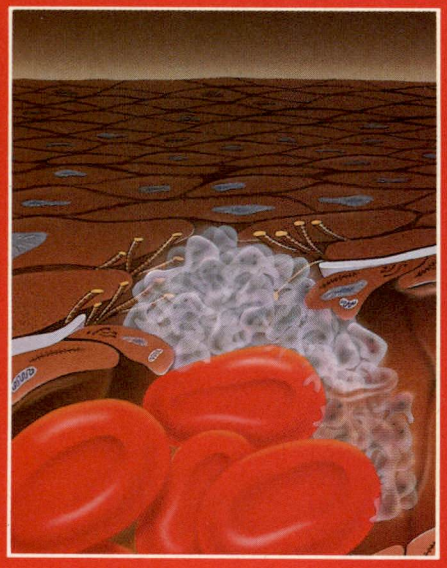

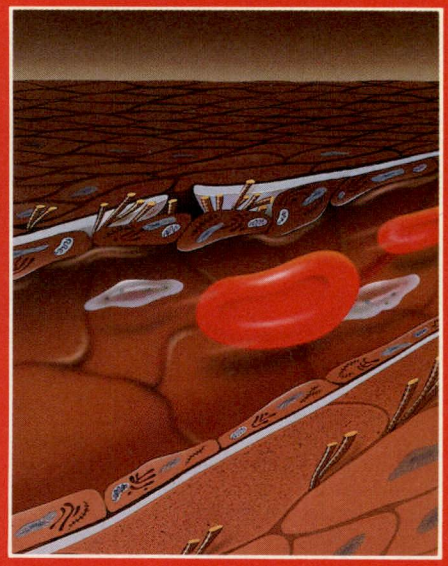

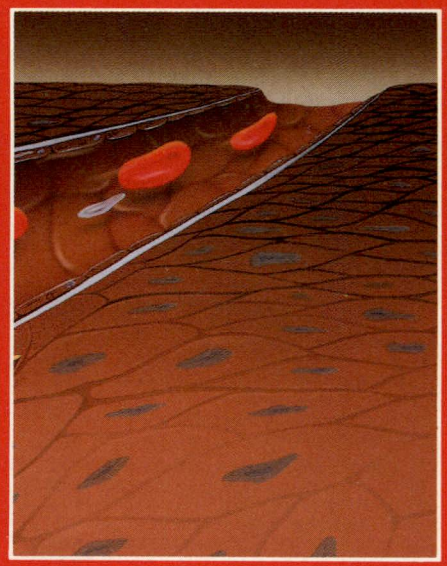

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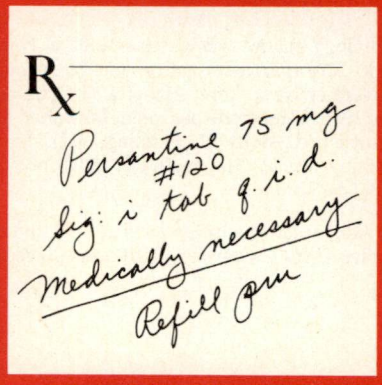

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Brief Summary of Prescribing Information

CONTRAINDICATIONS None known.

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Teratogenic Effects *PREGNANCY CATEGORY B* Reproduction studies have been performed in mice and rats at doses up to 125 mg/kg (15.6 times the maximum recommended daily human dose) and rabbits at doses up to 20 mg/kg and have revealed no evidence of harm to the fetus due to Persantine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers As dipyridamole is excreted in human milk, caution should be exercised when Persantine is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children below the age of 12 years has not been established.

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Abdominal distress	6.1%	3.5%
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Rash	2.3%	1.1%

Other reactions from uncontrolled studies include diarrhea, vomiting, flushing and pruritus. In addition, angina pectoris has been reported rarely. On those uncommon occasions when adverse reactions have been persistent or intolerable, they have ceased on withdrawal of the medication.

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Furniture for sale, ideal for incoming resident. Apartment close to all the hospitals, available if desired. Write Imran Samad, 1616 Liholiho St, Honolulu, HI 96822; or call (808) 599-5431 and leave a message.

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Second-year medical resident fascinated by medical history seeks antique medical instruments for his small yet carefully assembled collection. If you have medical antiques gathering dust in your attic, or even if you have advice for a young medical collector, please drop me a line. Thanks! Doug Arbittier, 4517 Pine St, Apt G-505, Philadelphia, PA 19143; or call (215) 748-5729.

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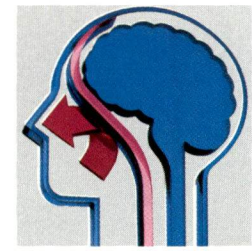

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CAUTION: Federal law prohibits dispensing without prescription.

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Seldane (terfenadine) is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, gelatin, lactose, magnesium stearate, and sodium bicarbonate.

INDICATIONS AND USAGE

Seldane is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

CONTRAINDICATIONS

Seldane is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

PRECAUTIONS

Information for patients

Patients taking Seldane should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting Seldane therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should be instructed to take Seldane only as needed and not to exceed the prescribed dose. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, mutagenesis, impairment of fertility

Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C

There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Seldane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Seldane is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to Seldane only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use

Safety and effectiveness of Seldane in children below the age of 12 years have not been established.

General

Consideration should be given to potential anticholinergic (drying) effects in patients with lower airway disease, including asthma.

ADVERSE REACTIONS

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received Seldane, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported adverse effects in patients receiving Seldane was similar to that reported in patients receiving placebo. (See Table below.)

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

Adverse Event	Percent of Patients Reporting				
	Controlled Studies*			All Clinical Studies**	
	Seldane N=781	Placebo N=665	Control N=626***	Seldane N=2462	Placebo N=1478
Central Nervous System					
Drowsiness	9.0	8.1	18.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.6	0.5
Appetite Increase	0.6	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress (Abdominal distress, Nausea, Vomiting, Change in Bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/ Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

*Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 DAYS.

**Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.

***CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (146 patients)

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of Seldane that warrant listing as possibly associated with drug administration. These include: alopecia, (hair loss or thinning), anaphylaxis, angioedema, arrhythmia (including ventricular tachyarrhythmia), bronchospasm, confusion, depression, galactorrhea, hypotension, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, palpitation, paresthesia, photosensitivity, prolonged QT interval, seizures, sweating, syncope, tachycardia, tremor, urinary frequency, and visual disturbances. In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving Seldane. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis; in most cases available information is incomplete. In neither the clinical trials nor marketing experience is a causal relationship of liver abnormalities to Seldane use clear.

OVERDOSAGE

Information concerning possible overdosage and its treatment appears in Full Prescribing Information.

DOSAGE AND ADMINISTRATION

The usual dosage for adults and children 12 years and older is 60 mg (1 tablet) twice daily.

Product Information as of June, 1988 Y352D

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
Cincinnati, Ohio 45215, U.S.A.

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Allelic Loss in Colorectal Carcinoma

Scott E. Kern, MD; Eric R. Fearon, BA; Kasper W. F. Tersmette, MD; John P. Enterline, MS; Mark Leppert, PhD; Yusuke Nakamura, MD, PhD; Ray White, PhD; Bert Vogelstein, MD; Stanley R. Hamilton, MD

Clinical and pathological associations with molecular genetic alterations were studied in colorectal carcinomas from 83 patients. Fractional allelic loss, a measure of allelic deletions throughout the genome, and allelic deletions of specific chromosomal arms (the short arm of 17 and long arm of 18) each provided independent prognostic information by multivariate analysis when considered individually with Dukes' classification. Distant metastasis was significantly associated with high fractional allelic loss and with deletions of 17p and 18q. Mutations of *ras* proto-oncogenes and deletions of 5q had no prognostic importance. Statistically significant associations were also found between allelic losses and a family history of cancer, left-sided tumor location, and absence of extracellular tumor mucin. Allelic deletion analysis thus identified subsets of colorectal carcinoma with increased predilection for distant metastasis and cancer-related death. Further studies may define a subset of genetic alterations that can be used clinically to help assess prognosis.

(*JAMA*. 1989;261:3099-3103)

COLORECTAL carcinoma is the second most common cause of cancer death in the United States, estimated to account for about 62 000 deaths in 1988.[1] Dukes' classification, or one of its many modifications, is the mainstay for estimating prognosis. Most patients, however, are placed in categories having little prognostic power, and the determinants of tumor biology that account for disparate outcome among patients of identical classification are unknown.[2] More sophisticated measurements such as DNA ploidy and cell-cycle analysis by flow cytometry are available, but the magnitude of their independent contribution to prognosis, as assessed by multivariate analysis, is controversial.[3-7] Because phenotype of tumors likely reflects their underlying genetic alterations, direct molecular study of these alterations may prove useful in understanding pathological characteristics and biologic potential of tumors.

Two types of genetic alterations have been reported in colorectal tumors. The first type involves point mutations in *ras* proto-oncogenes.[8,9] Such mutations have been found to convert the proto-oncogenes to oncogenic forms with the capability of participating in neoplastic transformation in vitro and in vivo. *Ras* gene mutations have been reported in nearly 50% of colorectal carcinomas[10,11] and in a similar percentage of large colorectal adenomas.[12]

The second type of alteration involves deletions of specific chromosomal regions. Deletions can be detected by restriction fragment length polymorphism analysis of tumor DNA. The deleted sequences have been hypothesized to include tumor-suppressor genes whose products would normally inhibit neoplastic growth.[13,14] The inactivation of such genes (through deletion or other mutational events) therefore may lead to neoplastic progression. We and others have reported allelic deletions on several chromosomal arms in colorectal tumors.[12,15-18] The most frequent sites of allelic deletion found thus far are on the short arm (p) of chromosome 17 and the long arm (q) of chromosome 18, wherein deletions occur in nearly 75% of carcinomas. A region of the long arm of chromosome 5 containing the gene for familial adenomatous polyposis[19-21] is deleted in nearly 35% of sporadic colorectal carcinomas.[12,16] We have also described a measure of the extent of allelic deletions present throughout the genome, termed *fractional allelic loss* (FAL), based on the fraction of chromosomal arms on which deletions are found.[22] Such analysis has demonstrated that a median of 20% of chromosomal arms have undergone allelic deletions in colorectal carcinomas.[22]

We investigated the clinical and pathological associations of various genetic alterations of colorectal carcinoma. We used multivariate analysis to investigate whether independent contributions to prognosis were attributable to *ras* gene mutations or to specific and global molecular measures of allelic deletions.

METHODS

Patients and Tumor Specimens

Patients who underwent resection of colorectal cancer at The Johns Hopkins Hospital (Baltimore, Md), and whose tumors were collected for the Bowel Tumor Working Group frozen-tissue bank, were the basis of the study. Colorectal carcinoma and grossly normal mucosa were obtained from each surgical resection specimen. Eighty-seven tumor samples, constituting 82% of the samples in the bank, were suitable for study (see below). Although the cases spanned the years from 1982 to early 1987, most (n = 63) in the study were from a 19-month period in 1985 and 1986 during which 62% of all cases of resected primary carcinomas (n = 124) were sampled for the tissue bank. The distribution of Dukes' classification among carcinomas in the study (see below) was similar to that among those not sampled for the bank within this 19-month period and similar to our experience in a previous report from this hospital.[23]

Information from the Johns Hopkins Cancer Registry, chart review, and physician contact was obtained to determine tumor site, family history, and follow-up in the 83 patients in whom genetic analysis of 87 carcinomas had been performed. There were 44 men (53%). Mean age was 66 years (SD, 11.4 years; range, 35 to 84 years). Thirteen carcinomas were Dukes' A (15%), 33 B (38%), and 41 C (47%). The 4 patients with synchronous carcinomas were excluded from analysis of prognostic factors due to uncertainty in determining the "dominant" tumor (2 patients had a Dukes' B and a C carcinoma, 1 had 2 B carcinomas, and 1 had an A and a B carcinoma). Four patients from outside institutions, whose tumors were included in other reports,[12,22] were not included in this study, as the comparability of the effects of entry or other biases on the survival data could not be assumed.

From the Department of Pathology (Drs Kern, Tersmette, and Hamilton) and the Oncology Center (Drs Kern, Vogelstein, and Hamilton and Messrs Fearon and Enterline), The Johns Hopkins Medical Institutions, Baltimore, Md; and the Department of Human Genetics, The University of Utah School of Medicine, Salt Lake City (Drs Leppert, Nakamura, and White).

Reprint requests to the Department of Pathology, The Johns Hopkins Hospital, 600 N Wolfe St, Baltimore, MD 21205 (Dr Kern).

Genetic Analysis

Studies of genetic alterations in these tumors have been published.[12,17,22] DNA was derived from cryostat-dissected tumors (n = 87) in which regions for *ras* mutation analysis containing at least 50% neoplastic cells were obtained, as previously reported.[11,12] Mutations of *ras* genes were detected by hybridization to oligonucleotide probes following polymerase chain reaction.[12] A subset of tumors (n = 56) with a proportion of neoplastic cells in excess of 70% was studied for allelic deletions, as use of tumors with a lower percentage of neoplastic cells obscured the detection of allelic deletions.

DNA probes detecting restriction fragment length polymorphisms were used to determine whether one of the two parental alleles that were present in the DNA from nonneoplastic mucosa was lost in DNA from the tumor. These probes, and the corresponding loci they detected, could be "informative" for a given patient only if the patient were heterozygous; that is, the two parental alleles in the DNA of the nonneoplastic cells of the patient must migrate to different locations in an electrophoretic gel. All nonacrocentric autosomal arms were studied. Comparing the migration pattern of the control's DNA with that of the tumor determined whether the tumor had lost one of the normal alleles. For each of these 39 chromosomal arms, enough probes were used to ensure that informative loci were present in the nonneoplastic mucosa of at least 20 patients.

The FAL was defined as the number of chromosomal arms in which allelic loss was observed, divided by the number of chromosome arms for which allelic markers were informative in the patient's nonneoplastic cells.[22] The FAL thus served as a global measure of allelic loss in tumors.

Pathological Study

Routine histopathologic sections and surgical pathology reports were reviewed, without knowledge of patient outcome or genetic analysis. Tumor size, level of direct invasion, and regional lymph node status were determined from records, while all other data were obtained from regrading of the primary tumors by one observer (S.E.K.). The classic Dukes' three-class system was used.[24] Histological grading was according to Wiggers et al.[25] Classification of tumors having extracellular mucin was according to Halvorsen and Seim.[26] Assessment for presence of peritumoral lymphocytic infiltrates and irregularity of the invasive border was used to construct the classification of Jass et al.[2] Right-sided tumors were defined as those proximal to the descending colon (n = 42 [48%]).

Table 1.—Univariate Association of Variables With Survival*

Variable	Categories	No. of Observations	No. (%) of Deaths From Metastasis	P†
Dukes' classification	A	12	0 (0)	.011
	B	28	13 (46)	
	C	39	19 (49)	
FAL‡	<0.2	25	7 (28)	.005
	>0.2	23	14 (61)	
17p	No deletion	12	2 (17)	.059
	Deletion	39	19 (49)	
18q	No deletion	13	2 (15)	.109
	Deletion	35	18 (51)	
Histological grade	Well differentiated	13	2 (15)	.169
	Moderately differentiated	55	25 (45)	
	Poorly differentiated	11	5 (45)	
Family history of cancer	Negative	47	18 (38)	Not significant (NS)
	Positive	32	14 (44)	
5q	No deletion	30	13 (43)	NS
	Deletion	20	8 (40)	
ras genes	No mutation	42	16 (38)	NS
	Mutation	37	16 (43)	
Evaluable for allelic loss§	Not evaluable	31	11 (35)	NS
	Evaluable	48	21 (44)	
Mucinous component	Absent	60	26 (43)	NS
	Present	19	6 (32)	
Size of tumor	<6 cm	48	18 (38)	NS
	≥6 cm	31	14 (45)	
Site of tumor	Right-sided	38	16 (42)	NS
	Left-sided	41	16 (39)	
Sex	M	41	15 (37)	NS
	F	38	17 (45)	
Age	<68 y	42	17 (40)	NS
	≥68 y	37	15 (41)	

*Excludes four patients with synchronous tumors.
†Wilcoxon-Gehan test. Not significant, $P > .30$.
‡FAL indicates fractional allelic loss, a measure of widespread allelic deletions (defined as the number of chromosomal arms in which allelic loss was observed, divided by the number of chromosome arms for which allelic markers were informative).
§Patients with and without FAL determination. Tumors with greater than 30% content of nonneoplastic cells could not be evaluated by analysis of restriction fragment length polymorphisms (see "Methods" section).

Statistical Analysis

Survival was analyzed by the statistical program STATA (Computing Resource Center, Los Angeles, Calif) by means of the two-tailed Wilcoxon-Gehan Test on individual variables (analysis by logrank test was similar except as noted), and by both Cox proportional-hazards and logistic regression models when multiple variables were tested in the presence of each other. Deaths in seven patients due to causes other than metastatic disease were treated as censored events. For survival analysis,[27,28] survival time was determined from date of resection. For logistic analysis, outcome was defined as the presence or absence of distant metastasis during follow-up. Two-sample comparisons on continuous variables was by Wilcoxon Rank-Sum Test. Where required, ordered categorical data were converted to "dummy" variables[25] and continuous variables converted to categorical ones by break points at their median values. All 2×2 χ^2 tables were analyzed by Fisher's Exact Test.

The Cox model is a life-table method of survival analysis and has the form $h(t) = h_o(t)e^{\beta 1 + \beta 2 + \cdots}$. The risk at any time, $h(t)$, is a product of the baseline hazard, $h_o(t)$, and the independent hazard ratios, e^{β}, for each variable. Logistic analysis, by contrast, treats the dependent variables (outcomes) as binary events without consideration of time periods and treats independent variables as predictors of such events.

RESULTS

Genetic Alterations

The FAL of 52 assessable tumors ranged from 0.00 to 0.67, with a median of 0.20. Allelic deletions of chromosomal arm 18q were present in 40 (74%) of 54 carcinomas, deletions of 17p in 43 (77%) of 56, deletions of 5q in 20 (36%) of 56, and *ras* mutations in 40 (46%) of 87 tumors. Every probe was not informative

Table 2.—Multivariate Contribution to Cox Model Containing Dukes' Classification

Variable	*P* Value* of Loglikelihood Ratio χ^2	β Coefficient	Hazard Ratio	*P* Value in Model†
Fractional allelic loss	.016	1.087	2.97	.025
17p deletion	.014	1.524	4.59	.048‡
18q deletion	.025	1.429	4.17	.065
Histological grade	.245	...	...	...
Family history of cancer	.198	...	...	...
5q deletion	Not significant (NS)	...	...	...
ras gene mutation	NS	...	...	...
Evaluable for allelic loss	NS	...	...	...
Mucinous component	NS	...	...	...
Size of tumor	NS	...	...	...
Site of tumor	NS	...	...	...
Sex	NS	...	...	...
Age	NS	...	...	...

*A test of the improvement in the model due to addition of the new variable. Performance of a variable in the model is detailed when its addition resulted in a significant ($P<.05$) improvement in the model. Not significant, $P>.30$.

†A test of the reliability of the β coefficient and hazard ratio of the new variable in the model, in competition with Dukes' classification.

‡The individual deletion data of 17p and 18q result in a higher *P* value despite a higher hazard ratio as compared with fractional allelic loss. This statistical phenomenon is due to the small numbers of tumors lacking deletions of 17p and 18q.

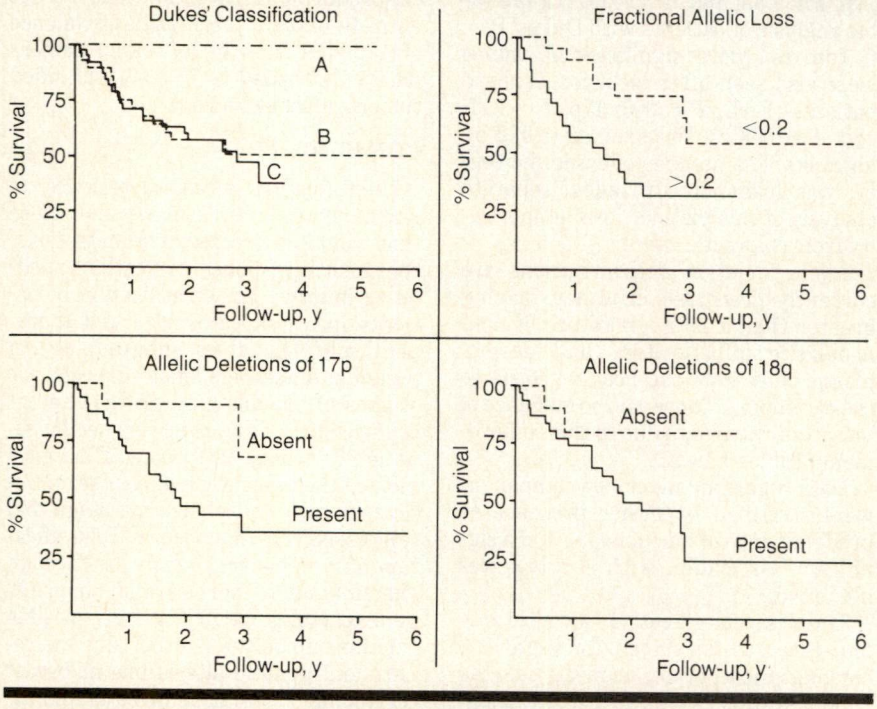

Fig 1.—Kaplan-Meier survival curves in patients with a single carcinoma, from time of operation. Deaths due to causes other than metastatic disease were censored at time of death. Curves showing the influence of genetic alterations include only patients with Dukes' B or C carcinoma.

for every tumor (see "Methods"), so that the number of tumors assessable for allelic deletions of chromosomes varied. Fractional allelic loss; specific allelic deletions of 17p, 18q, and 5q; and *ras* gene mutations had no association with Dukes' classification ($P>.25$). Fractional allelic loss was positively associated with deletions of either 17p ($P=.0002$) or 18q ($P=.028$), but not with deletions of 5q or *ras* gene mutations ($P>.10$). Deletions of 17p were also positively associated with those of 18q ($P=.004$), as noted previously.[12]

Prognosis

Survival analyses are presented in Tables 1 and 2. Mean follow-up in survivors was 40.5±12.0 (SD) months (range, 21 to 79 months). There was no mortality attributable to colorectal cancer among patients with Dukes' A carcinomas. Survival curves of patients with Dukes' B or C carcinomas were similar (Fig 1). This, as well as the predominance of higher Dukes' classes, likely reflected referral bias. The number of lymph nodes examined in our cases (mean of 11.7 lymph nodes per tumor) was also considerably higher than in some reports,[29] and potentially could classify more specimens as Dukes' C than otherwise would occur.

The inclusion of either the FAL, 17p, or 18q allelic deletion data improved the Cox survival model over that produced by Dukes' classification alone (Table 2). Among patients with a Dukes' B or C carcinoma, comparison of patients with high and low FAL ($P=.009$) or with and without deletions of 17p ($P=.024$) produced significantly different survival curves (Fig 1). (Curves of patients with and without deletion of 18q produced $P=.11$ by Wilcoxon test, which emphasizes short-term follow-up, and $P=.045$ by logrank test, which treats time periods more evenly [Fig 1].) Other variables, including deletions of 5q and *ras* gene mutations, had no associations with survival. The number of informative tumors was insufficient to determine whether the prognostic information provided by the specific deletions of 18q and 17p was independent of that of the FAL measure. In all combinations, Dukes' classification retained independent significance ($P<.001$).

Twenty-four (30%) of the 79 patients had clinically documented metastatic disease at the time of resection, and 13 had metastases detected during follow-up. As expected, the survival of the 24 initially positive patients was shorter than that of all other patients ($P<.0001$), even when the comparison is restricted to the 13 who subsequently developed metastatic disease ($P=.008$). The tumors with a greater number of allelic deletions were highly represented among these 24 patients: 71% had high FAL, 94% had 18q deletions, and 88% had 17p deletions. Analysis of the association of survival with specific deletions within the 24 patients was thus precluded, and high FAL produced a trend toward lower survival that was not statistically significant ($P=.14$). To determine whether allelic deletions of the primary tumors were merely mirroring advanced clinical stage, the 37 cases in which metastases developed were stratified by clinical stage at presentation; no significant differences in the presence of genetic alterations were found between those positive and negative for metastases on initial examination ($P>.3$). (This was as expected; all of these patients had metastatic involvement at time of operation, and the stratification was provided solely by the insensitivity of clinical detection of small metastases.) However, of those with Dukes' B and C carcinomas who were without clinical metastases at the time of resection, 6 of 18 patients

Table 3.—Association of Allelic Deletions With Distant Metastasis (Patients With a Single Dukes' B or C Carcinoma)

Variable	Category	Distant Metastasis During Follow-up: Absent	Distant Metastasis During Follow-up: Present	P
Fractional allelic loss	<0.2	13	8	.031*
	>0.2	6	15	
18q	No deletion	9	2	.010
	Deletion	11	20	
17p	No deletion	10	2	.006
	Deletion	12	21	
Mean follow-up in survivors, mo	...	38.7	38.1	Not significant†

*Fisher Exact Test.
†Wilcoxon Rank-Sum Test. Not significant, $P>.30$.

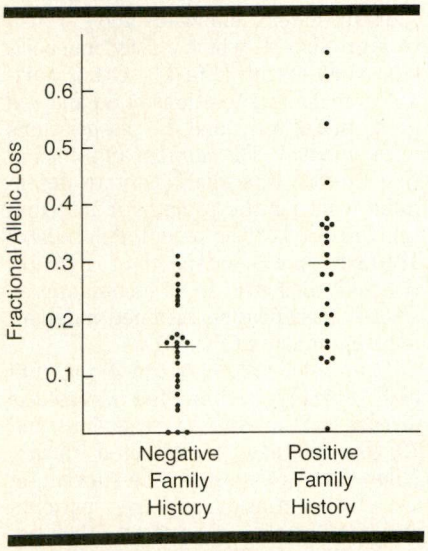

Fig 2.—Fractional allelic loss in colorectal carcinomas of patients with and without a family history of cancer in a first-degree relative. Points represent data from individual tumors. Horizontal bars denote means. $P=.0002$.

with 17p deletion were found to have metastases during follow-up, but all 10 patients without 17p deletion remained clinically metastasis free ($P=.049$).

To directly analyze tumor characteristics for their association with metastatic potential, logistic analysis was done using the presence of distant metastasis during follow-up as the outcome. This produced patterns similar to Cox analysis but emphasized the effect of specific deletions. Fractional allelic loss and deletions of 17p and 18q significantly improved the model containing Dukes' classification ($P=.031$, $P=.003$, and $P=.006$, respectively), with the coefficients being statistically significant (FAL, $\beta=1.4$, $P=.042$; 17p, $\beta=2.23$, $P=.013$; 18q, $\beta=2.13$, $P=.019$).

Fractional allelic loss and 18q and 17p deletions were each associated with the occurrence of distant metastasis during follow-up (Table 3). Length of follow-up did not bias against detection of metastatic disease (Table 3).

Two patients died of local recurrence but had no metastatic disease. When failure in the Cox model including Dukes' classification was redefined as "death with disease" to include these patients, P values for β coefficients became more significant (FAL, $P=.014$; 17p, $P=.035$; 18q, $P=.049$). In life-table analysis of patients with Dukes' B or C tumors, more significant P values were also seen after inclusion of these patients (FAL, $P=.006$; 17p, $P=.017$; 18q, $P=.084$ by Wilcoxon, $P=.032$ by logrank). The number of cases, however, was inadequate to allow separate analysis of this distinct form of mortality from colorectal cancer.

Allelic deletion determinations are currently precluded in tumors having greater than a 30% admixture of nonneoplastic inflammatory and desmoplastic cells from the host response to the carcinoma. There was no evidence of bias in survival data due to this requirement (Tables 1 and 2).

Data regarding mucinous component were stratified by either presence or predominance of mucin pools, and a significant association with survival was not found.

The Jass classification, an alternate four-class scoring system for rectal carcinoma, incorporates aspects of the Dukes' system as well as histopathologic gauges of host-tumor interaction.[2] Classes I and IV were associated with better and worse survival ($P=.033$ and $P=.016$), respectively. In a Cox model with FAL, these classes lost significance to the FAL measurement (any class, $P>.10$; FAL, $P=.03$).

Family History

A history of cancer in a first-degree relative was found in 35 (42%) of 83 patients, including 25 (50%) of 50 studied for FAL. The positive family history of carcinoma was established by an affected parent in 71%. For a majority of these reported malignancies in first-degree relatives, no type or site was recorded. The mean FAL of tumors from patients with a family history of cancer was twice that of patients without such a history (0.296 vs 0.150, $P=.0002$) (Fig 2). A family history was also associated with deletions of 17p ($P=.010$).

Site and Histology

Allelic deletions of 17p were more common in left-sided tumors than in right-sided ones (93% of left-sided vs 60% of right-sided tumors, $P=.004$). Twenty-one (24%) of 87 tumors were mucin producing, and in 17 of these, the mucinous areas represented the main pattern of the tumor. Allelic deletions of 17p and of 18q were less common in mucin-producing carcinomas (17p, 44% of mucin-producing vs 88% of non–mucin-producing tumors, $P=.001$; 18q, 47% vs 85%, $P=.007$). Thirty-six percent of the right-sided tumors were mucin containing, compared with 13% of those on the left. Exclusion of the mucin-producing tumors, however, did not entirely explain the higher prevalence of 17p deletions in left-sided tumors (96% of left-sided vs 78% of right-sided tumors, after exclusion).

COMMENT

Identification of characteristics of malignant tumors, in particular those that would be predictive of metastasis, therapeutic response, or death, is needed to improve the stratification of patients into risk categories and therapeutically valuable subgrouping of patients. A number of molecular genetic studies in humans have drawn interest to the clinical significance of specific genetic alterations in tumors. Examples include the association of N-*myc* amplification with neuroblastoma stage and prognosis,[30] the diagnosis and classification of lymphoid malignancies through examination of normal and abnormal gene rearrangements,[31] and the possible relationship between tumor aggressiveness and genetic alterations in breast carcinoma.[32-34] We have investigated colorectal neoplasms with respect to their genetic abnormalities, specifically allelic chromosomal deletions.

We found that some specific sites of allelic deletion, ie, those on chromosomal arms 17p and 18q, were associated with lower survival rates. These sites have been suggested as locations of tumor-suppressor genes, because of the high prevalence of their deletion in colorectal carcinoma[12] and, in the case of 17p, also in breast carcinoma,[35] gliomas,[36] lung carcinomas,[37] and osteosarcomas.[38] As more sensitive means of study are applied to these loci, the proportion of tumors found to contain genetic alterations will probably increase.

Thus, the argument is raised about whether the alterations of 17p and 18q as currently assayed are causally associated with metastatic potential or only represent sensitive markers of a multifactorial set of chromosomal changes accounting for tumor aggressiveness. It is in light of this question that a measure of allelic deletions throughout the genome was studied. Fractional allelic loss was strongly associated with both the occurrence of and death from metastatic disease. Thus, the relative importance of specific vs general measures of allelic loss is as yet unknown.

Clinical documentation of metastatic disease has remained the best single predictor of poor prognosis in colorectal cancer.[7,25] A major goal of studies of the pathology and cellular biology of primary tumors is to explain the occurrence of the metastatic phenotype, ie, the characteristics that lead to the development of metastasis. Identification of such characteristics should eventually prove to aid prognostication among these patients without initial evidence of disseminated disease.

The recognition of a strong association of high FAL with a family history of cancer is intriguing and raises at least two possibilities. First, the sporadic, as opposed to familial, carcinomas may differ in pathogenesis and thus may represent different tumor subtypes. Alternately, familial factors may act to increase the tendency for an established tumor to tolerate or promote the accumulation of clonal genetic abnormalities. These possibilities are not mutually exclusive and do not necessarily assume an increased risk of development of neoplasia related to this familial influence.

The lower rate of allelic deletions of 17p and 18q in mucin-producing carcinomas and in right-sided tumors is currently unexplained. Further exploration of these associations is needed because of the epidemiologic evidence suggesting different pathogenetic factors in right-sided as opposed to left-sided carcinomas and the recent historical trend toward a higher proportion of right-sided tumors.[39,40] What is clear, however, is that routine pathological and clinical distinctions delineate important confounders in the interpretation of molecular analyses.

Molecular techniques for genetic analyses of tumors are currently limited by the requirement for tumor areas having a high proportion of neoplastic cells. These problems are not unique, and they apply as well to hormone-receptor assay and flow cytometric DNA analysis. However, any routine application of the technique would likely be conditional on further increases in sensitivity to allow assay of those tumors that currently cannot be studied.

In conclusion, a cautious view toward the prognostic influences of individual molecular markers is advised, in that specific changes may only mirror a more general, but prognostically consequential, tendency of malignant tumors to accumulate clonal genetic alterations. A global measure, such as the FAL, can provide a benchmark value against which the pathological or clinical importance of any specific allelic deletion ultimately should be compared.

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Serum Immunoreactive Erythropoietin in HIV-Infected Patients

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Serum immunoreactive erythropoietin (SIE) and hemoglobin levels were measured in 152 patients infected with the human immunodeficiency virus. Anemia was present in 18% of asymptomatic patients who tested positive for the human immunodeficiency virus, 50% of patients with a condition related to the acquired immunodeficiency syndrome (AIDS), and 75% of patients with AIDS. The mean SIE level for untreated AIDS patients (26.2 ± 2.4 mU/mL) was greater than for patients who tested positive for human immunodeficiency virus or patients with an AIDS-related condition but not outside the normal range for SIE (4 to 26 mU/mL), and the incremental increase in SIE level for a given decline in hemoglobin level was much less in AIDS patients than in patients with uncomplicated iron deficiency anemia. Forty-two patients were treated with zidovudine, and the hemoglobin level fell 10 g/L or more in 48%. In contrast to the untreated patients, however, the mean SIE level rose 10-fold to 214 mU/mL, and the incremental change in SIE level for a given decline in hemoglobin level was markedly increased. In the zidovudine-treated patients, erythrocyte mean corpuscular volume also rose significantly from a mean of 88.1 fL to 102 fL. However, in only 1 patient was there a corresponding increase in reticulocytes and in none was there amelioration of anemia. The data indicate that SIE level is inappropriately low in anemic AIDS patients. The ability of these patients to produce erythropoietin is intact and can be expressed with zidovudine therapy. However, even very high levels of SIE fail to stimulate erythropoiesis adequately.

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THE BLOOD is a target organ for the human immunodeficiency virus (HIV), and anemia, leukopenia, or thrombocytopenia, alone or in combination, invariably occurs during the course of HIV infection.[1,2] Although numerous morphological abnormalities have been identified in the bone marrow of HIV-infected patients,[3] the mechanisms for the reduction in the circulating formed elements of the blood are not fully understood. Anemia is the most common hematologic abnormality in HIV infection, and its incidence increases with progression of the disease.[2] Morphologically, the red blood cells in HIV-infected patients are normochromic and normocytic and the reticulocyte count is usually low. Despite a high incidence of direct antiglobulin tests,[4,5] overt hemolysis is unusual, and low serum cobalamin levels have not been correlated with tissue deficiency of vitamin B_{12}.[6]

Human immunodeficiency virus infection is characterized by a chronic and systemic inflammatory process and recurrent microbial infections, settings in which the level of serum erythropoietin is characteristically low.[7,8] To determine whether anemia occurring with HIV infection was associated with erythropoietin lack, we measured serum immunoreactive erythropoietin in 152 HIV-infected patients. Our data indicate that inadequate increments in serum erythropoietin may be involved in the anemia associated with HIV infection.

PATIENTS AND METHODS

The study population consisted of patients 17 years of age or older with HIV infection documented by positive results from both enzyme-linked immunosorbent (Organon-Technika, Charleston, SC) and Western blot (DuPont, Wilmington, Del) assays, who were enrolled in a longitudinal study of HIV infection at The Johns Hopkins Hospital. Patients were classified as having the acquired immunodeficiency syndrome (AIDS) or an AIDS-related condition (ARC) according to the criteria of the Centers for Disease Control.[9] Forty-two patients were treated with zidovudine (3′-azido-3′-deoxythymidine, or AZT) during the course of the study. Patients with a history of blood transfusion up to 30 days before evaluation or treatment with radiation or chemotherapy were excluded from the study. Blood samples were collected for measurement of the hemoglobin level, erythrocyte mean corpuscular volume, and levels of serum creatinine, erythropoietin, albumin, aspartamine aminotransferase, and alanine aminotransferase. Serum erythropoietin was measured with a sensitive and specific commercially available radioimmunoas-

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say (Smith Kline Bio-Science Laboratories, Van Nuys, Calif) that uses recombinant-derived reagents.[10] The interassay coefficient of variation for this radioimmunoassay ranges from 14.5% at a mean serum erythropoietin level of 9.6 mU/mL to 8.6% at a mean serum erythropoietin level of 99.3 mU/mL, and the correlation between repeated determinations in the same patient was 0.997. With this assay, serum immunoreactive erythropoietin correlates well with biologically active erythropoietin.[10,11] The lower limit of sensitivity of the assay is 2.0 mU/mL and the suggested normal range is 4 to 26 mU/mL. In 33 nonanemic men evaluated by us, the mean serum immunoreactive erythropoietin level was 12.0 ± 0.8 mU/mL (range, 3 to 21 mU/mL); in 42 nonanemic women, the erythropoietin level was 11.0 ± 0.7 mU/mL (range, 2 to 23 mU/mL).

The experimental protocol was approved by the Joint Committee on Clinical Investigation at The Johns Hopkins Hospital. The significance of the difference of means was assessed with Student's two-tailed *t* test and the comparison of regression lines by analysis of covariance.[12]

RESULTS

One hundred sixty-one HIV-infected patients were studied but 9 were excluded because of a serum creatinine level greater than 132.6 μmol/L.[11] Of the rest, 22 (16 men and 6 women) were asymptomatic (HIV+), 26 (20 men and 6 women) had an ARC, and 104 (103 men and 1 woman) had AIDS.

Mean hemoglobin and serum immunoreactive erythropoietin levels are shown in Table 1 for each group. Although the mean hemoglobin level for asymptomatic HIV+ individuals was normal, 3 men and 1 woman had a mild anemia. The mean hemoglobin level of the ARC patients was lower than normal and 10 men and 3 women in this group were anemic. Although both HIV+ and ARC men had higher hemoglobin levels than HIV+ or ARC women, serum immunoreactive erythropoietin levels were not different between men and women in these groups, nor were they outside the range of normal.

Fifty-five (75%) of 73 AIDS patients not receiving zidovudine were anemic, and the mean hemoglobin level in this group was substantially lower than for the HIV+ or ARC groups (Table 1) ($P<.001$). Serum immunoreactive erythropoietin was also higher in the AIDS patients than in the HIV+ or ARC patients ($P<.01$) but was still not outside the normal range. The reason for this became apparent when serum immunoreactive erythropoietin was plotted as a function of the hemoglobin level for the anemic AIDS patients and compared with that of 23 adults with uncomplicated iron deficiency anemia (Fig 1). As shown, for any given decrease in hemoglobin level, the increment in the level of serum immunoreactive erythropoietin in the AIDS patients was less than in the iron-deficient patients ($P<.01$).

Forty patients with AIDS and 2 with ARC received zidovudine as therapy for their disease for periods of 4 to 48 weeks. The initial dose of zidovudine was 1500 mg/d, administered orally, with dosage reductions for increasing severity of anemia. During zidovudine therapy, the hemoglobin level fell 10 g/L or more in 14 of the 29 patients for whom pretreatment values were available. In contrast to untreated patients, however, serum immunoreactive erythropoietin levels increased in the zidovudine-treated patients such that the mean level (214 mU/mL; range, 13 to 1940 mU/mL) was 10-fold greater with treatment than before (Table 2). The incremental response in serum immunoreactive erythropoietin for the zidovudine-treated patients as their hemoglobin levels declined was significantly different than for the untreated patients (Fig 2) or patients with uncomplicated iron deficiency anemia ($P<.01$).

In the 26 zidovudine-treated patients for whom measurements were avail-

Table 1.—Hemoglobin and Serum Immunoreactive Erythropoietin Levels in HIV-Infected Patients*

		Stage of Infection		
	Sex	HIV Positive	ARC	AIDS
Hemoglobin, g/L	M	145 ± 10†‡(16)	138 ± 14 (20)	108 ± 02 (72)
	F	132 ± 10 (6)	116 ± 14 (6)	107 (1)
Serum immunoreactive erythropoietin, mU/mL	M	12.2 ± 2.9 (16)	13.9 ± 5.4 (20)	26.2 ± 2.4 (72)
	F	12.8 ± 3.1 (6)	15.5 ± 5.0 (6)	10.0 (1)

*HIV indicates human immunodeficiency virus; AIDS, the acquired immunodeficiency syndrome; and ARC, AIDS-related complex.

†Mean ± SEM. The numbers in parentheses indicate the number of patients in each group.

‡Hemoglobin levels between HIV-positive men and women and between men and women with ARC were significantly different ($P<.02$), but their erythropoietin levels were not. Untreated AIDS patients had lower hemoglobin levels ($P<.001$) than either HIV-positive or ARC patients and higher serum erythropoietin levels ($P<.01$).

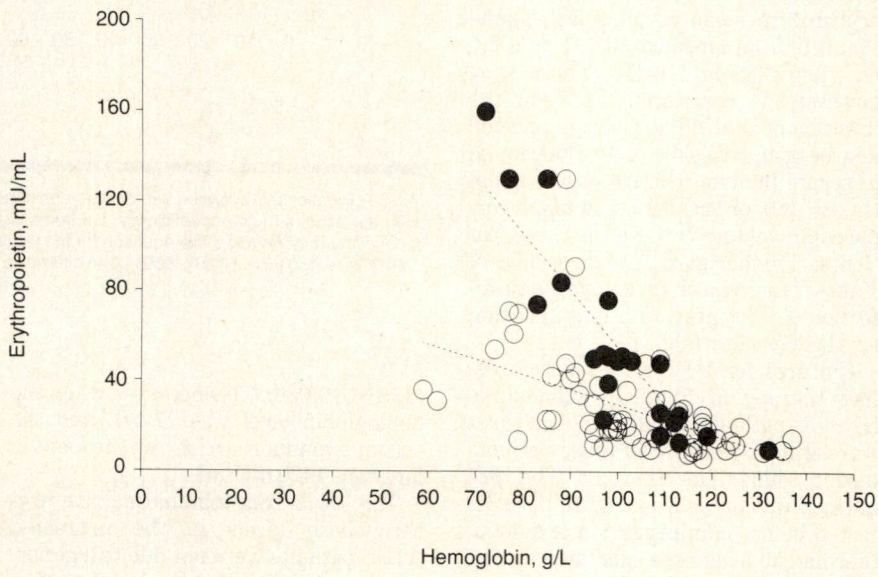

Fig 1.—Relationship between hemoglobin and serum immunoreactive erythropoietin in 55 anemic, untreated patients with the acquired immunodeficiency syndrome (AIDS) (open circle) and 23 patients with iron deficiency anemia (black circle). For the AIDS patients, the equation for the regression line was $y = -6.6x + 96.1$ ($r = .50$, $P<.01$). For iron deficiency, the equation for the regression line was $y = -25.8x + 316$ ($r = .90$, $P<.01$). The difference between the slopes was significant ($P<.01$).

Table 2.—Hemoglobin, Serum Immunoreactive Erythropoietin, and MCV* Levels Before and During Zidovudine Therapy

	Pretreatment	Treatment	
Hemoglobin, g/L	118±30†(27)	107±40	(27)
Serum immunoreactive erythropoietin, mU/mL	20.7±1.9 (27)	214.3±89.3	(27)
Erythrocyte MCV, fL	89.1±0.9 (26)	102.0±1.4	(26)

*MCV indicates mean corpuscular volume.
†Mean±SEM. The difference for each mean between the pretreatment and treatment groups was significant ($P<.05$). The numbers in parentheses indicate the number of patients in each group.

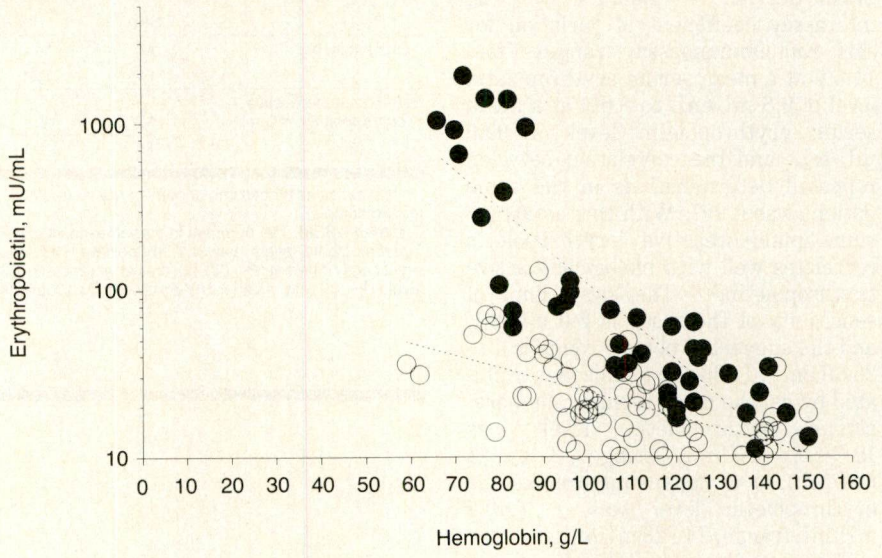

Fig 2.—Relationship between hemoglobin and serum immunoreactive erythropoietin in untreated patients with the acquired immunodeficiency syndrome (AIDS) (open circle) and 31 AIDS patients treated with zidovudine (black circle). The equation for the regression line for the zidovudine-treated patients was $y = -127.7x + 1561$ ($r=.63$, $P<.0001$). The difference between the slopes was significant ($P<.01$).

able, there was a significant increase in erythrocyte mean corpuscular volume (Table 2) from a mean of 88.1 fL to 102.0 fL (range, 85 to 116 fL). There was, however, no correlation between the duration of zidovudine therapy and the degree of anemia ($r=-.19$), the change in serum immunoreactive erythropoietin ($r=.30$), or the change in mean corpuscular volume ($r=.01$) in these patients. Furthermore, the presence of Kaposi's sarcoma or an opportunistic infection did not prevent a rise in serum erythropoietin level.

Cultures for HIV were positive before therapy in 15 of 18 zidovudine-treated patients, and HIV cultures were still positive in 3 of these patients during zidovudine therapy. The p24 antigen was present in 6 of 10 patients tested before administration of zidovudine and all 3 patients examined during zidovudine therapy. In HIV culture–positive and p24 antigen–positive patients, serum immunoreactive erythropoietin levels rose from 3- to 80-fold during zidovudine therapy.

CD4 lymphocyte counts were less than 400/mm^3 before zidovudine treatment in the 12 patients in whom these counts were obtained. In only 1 of 5 patients did the CD4+ lymphocyte count increase above 400/mm^3 during zidovudine therapy, although serum immunoreactive erythropoietin levels increased in all 5 patients.

Reticulocyte counts were obtained before therapy in 10 of the zidovudine-treated patients and were low in all those who were anemic. In 4 patients, serial reticulocyte counts were obtained during zidovudine therapy. These patients were either anemic or became anemic during zidovudine treatment, and in all a rise in serum immunoreactive erythropoietin of 3- to 80-fold (range, 114 to 1940 mU/mL) occurred. In only 1 patient, however, whose CD4+ lymphocyte count normalized, was there an increase in reticulocytes (0.016 to 0.036). This occurred when the hemoglobin level was 77 g/L and the serum immunoreactive erythropoietin level was 1420 mU/mL.

The low serum immunoreactive erythropoietin levels in the untreated AIDS patients were not due to a generalized reduction in levels of serum proteins or related to impaired liver function. The serum albumin level in most of the AIDS patients was normal, and there was no correlation between serum albumin level, even when low, and the level of serum immunoreactive erythropoietin ($r=.19$) or hemoglobin ($r=.13$). Furthermore, there was no correlation between serum immunoreactive erythropoietin and elevated serum aspartamine aminotransferase or alanine aminotransferase levels in either untreated AIDS patients or those receiving zidovudine (data not shown).

COMMENT

The mechanism for the anemia that occurs in the setting of chronic inflammation or infection is complex. Red blood cell life span is slightly shortened, but this of itself would not lead to anemia if erythropoiesis was normal.[13] Erythropoiesis, however, is impaired due to a variety of factors including reduced recycling of iron by macrophages,[14] production of molecules such as interferon and tumor necrosis factor that inhibit erythropoiesis,[15,16] and a reduced increment in serum erythropoietin in response to anemia.[7,8] In the present study, we examined serum immunoreactive erythropoietin levels in HIV-infected patients at various stages of the infection and during zidovudine therapy. The incidence of anemia increased with the severity of the HIV infection, but the level of serum immunoreactive erythropoietin failed to rise commensurately with increasing anemia, suggesting that one cause for anemia in this situation is lack of adequate quantities of this hormone. Similar observations have been made in patients with other chronic inflammatory disorders.[7,8]

The serum immunoreactive erythropoietin determination is, of course, a static measurement and provides no information concerning the production or catabolism of the hormone. Although erythropoietin is produced primarily in the kidney,[17,18] the liver produces a small amount of the hormone,[18,19] and in patients with end-stage renal disease, hepatitis has been associated with amelioration of anemia.[20-22] However, liver damage did not account for the serum erythropoietin levels in either untreated AIDS patients or those treated with zidovudine, since there was no correlation between hepatocellular injury as measured by the serum enzymes aspartamine aminotransfer-

ase and alanine aminotransferase and serum immunoreactive erythropoietin levels.

The serum albumin level is often low in patients with chronic inflammation or infection,[23] but in the present study the serum albumin level was normal in most of the patients, and even when it was low, there was no correlation between serum albumin and erythropoietin levels, suggesting that changes in protein synthesis or catabolism, if present, are selective in this situation.

Serum testosterone levels are low in AIDS patients,[24] and although this could be associated with a fall in hemoglobin, at least to the levels maintained in women, it would not be expected to alter the serum immunoreactive erythropoietin level.[25]

The marked change in serum immunoreactive erythropoietin level in the patients treated with zidovudine was of interest for several reasons. First, it demonstrated that the erythropoietin response to anemia could be restored in AIDS patients and second, that paradoxically, despite marked elevations in the level of serum erythropoietin, the bone marrow in these patients was unresponsive to the hormone.

The mechanism for the marked rise in serum erythropoietin levels in response to anemia during zidovudine therapy is unknown. It could involve amelioration of the HIV infection, a direct effect of zidovudine on erythropoietin-producing cells in the kidneys or liver, an effect on the cells responsible for erythropoietin catabolism, a change in hemoglobin-oxygen affinity, or a combination of these factors. Pharmacokinetic studies will be required to settle this issue. A marked increase in levels of serum immunoreactive erythropoietin out of proportion to the extent of anemia has also been observed in patients with other types of refractory anemia.[11]

Failure of the marrow to respond to erythropoietin may have been due to the HIV infection, but zidovudine therapy alone causes anemia[26] with marrow erythroid hypoplasia, aplasia, or megaloblastic maturation.[27] An increase in mean corpuscular volume was a consistent feature of zidovudine therapy, and, as noted in a previous study, macrocytosis occurred in over 70% of the patients taking zidovudine.[26] In this regard, zidovudine appears similar to azathioprine, which is known to cause both macrocytosis and red blood cell hypoplasia.[28] In a previous report involving a small number of patients treated with zidovudine, macrocytosis was not correlated with the development of anemia.[27] In the present study, however, macrocytosis was associated with anemia. This discrepancy may relate to the number of patients studied as well as the dose of zidovudine employed, which was higher in our patients.

In conclusion, the data indicate that the level of serum immunoreactive erythropoietin is inappropriately low in the anemia associated with HIV infection. The ability of HIV-infected patients to produce erythropoietin appears intact and can be expressed with administration of zidovudine, but the mechanism for this is unknown. However, even in the presence of very high serum erythropoietin levels, either intrinsic marrow failure, zidovudine toxicity, or both prevented an increase in erythropoiesis in response to the elevated erythropoietin level. Whether increasing circulating erythropoietin to even higher levels by administration of exogenous recombinant human erythropoietin might be beneficial in this situation remains to be determined.

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Presymptomatic Diagnosis of Delayed-Onset Disease With Linked DNA Markers

The Experience in Huntington's Disease

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Clinical medicine in the 21st century is almost certain to include wide-scale use of molecular genetic diagnostic tests. In September 1986, The Johns Hopkins University School of Medicine initiated a voluntary program of presymptomatic genetic testing for Huntington's disease for persons at 50% risk. DNA analyses using the D4S10 (G8), D4S43, and D4S95 locus probes have been performed for 55 people. Twelve of the tests have yielded positive results, 30 were negative, and 13 were uninformative. Initial reactions ranged from joy and relief to disappointment, sadness, and demoralization. Thus far, there have been no severe depressive reactions. Although the sample size is small, our data suggest that people who receive genetic test results cope well, at least over the short term, when the testing is performed in a clinical context that includes education, pretest counseling, psychological support, and regular follow-up.

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PSYCHIATRY in the 1980s has undergone a major "paradigm shift"[1] as advances in the basic biomedical sciences have found their way into the psychological laboratory and psychiatric clinic. One source of this shift has been the exponential growth of the field of molecular genetics. While the familial aggregation of several neuropsychiatric diseases (eg, major affective disorder, panic disorder, schizophrenia, Alzheimer's disease) has been appreciated at least since Kraepelin,[2] the discovery of restriction fragment length polymorphisms (RFLP) and the development of recombinant DNA probes have allowed researchers to study the linkage of these disorders to particular chromosomal loci.[3-5] For one neuropsychiatric disorder, Huntington's disease (HD), technological developments have progressed to the point where DNA diagnosis of asymptomatic, at-risk individuals is a reality.

Huntington's disease is a progressive disease of the central nervous system, characterized by involuntary movements (chorea), abnormal voluntary movements, cognitive deterioration, and affective symptoms. There is no cure for the illness, and, at present, the only treatments are symptomatic (eg, tricyclic medications for the often-present depression). Symptoms progress relentlessly, with death occurring an average of 15 to 17 years after disease onset.[6,7]

Huntington's disease is inherited as an autosomal dominant trait with complete lifetime penetrance; each son or daughter of an affected person has a 50% chance of developing the disease. Onset of symptoms is typically delayed until the fourth or fifth decade of life.[6,7] Thus, children of patients with HD make many life decisions (eg, concerning their education, careers, marriage, and childbearing) without knowing whether they will develop this progressive, neurodegenerative disease or have the potential to pass it along to their children.

In 1983, Gusella and coworkers[8] discovered an RFLP on the short arm of chromosome 4 that is linked to the HD locus. *Restriction fragment length polymorphisms* refer to the variable but predictable ways in which a particular DNA segment breaks apart when digested with enzymes. This variability at a particular chromosomal location close to a disease gene can be used as a marker for that gene. By analyzing DNA samples from both affected and elderly unaffected individuals in a family, it can be determined which RFLP pattern segregates with HD. At-risk persons in that family can then be tested to determine whether they have the RFLP pattern (haplotype) associated with the HD gene.

Linkage studies of many large, phenotypically different families with HD have all confirmed the close proximity of Gusella's RFLP marker (named G8, or D4S10) to the HD gene,[9,10] and it is now virtually certain that there is only one chromosomal locus for HD. The odds that D4S10 and the HD gene locus are linked is at least 10^{71} to 1 (reference 10).

The marker identified by Gusella et al is estimated to be approximately 4 to 5 centimorgans (ie, 4 to 5 million base pairs) from the HD gene. Because of this, any test of a presymptomatic at-risk person using this probe is, at best, 95% predictive of having, or not having, the gene. Recently, several new markers have been discovered: D4S43,[11] D4S62,[12] and D4S95.[13] Some of these new markers are much closer to the HD gene than is D4S10. D4S95, for example, is a highly polymorphic DNA locus that has so far displayed no recombinations with the HD gene.[12] This gives any predictive test with this probe an accuracy of approximately 99%.

The decision to be tested for HD is not an easy one for the majority of at-risk persons. While testing negative probably leads to a reduction in anxiety, and indicates that one can make decisions without the worry of HD or concern

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about passing it along to offspring, testing positive (without proper preparation) could result in a variety of adverse effects including severe depression, anxiety about onset of symptoms, family discord, and job- and insurance-related discrimination.

In September 1986, the Baltimore (Md) Huntington's Disease Project at The Johns Hopkins University School of Medicine became one of the first two centers in the United States to offer presymptomatic genetic testing for HD to adults at 50% risk for the illness. Testing has been offered only as part of a research program, designed primarily to determine (1) the psychiatric, psychological, and social consequences of informing people of their HD genetic status; (2) whether pretest characteristics can discriminate those who adapt well to their genetic status from those who adapt poorly; and (3) whether educational and therapeutic interventions can mitigate morbid psychological and social outcomes.

To date, there have been two published accounts of the outcome of presymptomatic testing for HD. Hayden et al[14] reported the results of 20 informative tests on individuals at 50% risk of developing HD (having an affected parent) and individuals at 25% risk of developing HD (having an affected grandparent but an unaffected, still-at-risk parent). Twelve individuals (60%) received a decreased risk and 8 (40%) received an increased risk of having inherited the HD gene. In the group found to have increased risk, 2 persons were said to have clinical signs consistent with early-stage HD. Although Hayden et al did not report on the psychological impact of testing, including persons at less than 50% risk and those already mildly affected with HD complicates determination of the psychological risks associated with testing.

Meissen et al[15] reported that of 16 DNA tests performed on individuals at 50% risk for HD, 4 yielded positive results (those individuals would likely develop HD), 7 yielded negative results (would not develop HD), and 5 were uninformative. The authors reported that those who were told they probably have the gene were "surprised or shocked" by their test results. Half of them (ie, 2 people) had periods of severe depression, while the other 2 had periods of moderate depression, at 3-month follow-up. Nonetheless, the authors stated that "no psychiatric care had been necessary." The instruments used to make the psychiatric diagnoses or actual scores on depression inventories were not specified. Like the study by Hayden et al,[14] that by Meissen and coworkers was not strictly limited to asymptomatic individuals, as "persons with neurologic findings only moderately suggestive of Huntington's disease" were included.

We report herein the findings from the first 2 years of the Baltimore Huntington's Disease Project presymptomatic testing program.

Table 1.—Psychological Tests and Questionnaires Administered During the Baseline Assessment

Personal History Questionnaire: This instrument was designed specifically for this project and covers a variety of topics, including demographic information, educational and work histories, medical history, drug and alcohol use, friendships, affiliations, and social supports.
Family Environment Scale[19]: This 90-item true-false inventory allows us to quantify the quality of the home environment.
Life Events Scale: This instrument is a modification of the Psychiatric Epidemiology Research Interview Life Events Scale[20] and is used as an indicator of life stress.
Social Support Inventory: This instrument is composed of 2 parts. Part A is the 26-item Instrumental-Expressive Support Scale,[21] which assesses 5 factor–analytically derived domains of social support. Part B is a very brief rating scale that assesses the frequency with which the respondent has been the recipient of the supportive actions of others. It has been developed specifically for the current project and is derived from the Inventory of Socially Supportive Behaviors.[22]
Miller Behavioral Style Scale[23]: This instrument is a 32-item measure of coping style designed to identify information-seekers ("monitors") and information-avoiders ("blunters") based on their self-reported preferences for information or distraction in a variety of naturalistic stress situations.
Symbol Digit Modalities Test[24]: This coding task is a quick test of cognitive efficiency and psychomotor speed that is extremely sensitive to both brain dysfunction and the effects of anxiety and depression.
Cognitive Failures Questionnaire[25]: This 25-item questionnaire of established validity and reliability evaluates the individual's self-perception of cognitive efficiency. It estimates the relative frequency with which various "slips" of perception, action, and memory are made.
Symptom Checklist (SCL-90R)[26]: This instrument assesses 9 domains of psychiatric symptoms: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism.
Beck Depression Inventory[27,28]: This well-known 21-item questionnaire is a highly valid and reliable self-report measure of depression.
Beck Hopelessness Scale[29]: This 20-item true-false questionnaire provides an assessment of pessimism and sense of hopelessness.
Millon Clinical Multiaxial Inventory–II[30]: This is a relatively new psychometric instrument, composed of 175 true-false statements. Both acute clinical disorders and more enduring personality characteristics (normal and abnormal) are assessed by 20 clinical scales keyed to the nomenclature of the *Diagnostic and Statistical Manual,* 3rd edition, revised.
Subjective Risk Scales: Both the person being tested and his or her confidant(e) are asked to indicate the likelihood that the at-risk person will develop HD.* A 200-mm visual analogue scale is used, with the end points marked "definitely *will not* develop HD" and "definitely *will* develop HD."

*HD indicates Huntington's disease.

METHODS

The protocol for predictive testing consisted of baseline assessment, DNA analysis, disclosure, and follow-up. These methods were developed in consultation with an ethics committee and the Joint Committee on Clinical Investigation (institutional review board) at The Johns Hopkins Medical Institutions.

Baseline Assessment

The baseline assessment took place during an average of five visits over a period of several months.

Neurological/Psychiatric Assessment.—For at-risk persons not previously known to our program, an extensive interview was conducted during the first visit to establish the family history of HD and to draw the pedigree. Medical and other records were sought, and documentation of HD and its age of onset in affected relatives was obtained. For all subjects, the Quantified Neurological Examination[16] was performed to detect subtle, preclinical neurological signs. Also during this visit, a psychiatric interview using the Schedule of Affective Disorders and Schizophrenia—Lifetime Version (SADS-L)[17] was performed to establish whether the at-risk person presently had a diagnosable psychiatric disorder. The Mini–Mental State Exam,[18] a brief cognitive screening test, was given to rule out a present state of dementia or delirium. If a potential subject was found to be symptomatic with HD or had a major mental illness (major affective disorder was the only illness detected), he or she was counseled appropriately and referred to the HD Clinic or another appropriate clinical facility for treatment.

Psychological Assessment.—Subjects who qualified to proceed with the study were evaluated psychologically over several sessions. This evaluation consisted of a large number of psychological tests, rating scales, and inventories (Table 1). The hypothesis guiding the selection of these tests and procedures as baseline measures was that the impact of receiving information about one's genetic status would vary depending on family history, preexisting personality features and coping style, psychological symptoms, cognitive efficiency, life stresses, and environmental support.

Counseling.—Each subject participated in at least three (typically five) 90-

minute individual counseling sessions with a psychologist. All visits took place at least 2 weeks apart, and the total number of visits was determined by individual needs. The purpose of these counseling sessions was to discuss with participants the nature of the genetic linkage test, the various outcomes that might be expected, and the impact that the results of this test might have on their lives. It was explained that a chromosomal marker for the HD gene, and not the gene itself, was detected by this test. This implies that there would still be some uncertainty as to whether the defective gene had been inherited. In addition, assistance was given in clarifying the family history, obtaining medical information about affected and unaffected relatives, and collecting the blood or tissue samples necessary for the DNA analysis to be performed. During each counseling session, the voluntary nature of the decision to be tested was emphasized. Informed consent was obtained prior to analysis of the DNA.

Each subject undergoing testing was asked to identify an individual he or she knew well to be his or her advocate or confidante. This individual attended a minimum of one counseling session and was required to be present at the time of disclosure of the test results. The role of the confidante was to provide emotional support for the person being tested and to serve as a liaison with the project staff. The availability of the project's professional staff for psychological support and assistance after testing was underscored.

DNA Analysis

To perform the linkage test, DNA samples are needed from multiple family members, including those affected with HD and, in most cases, elderly unaffected persons ("escapees"). Informed consent was obtained from all individuals who donated tissue samples.

DNA was prepared from peripheral blood lymphocytes or from frozen brain tissue. Lymphoblast DNA was prepared using sucrose–octyl phenoxy polyethoxyethanol (Triton X-100). Brain tissue samples were processed by homogenization in saline-sucrose-Triton X-100, followed by digestion of the centrifuged pellet with proteinase K. After extraction of this material with phenol and chloroform, DNA was recovered by ethanol precipitation. Five micrograms of DNA was digested overnight with 10 U of restriction enzyme. The resulting DNA fragments were separated on 1% agarose gels and transferred to a positively charged nitrocellulose membrane by Southern blot.

The D4S10 (G8), D4S43, and D4S95 locus probes were used for DNA analysis. The D4S10 probe recognizes 6 RFLPs, produced by digestion with *Hind*III (two RFLP sites), *Pst*I, *Eco*RI, *Bgl*I, and *Msp*I. The D4S43 probe recognizes 8 RFLPs; the 3 enzymes that have been most informative (*Sac*I, *Pvu*II, and *Msp*I) were used. The D4S95 probe recognizes 4 RFLPs; 3 enzymes were used (*Acc*I, *Mbo*I, and *Taq*I). Thus, three probes and 10 restriction enzymes were used to examine 12 RFLP sites and one variable number tandem repeat polymorphism. Our procedure has been to use the D4S95 probe first, followed by D4S43 and D4S10 as needed.

The DNA probes were generated from recombinant plasmid by restriction endonuclease digestion to release the insert. This procedure was followed by agarose-gel electrophoresis and excision of the insert fragment from the gel. Insert fragments were labeled with phosphorus 32 by nick translation or oligomer priming. The filters were prehybridized and hybridized and washed under stringent conditions of salt and temperature. Results were obtained by autoradiography at −70°C for 1 to 5 days.

Linkage analysis was performed with the LIPED program.[31] The risk for HD, given the linkage test results, age of the subject and relevant family members, and sex of the affected parent, was calculated by the methods of Conneally et al[32] and Chase et al.[33]

Disclosure

Uninformative test results were conveyed over the telephone. If the results from the genetics laboratory were either positive or negative, subjects were telephoned and told that a result was available, and a disclosure session was scheduled.

At disclosure, the results of the linkage study and the risk estimate were conveyed to the subject and his or her confidante. Sufficient time was allowed to ensure that the subject understood the results and for the expression of emotions that invariably followed. All questions were answered and subjects were helped to decide to whom the results should be conveyed. The continued support of the staff was reiterated.

All subjects, regardless of test outcome, were randomly assigned to one of two therapists (a social worker or a psychiatrist) associated with the project. Subjects were instructed to contact their therapist within 1 week to discuss the nature and frequency of visits, telephone calls, etc. Those subjects who tested positive were asked to telephone their counselor 24 hours later. Any subject who did not call at the designated time was contacted.

Follow-up

All subjects, regardless of their genetic test results, return for research follow-up every 3 months for the first year after disclosure and every 6 months for the next 2 years. In addition, they may have as many visits with their therapists as they desire. At every research visit, the SADS–Change Interview is administered to assess changes in psychiatric status. The following tests and rating scales are also readministered at these visits: Family Environment Scale (to evaluate changes in home environment), Beck Depression Scale, Beck Hopelessness Scale, Symptom Checklist (SCL-90R), Cognitive Failures Questionnaire, Symbol Digit Modalities Test, the Subjective Risk Scales, and the Life Events Scale (3-month version). At 6-month intervals, the Quantified Neurological Examination, and the Mini–Mental State Exam are added to the visit, to document the emergence of any symptoms of HD.

RESULTS

As of December 15, 1988, one hundred seven adults have entered the research protocol under which predictive testing for HD is offered. Ten were found to be affected with HD on clinical examination and were diagnosed. Three were found to have significant depression, and their testing was deferred. Six persons did not want DNA testing and entered as control subjects. Thirty-three people are still in the baseline phase.

Thus far, genetic analysis has been performed for 55 individuals using the D4S10, D4S43, and D4S95 DNA markers. D4S10 (G8) was the first marker available and allowed a test with 95% accuracy. Since D4S43 and D4S95 are closer to the HD gene locus, we have begun to use these markers as our "first choice" tests. If they yield uninformative results, we resort to using D4S10. Results can be uninformative if the affected marker cannot be determined, if both the affected and unaffected parent have the same marker alleles, or if the affected parent is homozygous for the marker. Twelve subjects have tested positive for the marker(s) and will likely develop HD, and 30 have tested negative and will likely *not* develop HD. Those subjects who had positive test results using D4S10 disclosed to them have had their status confirmed using D4S43 and/or D4S95.

Informative test results have been obtained from families previously thought to be too small to allow determi-

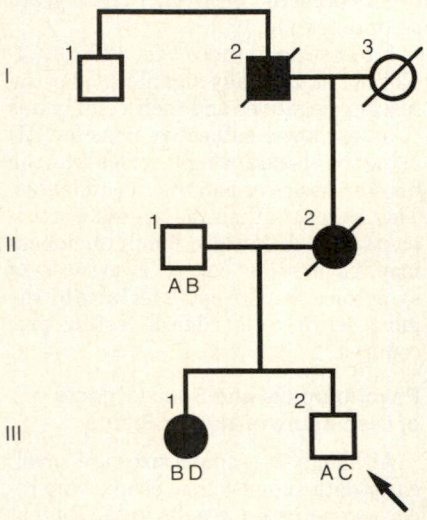

Fig 1.—Pedigree drawing of an at-risk person (III-2, designated by the arrow) testing negative for Huntington's disease (HD) using the G8 (D4S10) probe. Some nonessential details of the pedigree are altered to maintain confidentiality. *Hind*III, *Pst*I, *Eco*RI, *Bgl*I, and *Msp*I were used to produce six restriction fragment length polymorphism sites (two with *Hind*III and one each with the other four enzymes). The A haplotype represents the pattern (− + − + − +) at the six sites. The other haplotype patterns are B (− − − − − −), C (− − + − − +), and D (+ + − + + −). The consultant's affected mother is deceased, but it can be inferred from the father's haplotype that the affected sister (III-1) inherited haplotype D from her mother. The person requesting testing (III-2) has no allele in common with his affected sister and inherited the C haplotype from his affected mother. We can conclude that he has very likely not inherited HD. Using the LIPED program, his risk for HD is calculated to be 4%.

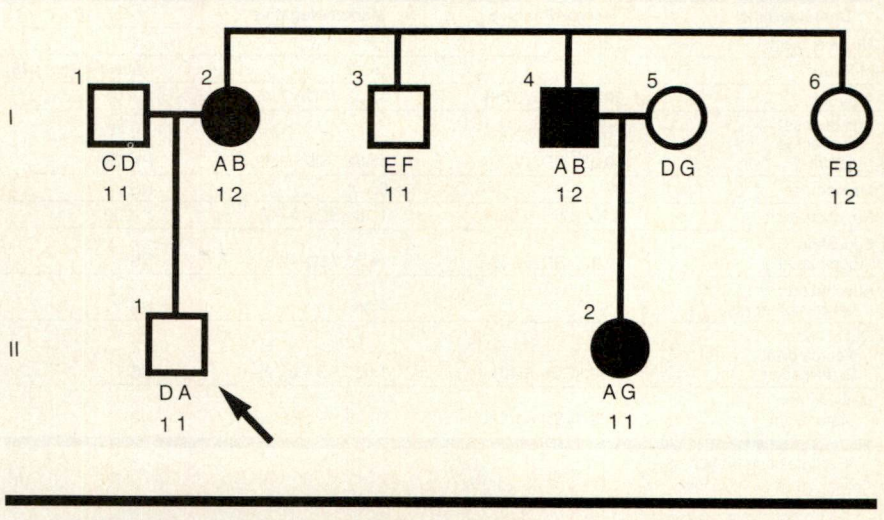

Fig 2.—Pedigree drawing for an at-risk person (II-1, designated by the arrow) testing positive for the Huntington's disease (HD) marker. In this family, the D4S10 haplotypes are coded as follows: A (− + − − − +), B (− + − − − −), C (− + + + − +), D (+ + − + + +), E (− + − + + +), F (− + − − + +), and G (+ + − − − +). The numbers 1 and 2 represent the restriction fragment length polymorphism site hybridizing to D4S43 after digestion with *Sac*I. All the patients affected with HD in this family share the A1 haplotype. The individual requesting testing (II-1) inherited the A1 haplotype from his affected mother. His risk of inheriting HD is estimated to be 99%.

nation of the affected marker type or linkage phase in the affected parent. Figure 1 shows the pedigree of a small family where the at-risk person had a negative test outcome. Figure 2 shows the pedigree of a somewhat larger family in which the at-risk consultant had a positive test outcome.

The results of the genetic analysis were uninformative in 13 cases. In 6 of these cases, the pedigrees appeared likely to be informative (ie, contained at least two affected persons from whom we could obtain DNA, or contained a surviving grandparent), but the probands could not be unambiguously haplotyped. For these individuals, the discovery of new, or flanking, markers for the HD gene may yet yield informative results. The remaining 7 cases were uninformative primarily due to family structure (eg, only one affected individual). For these cases, an informative test will have to wait until a second family member develops symptoms of the disease, or until the discovery of the HD gene itself.

Characteristics of Clinically Unaffected Persons Who Enter the Testing Program

Ninety-one clinically unaffected at-risk individuals participating in our study requested DNA predictive testing for HD. Men and women were equally represented (45 men and 46 women), and their mean age was 34.52 years (SD, 9.46 years). As is commonly found in those seeking genetic counseling, these individuals are better educated than the general population,[34] with 14.51 (SD, 2.60) years of education. On the average, they had known of their risk for HD for about 10 years, and were approximately 9 years younger than the age at which their affected parents first developed symptoms.

Thus far, six people (two men and four women) have entered the study as control subjects. They averaged 32.83 years of age (SD, 7.91 years) and had an average of 15 years of schooling (SD, 2.76 years). These control subjects volunteered to take all of the examinations and to be restudied at regular intervals, but they do not want genetic testing. As a group, the controls did not differ in demographic characteristics, psychiatric histories, or neurological features from those requesting testing. On baseline psychological testing, however, the controls had somewhat higher scores than those requesting testing on both the Beck Depression Scale (mean, 6.80 vs 2.82; $U=57$, $P<.05$) and Beck Hopelessness Scale (mean, 3.80 vs 2.28; $U=64$, $P<.05$). While a larger control sample will be needed for any definitive statements, these results suggest that those who choose not to learn of their genetic status may do so because they see themselves as more vulnerable psychologically and may fear the impact of a positive result.

Predisclosure Differences Between Marker-Positives and Marker-Negatives

Of the 42 informative test results, 12 have been positive for the marker(s) (risk of HD ≥95%) and 30 have been negative (risk ≤5%, except one). The distribution of positive and negative outcomes is unlikely to be due to chance ($P<.001$, binomial test). This is probably due to the sensitivity of our methods for detecting minor motor abnormalities diagnostic of HD and our postponing testing of people who were depressed or otherwise had a high probability of testing positive. Some of the 13 people who were not tested (10 clinically affected; 3 depressed and still in baseline) actually sought testing to confirm their suspicions that they were already affected with HD. An alternative explanation of the asymmetry of the test outcomes is that in the population of at-risk persons who are absolutely asymptomatic, those who do not carry the gene may, as a group, be better-functioning individuals. They may be more interested in scientific advances in HD and more eager to participate in research studies.

The actual risk estimates for the 42 cases with informative results is depen-

Table 2.—Characteristics of At-Risk Subjects Who Test Positive or Negative for the Linked DNA Marker

Characteristic	Marker-Positive	Marker-Negative	P
No. of subjects	12	29*	. . .
M-F ratio	5:7	16:13	Not significant (NS)
Age, y	30.17 (SD = 5.49)	37.52 (SD = 7.75)	$P<.01$
Age of onset of affected parent, y	40.33 (SD = 9.29)	46.82 (SD = 9.49)	$P<.06$
Married, %	67	66	NS
No. of children	0.75 (SD = 0.87)	1.76 (SD = 1.60)	$P<.02$
Education completed, y	14.17 (SD = 2.33)	14.20 (SD = 2.51)	NS
Affected parent, father-mother ratio	6:6	9:20	NS
Quantified Neurological Examination	2.42 (SD = 3.40)	1.62 (SD = 2.32)	NS
Mini–Mental State Exam	28.91 (SD = 1.22)	29.18 (SD = 0.95)	NS

*Excludes one 68-year-old.

Table 3.—Psychiatric Symptomatology as Revealed by Schedule of Affective Disorders and Schizophrenia–Change Interview Conducted by Therapists at Each Follow-up Period

Follow-up Period	Proportion With Symptoms*		Global Assessment Scale		P
	Marker-Positive	Marker-Negative	Marker-Positive	Marker-Negative	
3 mo	0/5	1/20	89.80 (2.75)†	93.90 (1.29)	Not significant (NS)
6 mo	1/6	3/16	89.17 (4.69)	88.75 (2.33)	NS
9 mo	1/2	1/12	85.50 (4.50)	93.30 (2.23)	NS
12 mo	1/4	1/6	80.75 (9.23)	93.17 (3.64)	NS

*Proportion of subjects with at least moderate symptom severity in one or more domains assessed by the Schedule of Affective Disorders and Schizophrenia–Change Interview.
†Mean (SE).

dent on the pedigree structure, the particular markers that were informative, the subject's age and that of other unaffected at-risk family members, and the sex of the affected parent (paternal transmission being associated with earlier age of onset).[33,35] For those testing positive, risk estimates ranged from 96% to 99%. One person who tested negative received a risk estimate of 30%; the risk estimates for the remaining marker-negative individuals ranged from 1% to 5%.

One subject who tested negative for the marker was 68 years old at entry to the study. Data from this person are excluded from further analyses, since his or her prior probability of ever developing HD was extremely low based on age alone. Even without this one elderly marker-negative individual, the subjects who tested positive for the marker were, as a group, younger than those who tested negative (Table 2). This might be expected, since the probability that one carries the HD gene decreases as one grows older and remains unaffected. The marker-positive and marker-negative groups did not differ in proportion of married individuals (67% and 66%, respectively) or mean level of education. A highly sensitive, standardized, neurological examination developed specifically for the evaluation of HD, the Quantified Neurological Examination,[16] failed to reveal differences between these clinically unaffected groups, as did the Mini–Mental State Exam.

There were no differences between the marker-positive and marker-negative groups in psychiatric history, as revealed by the SADS-L. Of the 12 marker-positives, two subjects met criteria for a lifetime history of any type of affective disorder. Nine of the 29 marker-negative subjects had histories of affective disorder, and three had histories of substance abuse.

While age was significantly correlated with certain demographic variables (eg, number of children), there were no significant correlations between age and baseline psychological test scores. The psychological symptom checklist (SCL-90R) completed before DNA analysis revealed that individuals who tested positive for the marker experienced no greater psychological distress than those who tested negative. The Beck Depression Inventory and the Beck Hopelessness Scale also failed to differentiate between the groups. The marker-positive and marker-negative individuals did not differ in the number of potentially stressful life events (of a variety of types) in the year preceding testing. Neither did they differ in the frequency with which these same events occurred between 1 and 5 years prior to testing.

Interestingly, there was a trend (albeit not statistically significant) for the marker-negatives and their confidantes to assign lower subjective risks for HD using the visual analogue scales than the marker-positives and their confidantes. This suggests that the at-risk participants and their close family members may have some covert awareness of symptoms that are not detectable by the most sensitive of clinical testing procedures.

Psychological and Social Effects of Disclosure of Marker Status

Although the sample sizes are small, early data suggest that people who receive genetic test results in the context of our protocol cope well with the news, at least over the short term. Initial reactions to the test results have ranged from extreme joy and relief to disappointment, sadness, and demoralization. Thus far, there have been no severe depressive reactions.

Of the 42 subjects who have been given linkage test results, 25 have been followed up for at least 3 months, 22 for at least 6 months, 14 for at least 9 months, and 10 for at least 1 year. During the first year after disclosure, there have been few signs of significant psychological distress or social morbidity. Table 3 presents the results obtained with the SADS–Change Interview at each of the four follow-up periods. There is no clear increase in psychiatric morbidity associated with receiving news of a positive test result. In fact, many subjects with positive as well as negative test results were judged as functioning exceptionally well.

A slight increase in psychological distress was revealed by the symptom checklist (SCL-90R). Figure 3 shows the SCL-90R Global Severity Index for the marker-positive and marker-negative groups from baseline to 12-month follow-up. The significant elevation of the marker-positives at 3 months was due to elevations on the interpersonal sensitivity, anxiety, and "psychoticism" subscales. The elevation at 12 months is largely accounted for by higher scores on the depression and anxiety scales for the marker-positives. It should be noted that the scores of the marker-positives remain well within normal limits.

The social consequences of presymptomatic testing are variable. Summary scores on the Life Events Scales show no differences between groups at 3, 6, 9, or 12 months. However, a baby girl has been born to a woman who tested negative for the marker. This woman had

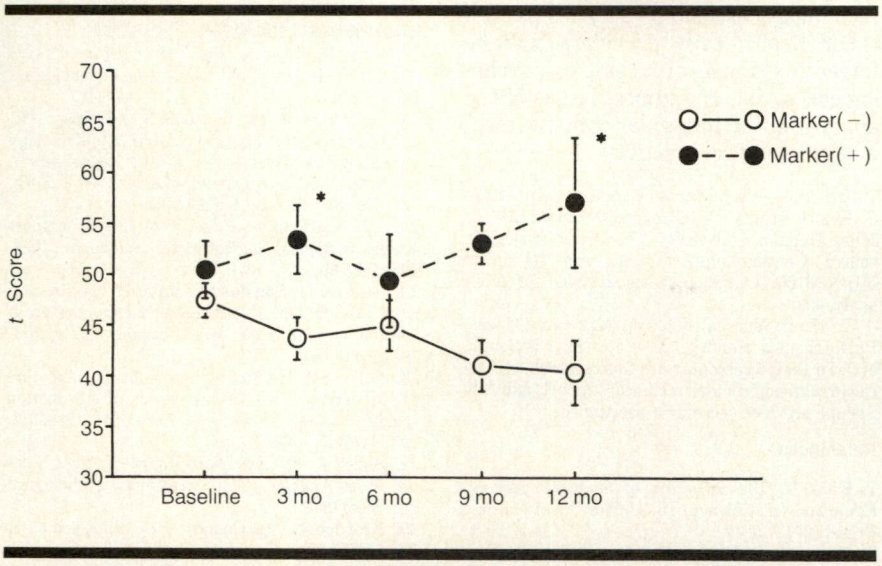

Fig 3.—SCL-90R Global Severity Index of marker-positive and marker-negative cases at baseline (prior to disclosure of test outcomes) and at each follow-up. The number of subjects at each time point is as follows: baseline: 12 marker-positive, 27 marker-negative; 3 months: 5 marker-positive, 19 marker-negative; 6 months: 6 marker-positive, 16 marker-negative; 9 months: 2 marker-positive, 12 marker-negative; and 12 months: 4 marker-positive, 6 marker-negative. Asterisks indicate $P<.05$.

previously decided not to have any children because of her at-risk status. Also in the group that tested negative, three engagements have been announced and one marital separation has occurred. In the group that tested positive, one person has been fired from his job, although his employer apparently never knew about his risk for HD.

COMMENT

This study of the effects of predictive testing for HD reports on the largest series to date followed up for the longest period of time. Neurological, psychiatric, psychological, and social variables collected at baseline were, by and large, ineffective in discriminating individuals who subsequently tested marker-positive from those who tested marker-negative. Our screening procedures resulted in identifying 10 individuals as mildly affected who, if included in the testing protocol, would have tested positive for the marker. Testing was postponed for another 3 individuals with significant affective disorder, which is known to be a precursor of HD in up to half of the families.[36] Thus, the group that went on to be tested was composed not only of those who displayed no detectable signs of HD, but also of those who were free of major psychiatric disorder and symptom free. They were also highly educated, a factor that might limit the generalizability of our results. However, experience has indicated that those who request genetic services tend to be well educated.

Our failure to find baseline differences between those who tested positive and negative for the marker may be a consequence of the low power of our statistical tests due to small sample sizes. With samples of 12 and 30, our ability to detect a moderate effect size (effect size, 0.5) with an independent t test ($\alpha = .05$) is less than 0.70.[37] Larger samples will allow us to test hypotheses concerning pretesting differences between marker-positive and marker-negative at-risk individuals with greater statistical power.

Although the sample sizes are small, our results suggest that people cope well when they receive genetic test results in the context of a highly structured protocol with careful screening, counseling, and follow-up care. We believe that an important part of the counseling is the opportunity for subjects to anticipate their possible responses to test results. This anticipation may account, in part, for the minimal emotional distress following delivery of "bad news." The supportive relationship in which these explorations take place and the commitment of the clinical staff to caring for HD patients and their families provide a context for predictive testing that is reassuring for our patients.

The slight increase in depression and anxiety subscores on the SCL-90R in those who test positive may indicate that longer-term follow-up is necessary to appreciate fully the impact of being told that developing HD is a near certainty. Alternatively, these increases may be heralding the onset of HD in these people. Whether the latter is true will become apparent in the longitudinal comparison of those who have had positive DNA marker test results disclosed to them and control subjects who carry the gene and become symptomatic. At the present time, we have no way of knowing how this foreknowledge will affect individuals as they approach the expected time of disease onset.

The number of eligible at-risk people who requested presymptomatic testing for HD has been much smaller than predicted on the basis of surveys of at-risk individuals.[38] The fact remains that HD is currently a disease with no cure and few, only palliative, treatments. If this situation changes, and treatments are found that can significantly delay the age of onset or slow the progression of the disease, many more at-risk persons may choose to be tested. A program of voluntary testing, in and of itself, will do little to alter the prevalence of HD, and hence its morbidity.

If the HD gene and the mutation(s) producing the disease are discovered, the technical aspects of predictive testing will be vastly simplified and virtually error free. Linkage analysis will not be necessary; only the at-risk person wanting to be tested will need to donate a blood sample for DNA analysis. Such a test would permit many more at-risk people to be tested, and the test would yield a certain diagnosis. Whether more people will opt for this certain test than the predictive test now available is unknown. Differences in psychological response to the current test, which diagnoses with 95% to 99% certainty, and a test that is absolutely diagnostic of HD are also of interest. Research in the area of risk perception suggests that this small difference in risk (the so-called certainty effect) can have a major impact on behavior.[39,40]

There has been great concern about how the revolution in molecular genetics will affect individuals with, or at-risk for, genetic diseases, as well as their families and society at large. One issue is the effect of a positive test result on an individual who must then live with the knowledge of a certain fate. Huntington's disease is, in some respects, a "worst case scenario," due to the current lack of an effective treatment. Our preliminary data suggest that presymptomatic testing can be done safely in a supportive setting with appropriate long-term monitoring of test-positive cases. Careful screening is important to avoid testing persons who are obviously psychologically vulnerable and to be certain that at-risk individuals who request testing are doing so without coercion from their families or others.

A second concern is the accuracy of genetic linkage tests and the nature of

the information derived from them. The fact that HD is an autosomal dominant condition with complete lifetime penetrance allows the currently available test to be 95% to 99% predictive in most families. Tests for disorders that are not fully penetrant will not likely be as conclusive, and it will be difficult to interpret a "positive" test outcome. Pretest counseling is essential to educate people about the genetic aspects of such tests, the concepts of risk and probability, and how to interpret personal risk to make decisions about the future.

A third concern is the possible misuse of information available through genetic testing. Previous experience with insurance companies denying coverage to those who test positive for human immunodeficiency virus antibodies[41] and employment discrimination based on screening for the sickle cell trait[42,43] has shown that concern for privacy and confidentiality is indeed justified. Huntington's disease is so rare, however, that our experience is not likely to tell us much about the effects of genetic tests on the practices of employers or insurance companies in the way that a genetic test for a common disease, such as schizophrenia or heart disease, is likely to do. The fear is that employers and insurers will require testing for persons with a family history of these and other conditions that require costly medical care. If this occurs, the possibility exists of unreasonable discrimination on the basis of one's genetic makeup. In the absence of knowledge of how insurance companies and employers are going to handle this information, individuals may be well advised to be cautious about disclosing either their participation in testing or test results.

The cost of predictive DNA diagnostic tests is another concern. One fear, currently a reality with HD testing as it moves from the research phase into clinical use, is that only individuals with sufficient means to pay for these tests outright will be able to make use of testing. Only by direct, out-of-pocket payment will they be able to keep private their genetic status and avoid disclosing their genetic vulnerability to third-party payers. This situation is unlikely to last long, however. If the gene for HD is found, the cumbersome and expensive linkage testing will soon give way to a less expensive, more rapid, more accurate, and more accessible test. Whether more people will opt to pay out of pocket for this less expensive test is unknown.

As more disease-causing genes are identified, and as the number of DNA diagnostic (or risk-altering) tests increases, the need for public and professional education about this new medical technology escalates. Physicians and other health care providers will be forced to grapple with complex psychological, social, and ethical issues in the application of molecular genetic technology to clinical practice.

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Knowledge, Attitudes, and Reported Practices of Medical Students and House Staff Regarding the Diagnosis and Treatment of Alcoholism

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Although alcoholism is prevalent in both general and inpatient populations, barriers to its timely diagnosis and effective treatment exist. These are often attributed to physicians' inadequate understanding and skill development and negative attitudes toward the disease. All Johns Hopkins' medical students and house staff, during 1986 through 1987, received a self-administered survey of their attitudes, skills, perceived role responsibility, knowledge, and reported practices with regard to alcoholism. Results indicate a strong relationship between perceived role responsibility, confidence in skills, and reported screening and referral practices among students and house staff. Knowledge levels strengthened the association between skills and practices for medical students. House staff perceived less of a responsibility for screening than medical students. There was a trend toward lower confidence and more negative attitudes among house staff than medical students. The results point to areas where educational interventions can be improved to enhance quality of care and outcomes for this major chronic disease.

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A GROWING body of research indicates that there is a high prevalence of alcoholism and alcohol abuse in the general population and specific patient populations.[1-5] Yet physicians often do not diagnose and effectively treat the patient with alcoholism, possibly because of inadequate understanding and skill development, as well as misbeliefs and negative attitudes with regard to the diagnosis and treatment of alcoholism.[6-11]

Despite the urgent need for training in alcohol issues, this problem has received inadequate attention in the curricula of medical schools and residency training programs. Recent initiatives[12] aimed at reducing the deficiencies of medical education in this area have revealed an increase in the number of hours devoted to alcoholism.[13] Nevertheless, curriculum inadequacies remain.

To address this problem, The Johns Hopkins Medical School and Hospital have developed an institution-wide program among whose goals is the enhancement of medical education and medical treatment for alcohol abuse and dependence. This article focuses on the medical education rather than the treatment component of the program (Figure) and, in particular, provides baseline data from a survey of medical student and house staff knowledge, beliefs (perceived role responsibility), confidence (perceived skill), attitudes, and reported practices regarding alcoholism. An improved understanding of each of these characteristics among medical students and house staff, as well as the interrelationships of these variables, was viewed as important to achieving program goals.

The specific hypotheses being investigated are as follows: (1) There is a positive association between increased knowledge, appropriate attitudes, perceived enhancement of skill level, and acceptance of a physician role in early diagnosis and treatment of alcoholism. (2) There is a positive association between perceived skill level, belief in physician's role responsibility, and reported practice in regard to screening, diagnosis, and treatment of alcoholism.

METHODS

Beginning in 1986, surveys of medical students and house staff at The Johns Hopkins Medical School and Hospital

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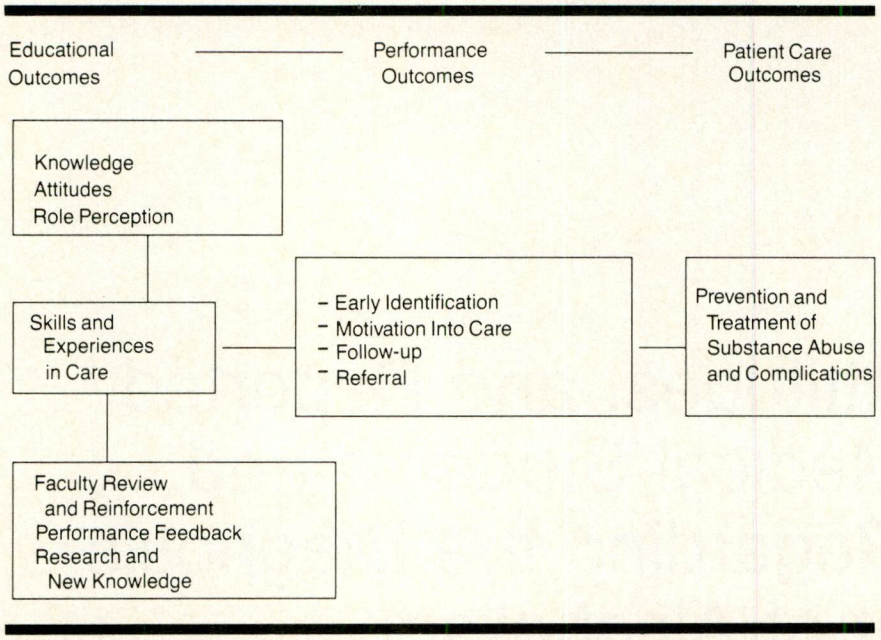

Model of educational process.

were conducted to ascertain baseline knowledge, beliefs about role responsibility, attitudes, perceived skills, and reported practices regarding alcohol abuse and dependence. These data were viewed as important for targeting areas of need in the curriculum and as a baseline against which to evaluate future changes.

The target groups for this self-administered survey were all medical students, as well as all house staff in the departments of internal medicine, surgery, obstetrics and gynecology, psychiatry, and neurology. Because of the sensitive nature of the questions, surveys were completely anonymous. Although this compromises our ability to follow up individuals, the guarantee of anonymity was essential in conducting the study. For house staff, such anonymity required the exclusion of demographic information because of the small numbers of residents in some departments. Anonymity was important to enhance both the validity of the responses and the response rates.

Response rates were also enhanced by the use of different methods for distribution of the surveys to each group. First-year medical students were surveyed during their orientation, as part of a preventive health screen. As a result, we obtained a response rate of 100%. Second-year medical students were surveyed during one of their basic science classes, with the endorsement of the professor, resulting in an 87% response rate. The small nonresponse rate was primarily attributed to absenteeism from class, rather than refusal to participate.

Third- and fourth-year students are dispersed in their clinical assignments throughout several hospitals, making access more difficult. Therefore the survey had to be mailed to their homes, with self-addressed envelopes enclosed. Follow-up telephone calls were then conducted to remind students about the survey. In addition, the third-year class officers called to motivate their classmates to complete and return the questionnaire. Fourth-year students' questionnaires were collected as part of an exit interview in the registrar's office. As a result of these efforts, we obtained a response rate of 54% and 88% from the third- and fourth-year students, respectively.

House staff surveys were administered or distributed at group events such as grand rounds or weekly meetings. This required the assistance and endorsement of the chief resident, as well as the department chairman. Questionnaires were returned to the chief resident's office.

Table 1 summarizes the response rates for each group of respondents. As noted, response rates were higher among medical students (82% overall) and varied by clinical department among house staff (56% overall). Although the anonymity of the questionnaires precluded a comparison of demographic characteristics of respondent vs nonrespondent *house staff,* we were, however, able to compare medical student respondents against the demographic distribution of their entire class. This information was obtained from the registrar. Because of the high response rate in years 1, 2, and 4, there were no significant differences in demographic characteristics between respondents and nonrespondents. Respondents in the third-year class, for which the response rate was lowest, were disproportionately female and white. However, no age differences were found.

The items chosen for these surveys were adapted from our own prior work (G.G., J.A.M., L.R.B., unpublished data, 1988), and that of other investigators,[14-16] to enhance the reliability and validity of the data, as well as its generalizability and comparability to other institutions. The house staff survey was similar to that of the medical students, except there is more concentration on reported practices. For the analyses presented herein, a few salient items were selected from each of the categories in the survey.

Knowledge was assessed using multiple-choice and true-or-false questions that fell into four areas: epidemiology and natural history, physiology and biochemistry, diagnosis and treatment, and prevention. All knowledge items reflected fundamental objectives of the curriculum and were expected to be learned by all students. Difficulty level, therefore, was viewed as comparable across knowledge categories. A three-step process of recoding the knowledge items was employed. First, each item was dichotomized into "correct" vs "incorrect." Second, a composite score was calculated, representing the percent of correct responses in each knowledge area. Third, the composite scores were dichotomized into "at least 70% correct" vs "less than 70% correct."

All students were asked about their attitudes as well as their perception of the physician's role in identification and treatment of this condition. Our investigation was interested in how students in *all* years perceived their role and how this might change, appreciating that those in years 1 and 2 have had no clinical experience. For those students in years 3 and 4, we did inquire about their reported practices. These students *are* required to assess alcohol consumption and abuse status in their patient histories and to make recommendations regarding the need for follow-up, referral, and consultation. Nevertheless, students are not *responsible* for the clinical decisions and do this under the aegis of both house staff and attending physicians.

Responses to questions about role responsibility for screening, referral, and

follow-up in the student survey consisted of "no responsibility," "very little responsibility," "moderate responsibility," and "major responsibility." The house staff survey also included a middle category called "some responsibility." Student and house staff responses were dichotomized into "major responsibility" vs "not major responsibility."

Response categories for reported screening practice included "never," "sometimes," "frequently," and "always." These responses were dichotomized into "frequently" vs "not frequently."

Confidence in (perceptions of) clinical skills was measured on a five-point scale in both the student and house staff surveys, with 1 reflecting low confidence and 5 reflecting high confidence. However, in a manner similar to the role responsibility items, confidence items were then dichotomized as "high/moderate confidence" vs "lower confidence."

Items that measure attitudes were drawn from scales developed by Marcus[14] and Chappel et al.[17] Attitudes were investigated in regard to alcoholism as a disease entity, types of individuals affected, and treatability. Each subscale consists of three to seven items, each coded according to a four-point scale ranging from "strongly disagree" to "strongly agree." We conducted both item analyses and scale analyses, to determine how well these scales clustered in our population. We ultimately used four of the Marcus subscales (with one item deleted from the original subscales) and a combined version of the subscales of Chappel et al. Table 2 indicates the items and reliability coefficients for all five subscales.

Table 1.—Questionnaire Return Rate

	Actual No. of Individuals in Cohort	No. of Surveys Returned	% Returned
	Students		
First year	121	121	100
Second year	114	99	87
Third year	116	63	54
Fourth year	117	103	88
Third and fourth year combined	233	166	71
Total	**468**	**386**	**82**
	House Staff		
Medicine	93	44	47
Psychiatry	30	27	90
Neurology	21	14	67
Obstetrics/gynecology	28	15	54
Surgery	54	26	48
Total	**226**	**126**	**56**

RESULTS

Knowledge

Levels of knowledge were examined in regard to epidemiology and natural history, physiology and biochemistry, diagnosis and treatment, and prevention.

Based on the percentage of "correct" responses, relatively high and similar levels of knowledge were found in the areas of epidemiology (except for first-year students) and prevention for both students and house staff (Table 3). Levels of knowledge in diagnosis and treatment were slightly lower and similar for students and house staff. Knowledge levels were lowest for physiology and biochemistry.

Attitudes Toward Alcoholism

Medical student and house staff attitudes are noted in Tables 4 and 5. Table 4 displays the mean scores on the attitude subscales for third-year students, fourth-year students, and house staff separately. The further along individuals are in their training, the more negative their attitudes. Fourth-year students feel more negative than third-year students and house staff feel more negative than fourth-year students.

Table 5 indicates that the percentage of respondents with positive attitudes does not differ between house staff and students. However, of respondents with *negative* attitudes, house officers are more likely than students to believe that alcoholics lack willpower ($P<.08$), that they tend to be unemployed ($P<.02$), and that rehabilitation does not work ($P<.03$).

Table 2.—Items and Reliabilities for Each Attitude Subscale

Subscale	Cronbach's α
Weak-willed person	.75
Alcoholics lack willpower	
Alcoholics are morally weak	
Alcoholics are spineless	
Low social status	.53
Alcoholics are unemployed	
Alcoholics are uneducated	
Alcoholics' parents are not abstainers	
Not an illness	.76
Alcoholism is a habit not an illness	
Alcoholism is the alcoholic's own fault	
Alcoholism is not a disease	
Poor prognosis	.54
Alcoholics drink for fun	
Treatment rarely helps	
Rehabilitation does not work	
Treatability	.74
An involved family helps treatment	
Group therapy helps treatment	
Paraprofessionals help treatment	
Outpatient long-term care is necessary	
Drug treatment depends on urine screening	
Drug addiction is treatable	
Alcoholism is treatable	

Role Responsibility (Beliefs)

Acceptance of responsibility for screening, referral, and follow-up regarding alcoholism are shown in Table 6. (Data were not collected on referral from first- and second-year students because they are neither exposed to nor responsible for situations in which referral occurs.)

There is wide variability among both medical students and house staff regarding their role in the care of patients with alcohol abuse. The percentage of respondents who felt they had a *major* responsibility for screening and referral was highest among third-year students (68% and 78%, respectively), while the percentage who felt a major responsibility for follow-up was highest among *first*-year students (61%). However, after the third year, the percentage who feel a major responsibility in all three areas progressively decreases (to 49%, 42%, and 7%, respectively). Only a minority of medical students and house staff perceived follow-up as a major responsibility. When broken down by specialty, this finding was even more pronounced among surgical than medical house officers.

Perceived Skill Level (Confidence)

Analyses of perceived confidence in skills in the area of screening, referral, and follow-up are reported in Table 7. These data were not collected from first- and second-year students because they have not yet been taught clinical skills.

The percentage of respondents who reported feeling confident was highest for screening, moderate for referral, and lowest for follow-up. In none of these areas did confidence significantly

Table 3.—Mean Knowledge Scores by Category and Year of Training

Year of Training	Mean Knowledge Scores in 4 Areas, %			
	Epidemiology (7 Items)	Physiology and Biochemistry (4 Items)	Diagnosis and Treatment (6 Items)	Prevention (4 Items)
First-year students (N = 121)	60	36	. . .	76
Second-year students (N = 99)	80	41	66	75
Third-year students (N = 63)	83	44	70	73
Fourth-year students (N = 103)	80	43	69	77
House staff (N = 126)	84	40	70	72

Table 4.—Mean Attitude Scores by Category and Year of Training

	Mean Attitude Scores in 4 Areas			
	Character Weakness*	Prognosis*	Nature of Disease*	Treatability†
Third-year students (N = 63)	1.18	1.80	1.93	3.34
Fourth-year students (N = 103)	1.72	1.76	1.80	3.31
House staff (N = 126)	2.62	2.64	2.59	2.49
F statistic	65.23	132.99	68.88	58.8
P value	<<.01	<<.01	<<.01	<<.01

*Negatively worded items, so the higher the score the more negative the attitude.
†Positively worded items, so the higher the score the more positive the attitude.

Table 5.—Association Between Attitudes and Year of Training

	Prognosis/ Rehabilitation		
	Positive, % (N = 199)	Negative, % (N = 21)	*P*
Students	48	24	<.03
House staff	52	76	
	Employability		
	Positive, % (N = 203)	Negative, % (N = 16)	*P*
Students	48	19	<.02
House staff	52	81	
	Character Weakness		
	Positive, % (N = 165)	Negative, % (N = 54)	*P*
Students	49	35	<.08
House staff	51	65	

increase with additional years of clinical experience. However, confidence in follow-up actually decreased.

Association Between Variables

To address the major study hypotheses, relationships between knowledge level, attitudes toward treatment, perception of role responsibility, perceived skill, and reported practice were investigated using χ^2 tests of association. For these analyses, we combined third- and fourth-year students, as the results in each class were similar.

The relationship between perceptions of skill level (confidence) and role responsibility in regard to alcoholism is displayed in Table 8. A significantly greater percentage of those reporting high confidence in screening (as opposed to low confidence) perceived that they had a major responsibility for screening. The pattern is the same for both medical students (70% vs 45%; $P<.01$) and house staff (58% vs 18%; $P<<.01$), although the association is stronger among house staff. The pattern is similar for referral behavior. A greater percentage of those who felt highly confident at referral perceived that they had a major responsibility for referral.

Further analyses examined the association between perceived responsibility for screening and referral and *an estimate of actual* screening and referral practice (Table 9). There is a positive association between perceived responsibility and reported practice, particularly for house staff. Eighty-two percent of house staff who perceive a major responsibility for screening report a high frequency of screening, as contrasted to only 47% who do not perceive this major responsibility ($P<<.01$). Similar results are noted for referral practice. Results from medical students are similar for screening ($P<.02$), but there is no difference in referral practice.

A similar analysis was conducted to examine the association between *confidence* (perceived skill) in screening and referral and reported practice and demonstrated similar results (Table 10). Seventy-one percent of house staff who are highly confident (vs 45% with low confidence) report a higher estimated frequency of screening ($P<.01$). Respective results for medical students were 70% vs 46% ($P<.01$). Similar results were noted for referral practice (house staff, 63% who are highly confident vs 39% with low confidence [$P<.01$]; students, 40% vs 22% [$P<.02$]).

Other analyses indicate a similar type of relationship between confidence, perceived responsibility, reported behavior, and attitudes toward treatment among house staff. Those who believe that rehabilitation does not work (ie, they believe that alcoholic patients have a poor prognosis) are significantly less likely to report frequent referrals (25% vs 75%; $P<.02$).

Knowledge levels alone, in any of the four areas, were not significantly associated with perceived responsibility for screening, referral, and follow-up, perceived confidence in clinical skills and reported behavior in these areas, and attitudes toward prognosis and treatment for either students or house staff.

Among house staff, controlling for knowledge caused no change in the relationships among these variables. That is, regardless of how knowledgeable house staff were about diagnosis and treatment, the associations between perceived responsibility, perceived confidence in clinical skills, and reported behavior remained strong. However, for medical students, high levels of knowledge strengthened most of the associations and low levels of knowledge weakened them, suggesting an interaction.

COMMENT

As part of a broad institutional effort, this article has presented initial findings related to the medical education process. The results of our surveys indicate a wide variation in knowledge, beliefs about role responsibility, perceived skills, attitudes, and reported practices in regard to the diagnosis and treatment of alcoholism. There is, moreover, a strong correlation between perceived confidence in skills, perceived role responsibility, attitudes toward alcoholism, and reported screening, treatment, and referral practices. There was no evidence of increased skills or greater acceptance of role responsibility in house staff compared with medical students. Notably, only a minority of house staff perceived either screening, referral, or follow-up as a major role responsibility. This finding is more pronounced among surgical than medical house officers, which is consistent with

Table 6.—Percentage Who Perceive Responsibility as Major in Each Year of Training

Year of Training	% Accepting Major Responsibility		
	Screening	Referral	Follow-up
First-year students (N = 121)	26	. . .	61
Second-year students (N = 99)	63	. . .	37
Third-year students (N = 63)	68	78	18
Fourth-year students (N = 103)	59	74	18
House staff (N = 126)	49	42	7*

*Examining differences between specialties was constrained by small numbers in psychiatry, neurology, and obstetrics and gynecology. However, there were significant differences between medicine and surgery, with medical house officers more likely to perceive a major role than surgical house officers. Although these departments had low response rates, and responders tend to have more positive attitudes and beliefs, the data still show a general need for improvement.

Table 7.—Percentage Who Report Feeling Highly Confident in Each Year of Training

Year of Training	% Who Report High Confidence		
	Screening	Referral	Follow-up
Third-year students (N = 63)	65	49	22
Fourth-year students (N = 103)	73	52	24
House staff (N = 126)	69	57	16*

*Examining differences between specialties was constrained by small numbers in psychiatry, neurology, and obstetrics and gynecology. However, this was done in medicine and surgery, with no significant differences in confidence found by specialty. Although these departments had low response rates, and responders tend to have more positive attitudes and beliefs, the data still show a general need for improvement.

Table 8.—Association Between Perceived Skill (Confidence) and Perceived Responsibility for Screening and Referral

Perceived Responsibility	Confidence Level					
	Students			House Staff		
	High, %	Low, %	P	High, %	Low, %	P
Screening						
Major responsibility	70	45	<.01	58	18	<<.01
Little responsibility	30	55		42	72	
Referral						
Major responsibility	87	62	<<.01	57	23	<<.01
Little responsibility	13	38		43	77	

reports of their actual performance behavior.[11] Follow-up skills and perceived role responsibility are low among both students and house staff.

Although this is a cross-sectional, not a prospective, study, the cohort nature of the design strengthens our ability to compare groups of respondents and draw conclusions about changes over time. The strength of "synthetic" cohort studies is that they follow successive groups of respondents through formal institutions and are based on the assumption that one cohort differs in only minor ways from its contiguous cohorts. To control for whether variables such as background characteristics were possible mediators of the outcomes of interest, sociodemographic, personal alcohol use, and family history information and information on changes in Hopkins admissions criteria over time were obtained. These revealed that, in fact, the classes were uniform at baseline.

The main limitations of the study include selection bias, possible measurement error, and generalizability. In terms of response rates, there was no selection bias in years 1, 2, and 4. However, there was a larger than desired refusal rate among third-year students, with those who responded being disproportionately female and white. Since the biggest differences found were between house staff and students, not between third- and fourth-year students, the high refusal rate among third-year students was not a problem in interpreting tests of hypotheses that compared fourth-year students, for whom the response rate was adequate, and house staff.

There was considerable variability in response rate by house staff specialty. Except for psychiatry, the response rates were not sufficient to be confident about the representativeness of the sample. However, assuming that those more interested and positive toward this problem were more likely to respond, which would be consistent with prior work in the field, and might have even expressed some social desirability in their self-report, the results still demonstrate considerable negativity in attitude toward alcoholism and toward acceptance of a primary role in treatment and follow-up.

To minimize problems having to do with measurement validity, an attempt was made to establish the psychometric properties of all subscales prior to analysis. Only the subscales that demonstrated sufficient reliability and validity were used in the correlational analyses.

Despite these limitations, the results lend support to the notion that the clinical environment in which physicians are trained might produce negative effects. While this was not specifically addressed in our study, potential factors related to the negativity of attitudes include the lack of a more appropriate curriculum in past years, which would particularly affect house staff; exposure mainly to end-stage alcoholism, with little chance for adequate control; and exposure to faculty who tend not to be well educated and skilled in the diagnosis and treatment of alcoholism and, therefore, are not likely to be good role models for house staff or student development.

Based on our results, specific strategies and activities have been developed to enhance skills and perceptions of role responsibility and decrease negative attitudes among medical students, house staff, and attending physicians regarding the early diagnosis and effective treatment of alcoholism. With medical students, these activities have been integrated into all years of medical school, with concentration in the second and third years through courses in clinical skills and the clerkship in internal medicine. Emphasis is placed on discussion of the high prevalence of alcoholism in the patient population to which students are exposed; on skill development in the use of state-of-the-art screening approaches (eg, use of the CAGE questionnaire[18]); and on structured patient care experiences with faculty review in small groups to reinforce and model effective diagnostic and treatment approaches. Use of and linkage to substance abuse counselors for longer-term follow-up is also demonstrated and modeled by faculty. A similar approach has been implemented with house staff. Specific approaches with faculty attending physicians include the following: (1) Feedback of findings from a companion study[11] that investigated the prevalence and practice patterns relevant to alco-

Table 9.—Association Between Perceived Responsibility and Reported Frequency of Screening and Referral

Reported Frequency	Perceived Responsibility					
	Students			House Staff		
	High, %	Low, %	P	High, %	Low, %	P
Screening						
High	69	51	<.02	82	47	<<.01
Low	31	49		18	53	
Referral						
High	31	31	.98	77	34	<<.01
Low	69	69		23	66	

Table 10.—Association Between Perceived Skill (Confidence) in and Reported Frequency of Screening and Referral

Reported Frequency	Confidence Level					
	Students			House Staff		
	High, %	Low, %	P	High, %	Low, %	P
Screening						
High	70	46	<.01	71	45	<.01
Low	30	54		29	55	
Referral						
High	40	22	<.02	63	39	<.01
Low	60	78		37	61	

hol abuse in hospitalized patients (in which about 40% of individuals with alcohol abuse were diagnosed and only about 20% adequately treated) in the hopes of motivating physicians to improve practice in their own patients. (2) A special three-phase seminar series (continuing medical education) reviewing the aforementioned findings and providing state-of-the-art interviewing and diagnostic approaches (eg, the CAGE questionnaire), as well as approaches to enhance patient motivation for entering care. Emphasis is also given to enhancing opportunities and skills for faculty to provide appropriate role modeling for students and residents regarding early identification and diagnosis and motivation of patients to enter and stay in care. (3) A core group of the primary teaching faculty are brought together periodically to maintain up-to-date knowledge and skills in the identification and successful treatment of alcohol abuse. (4) Special grand rounds and lectureships are held to reinforce up-to-date approaches in treating alcohol abuse effectively, as well as to present up-to-date research. This type of approach has been successfully institutionalized as part of the curriculum.

On a national level, Federal Career Teaching[12] and fellowship training[19] programs have been developed to improve medical education in alcoholism and drug abuse, but these have had varying degrees of success. While the Federal Career Teaching program was instrumental in helping to train individuals devoted to this area, it has not had sufficient effect either on dissemination in the individual's own institution or on training of medical students and house staff generally. More recently, there has been the development of fellowship training programs in this area. Many of these programs are still too young to know what their long-term effects will be. At this point, however, the majority are centered in psychiatry. Therefore, it is still incumbent on medical educators to attempt to enhance the broad base of education and training in this area for all medical students and house staff in addition to psychiatry.

This study has developed and implemented a methodology to improve our understanding of the educational process regarding the diagnosis and treatment of alcoholism. It suggests ways of both targeting educational interventions to enhance practice competencies in medical students and house staff and improving approaches to evaluate their effectiveness. Cohort analyses over time will allow for assessment of changes at the individual as well as the institutional level. Although this study was conducted at only one institution, considerable evidence suggests that students and house officers at other medical schools are likely to demonstrate similar responses to the diagnosis and treatment of alcoholism.[15]

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Unique Aspects of Heart and Lung Transplantation Exhibited in the 'Domino-Donor' Operation

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During the past 2 decades various refinements in heart and lung transplantation procedures have taken place. Improved preservation methods, new immunosuppressive medications, and advances in technical capabilities have allowed innovative procedures to be performed. In May 1987 the first "domino-donor" operation was performed in the United States. A 28-year-old man with cystic fibrosis and end-stage lung disease received the heart and lungs of an anonymous donor after he donated his heart to a 38-year-old man with end-stage ischemic cardiomyopathy. The technical and logistical aspects of this transplantation procedure are described herein. Other unusual features of this case that are discussed include heart-lung transplantation for a patient with cystic fibrosis, the use of cardiopulmonary bypass to allow lung procurement and transplantation across long distances, and the current role of heterotopic cardiac transplantation.

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THE DECADE of the 1980s has witnessed many developments in cardiac transplantation: the recognition of heart transplantation as accepted therapy for selected patients with end-stage heart disease,[1] the rapid proliferation of hospitals performing cardiac transplant procedures, the first successful heart-lung transplant operation,[2] and the use of various artificial devices as interim support for potential recipients who await heart transplantation.[3] In addition, refinement and experience in heart transplantation has resulted in a series of innovations, including the development of new techniques of organ preservation and transplantation; the extension of recipient selection criteria for heart-lung transplantation to include selected patients with cystic fibrosis; and most recently, the use of hearts from recipients undergoing heart-lung transplantation for individuals needing heart replacement. This article describes the first "domino-donor" operation performed in the United States (Fig 1) and illustrates the clinical application of recent developments in heart and lung transplantation.

REPORT OF CASES

Heart-Lung Recipient/Heart Donor

CASE 1.—A 28-year-old man with cystic fibrosis was initially evaluated for heart-lung transplantation in September 1984. At that time he met the clinical and social criteria for transplantation. Chest roentgenogram demonstrated marked apical scarring (Fig 2). However, although moderately symptomatic, he was able to maintain a daily work schedule without significant problems. Over the next 2½ years he became more dyspneic, and in April 1987 his name was placed on the active transplant list. Clinical examination of his heart was unremarkable, and echocardiography demonstrated only mild right ventricular hypertrophy with no other abnormalities. In our assessment his heart was thought to be an ideal transplant for an individual with elevated pulmonary vascular resistance. After appropriate discussion with the patient, he agreed to donate his heart at the time of his heart-lung transplantation.

An appropriate heart-lung donor was identified and the graft was procured at a distant hospital using cardiopulmonary bypass and deep hypothermia and transported in cold storage.[4] Total ischemic time was 4 hours 56 minutes.

Postoperatively, the patient's arterial blood gas values were excellent, and he was extubated on the second postoperative day. His immunosuppressive regimen consisted of cyclosporine (10 mg/kg) and azathioprine (1 to 2 mg/kg). Prednisone (1 mg/kg) was added 2 weeks later. He was treated with intravenous steroids for two episodes of pulmonary rejection (postoperative days 12 and 21).

The patient's postoperative course was complicated by significant epigastric pain that developed on postoperative day 20. Evaluation of this complaint was significant for the presence of a single gallstone, and, because of persistent abdominal pain, he underwent cholecystectomy on the 78th postoperative day. His recovery was uncomplicated and he subsequently was discharged on the 84th postoperative day, 12 weeks after his initial operation.

The patient did well during the first 3 months after discharge. However, in December 1987 he developed symptoms of shortness of breath and underwent bronchoscopy. Transbronchial biopsy findings were consistent with rejection of the transplant, and his prednisone dose was increased to 100 mg for 3 days and then tapered. Bronchoscopy in January 1988 revealed a continued rejection reaction, and he was treated with 3 g of methylprednisolone sodium succinate followed by a tapered dose of prednisone. Follow-up bronchoscopy in February 1988 demonstrated persistent rejection, and he was hospitalized for OKT3 monoclonal antibody therapy. The patient died in July 1988 from progressive pulmonary failure while awaiting a second heart-lung transplantation. Postmortem examination revealed pulmonary findings consistent with bronchiolitis obliterans, a presumed final stage of a chronic rejection reaction.

Heart Recipient

CASE 2.—A 38-year-old man experienced an anterior myocardial infarction in 1983. He did well during the subse-

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quent 2 years but developed increasing signs and symptoms of congestive heart failure in 1985. He was referred to The Johns Hopkins Hospital, Baltimore, for consideration of heart-lung transplantation because of the presence of moderate pulmonary hypertension. Right-sided heart catheterization at this time revealed a pulmonary artery systolic blood pressure of 90 mm Hg and a calculated pulmonary vascular resistance of 7.1 Wood units. The pulmonary vascular resistance was somewhat reversible (to 5 to 6 Wood units) with oxygen administration and sodium nitroprusside therapy. He was placed on the transplant waiting list with the understanding that he would need to undergo recatheterization at the time of operation. It was our intent to find a donor who was larger in weight to provide the best chance of success if the donor heart was placed in an orthotopic position.

When a compatible heart-lung donor was identified for the patient with cystic fibrosis, consideration was given to using the heart from the patient with cystic fibrosis for this recipient. Since the heart from the cystic fibrosis patient had right ventricular hypertrophy, it could be considered a "conditioned graft" and potentially would be ideal for a recipient with borderline elevated pulmonary vascular resistance. After receiving informed consent from both patients, the double transplant operation took place on May 11, 1987, in adjacent operating rooms.

Although the right ventricular hypertrophy observed in the heart of the patient with cystic fibrosis potentially would have facilitated orthotopic transplantation, a right-sided heart catheterization of the heart recipient revealed a pulmonary artery systolic blood pressure of 100 mm Hg and a calculated pulmonary vascular resistance of 18 Wood units. A heterotopic heart transplant, therefore, was performed, with a total ischemic time of 3 hours 31 minutes.

Postoperatively, the patient made a smooth recovery. He required vigorous respiratory therapy and eventual bronchoscopy because of right lower-lobe atelectasis. Following bronchoscopy, however, the atelectasis cleared and he has had no further pulmonary problems. A biopsy sample obtained on the ninth postoperative day demonstrated moderate rejection. He was treated with intravenous methylprednisolone and a tapered dose of oral prednisone. Echocardiography demonstrated good donor heart function, with no opening of the graft aortic valve. The patient was prescribed a triple-drug immunosuppressive regimen (azathioprine, prednisone, and cyclosporine) and was discharged on postoperative day 18. He has done well subsequently and has had no further rejection episodes. He returned to full-time employment in September 1987. His pulmonary artery pressure continues to decline (Table 1).

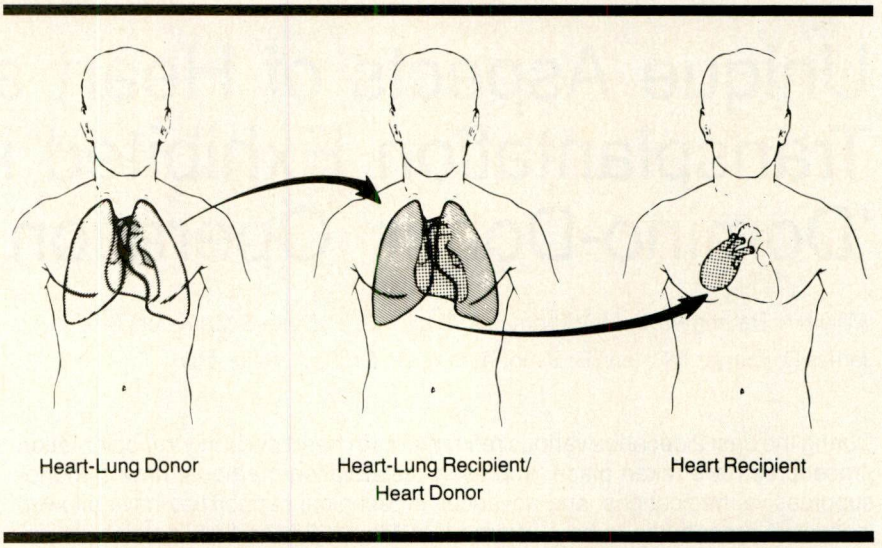

Fig 1.—Domino-donor operation (courtesy of The Johns Hopkins Hospital, Baltimore, Md).

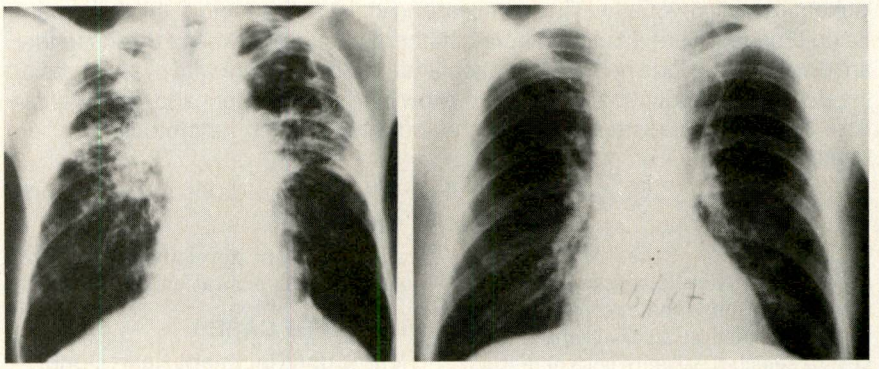

Fig 2.—Preoperative (left) and postoperative (right) chest roentgenograms of patient with cystic fibrosis.

METHODS

Technical Considerations in the Domino-Donor Procedure

The operative procedures employed in these two cases are similar to techniques described previously.[2] However, some modifications were necessary to ensure technical ease with each operation. Because the heart of the heart-lung recipient was itself a donor organ, the entire right atrium had to be included with the allograft. Unlike standard heart-lung transplant procedures in which a cuff of the right atrium remains for anastomosis, separate vena caval anastomoses were required. Right angle caval cannulas were helpful for separate cannulation of the superior and inferior vena cavae (Fig 3). The ascending aorta of the heart-lung recipient was divided at its midportion, and maximal aortic length of the heart-lung graft was obtained during the donor procurement operation. Anastomoses in the heart-lung transplant recipient consisted of trachea, superior vena cava, inferior vena cava, and aorta.

Donor heart preparation for heterotopic transplantation varied from the conventional orthotopic technique. The inferior vena cava and right-sided pulmonary veins were individually oversewn. The septum between the left-sided pulmonary veins was opened to provide one large orifice into the left atrium. Anastomoses in the heterotopic transplant procedure were left atrium, right atrium, aorta, and pulmonary artery. Since the length of the donor aorta was short relative to what would have been possible from a usual donor, a portion of Dacron graft (26 mm) was interposed between it and the native ascending aorta. Likewise, the donor pulmonary artery had to be lengthened with a Dacron tube graft (14 mm) for anastomosis to the native pulmonary artery (Fig 4).

Preservation Procedures

A number of techniques exist for the procurement, preservation, and transportation of the heart and lungs from the site of procurement to the recipient hospital. These techniques include autoperfusion of the heart-lung bloc,[5] pulmonary flush using a vasodilator,[6,7] and cooling of the donor heart and lungs with cardiopulmonary bypass.[8,9]

The autoperfused heart-lung model using substrate additives for myocardial preservation was first described by Robicsek and associates in 1963.[10] Successful distant procurement of heart and lungs by this method, with extracorporeal preservation times of 4½ to 6 hours, was reported in 1987.[11] However, due to the complexity of the procedure and a tendency for hypothermia to develop in the organs, the procedure has been replaced by less complicated techniques.

The first successful use of a high-volume pulmonary flush perfusate and prostaglandin infusion was reported in 1987 by Baldwin et al.[7] They reported the successful transplantation of the heart and lungs following an ischemic time of 3 hours 45 minutes. The use of epoprostenol, another potent pulmonary vasodilator, in combination with a single-flush technique also has been used successfully for the clinical procurement of the heart and lungs for transplantation.[6]

The efficacy of the various techniques for lung preservation has been compared in an experimental setting. Cardiopulmonary bypass with deep hypothermia was compared with flush perfusion of the lungs with Euro-Collins solution by Wahlers et al.[12] After 6 hours of preservation, pulmonary vascular resistance was the only measurement that was significantly lower in the group of organs preserved by extracorporeal circulation. This suggests that lung preservation may be superior using this method. Fraser et al[13] evaluated autoperfusion, extended pulmonary flush with prostaglandin administration, and cardiopulmonary bypass with profound hypothermia in a 4-hour bovine preservation model. Although extravascular lung water and histological score were increased significantly in the extended flush/prostaglandin group, all methods seemed adequate for up to 4 hours of cardiopulmonary preservation.

Cardiopulmonary preservation and deep hypothermia also have been used extensively by the Harefield group. They recently reported on 110 patients using this distant organ procurement technique. Mean organ ischemic time was 173 minutes, with a range of 65 to 270 minutes. Immediate graft function was satisfactory in all but 2 patients.[9] Because cardiopulmonary bypass is a less complex and potentially more efficacious method for multi-organ procurement, it was chosen as our preferred method for heart-lung procurement in this case.

The equipment for cardiopulmonary bypass and profound hypothermia in multi-organ procurement is compact and easily transported in either an airplane or an ambulance (Table 2, Fig 5). The technique is as follows: an arterial cannula is placed into the right femoral artery for inflow and a two-stage venous cannula in the right atrium/inferior vena cava for outflow. Cardiopulmonary bypass is initiated, the donor is

Table 1.—Sequential Right-Sided Heart Catheterization Data Following Heterotopic Heart Transplantation

Characteristic	Date					
	October 1986	5/11/87*	5/21/87	6/8/87	11/23/87	4/25/88
Pulmonary artery pressure (systolic/diastolic)	90/38	100/40	68/10	74/32	58/25	42/28
Pulmonary vascular resistance, Wood units	7.1	18	. . .	7	5.3	5.4

*Date of operation.

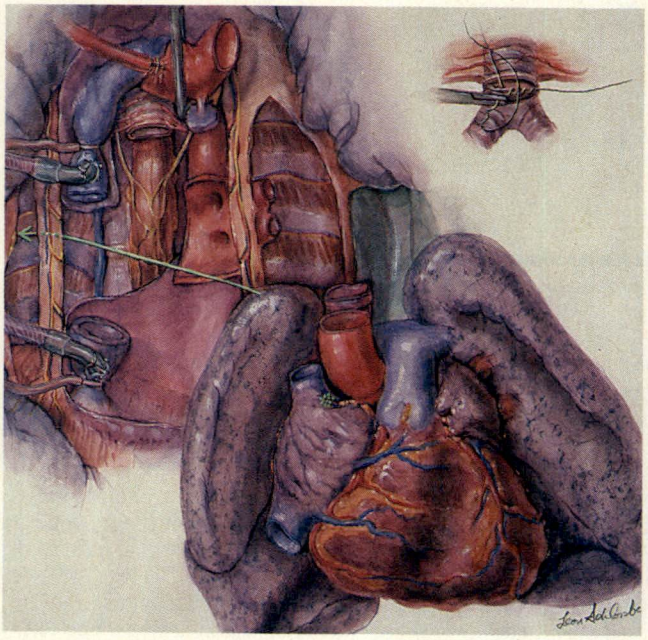

Fig 3.—Preparation of heart-lung recipient in domino-donor procedure illustrating right angle caval cannulas and removal of entire right atrium, necessitating caval anastomoses (reproduced with permission from Baumgartner WA, Reitz BA, Achuff SC, eds. *Heart and Lung Transplantation*. Philadelphia, Pa: WB Saunders Co. In press).

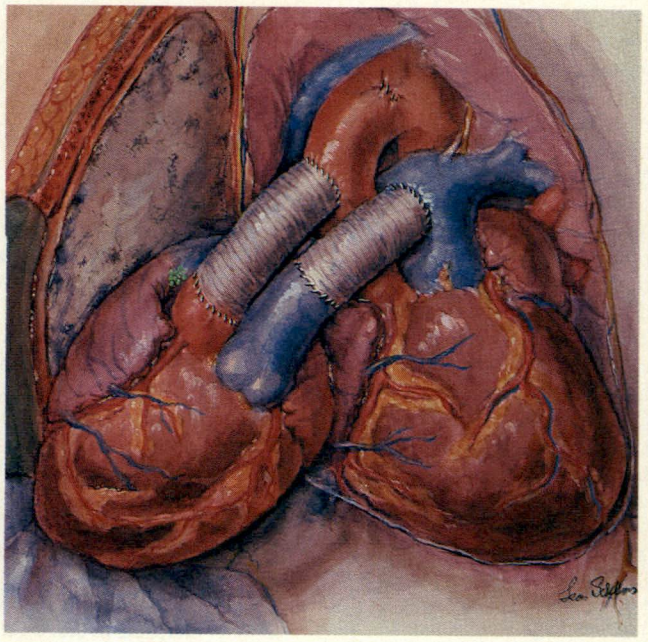

Fig 4.—Completion of heterotopic heart transplant procedure used in domino-donor operation illustrating use of interposition Dacron tube grafts to lengthen both donor aorta and pulmonary artery (reproduced with permission from Baumgartner WA, Reitz BA, Achuff SC, eds. *Heart and Lung Transplantation*. Philadelphia, Pa: WB Saunders Co. In press).

Table 2.—Components of the Portable Cardiopulmonary Bypass Circuit Used for Distant Heart-Lung Procurement

Modular roller pump*
Cooling system: utilizing a hardware store electric sump pump, ice water was pumped between a bucket and the oxygenator heat exchanger; a coil of 1/2-in copper pipe was placed in another bucket of ice distal to the pump to overcome waste heat imported to the coolant by the pump
Modified tubing pack†
Oxygen administered from an E-cylinder (supplied by the donor hospital)

*Sarns 2000, Sarns Inc/3M, Ann Arbor, Mich.

†TMP Tygon, William Harvey, C. R. Bard Inc, Billerica, Mass.

removed from the respirator, and the body temperature is lowered gradually. During the cooling period, preliminary mediastinal and abdominal organ dissection takes place. It takes approximately 30 minutes to systemically cool the donor organs to 10°C to 15°C. At this point, cardiopulmonary bypass is discontinued, allowing for an almost bloodless dissection of the various organs.

COMMENT

The concept of the domino-donor operation evolved as an extension of cardiopulmonary transplantation in specific situations and as a result of the need to maximize the number of donor organs. Since this initial procedure, five additional domino-donor procedures have been performed in the United States (Bartley Griffith, University of Pittsburgh; Nick Cavarrochi, Temple University; and Philip Oyer, Stanford University, oral communications, 1988). Thus, 12 patients have undergone heart-lung and heart transplantation. There have been three deaths due to infections acquired in the postoperative period but no deaths secondary to the domino-donor procedure itself.

Two weeks prior to our operation, Yacoub et al[14] performed two similar operative procedures in England and they subsequently have reported on the domino-donor operation in 16 patients. There were three deaths in the heart recipient group and two deaths among heart-lung recipients. They concluded that the use of hearts from heart-lung transplant recipients was feasible and particularly applicable for recipients with high pulmonary vascular resistance, as was contemplated in our case. Yacoub's group has performed the domino-donor operation in more than 30 patients (Ravi Pilai, oral communication, 1988).

As alluded to previously herein, one potential advantage of the procedure is the availability of a "conditioned" right ventricle for some recipients with lung disease. Theoretically, the mild right ventricular hypertrophy in the heart of a patient with cystic fibrosis might overcome the moderate pulmonary hypertension exhibited in some potential heart recipients.

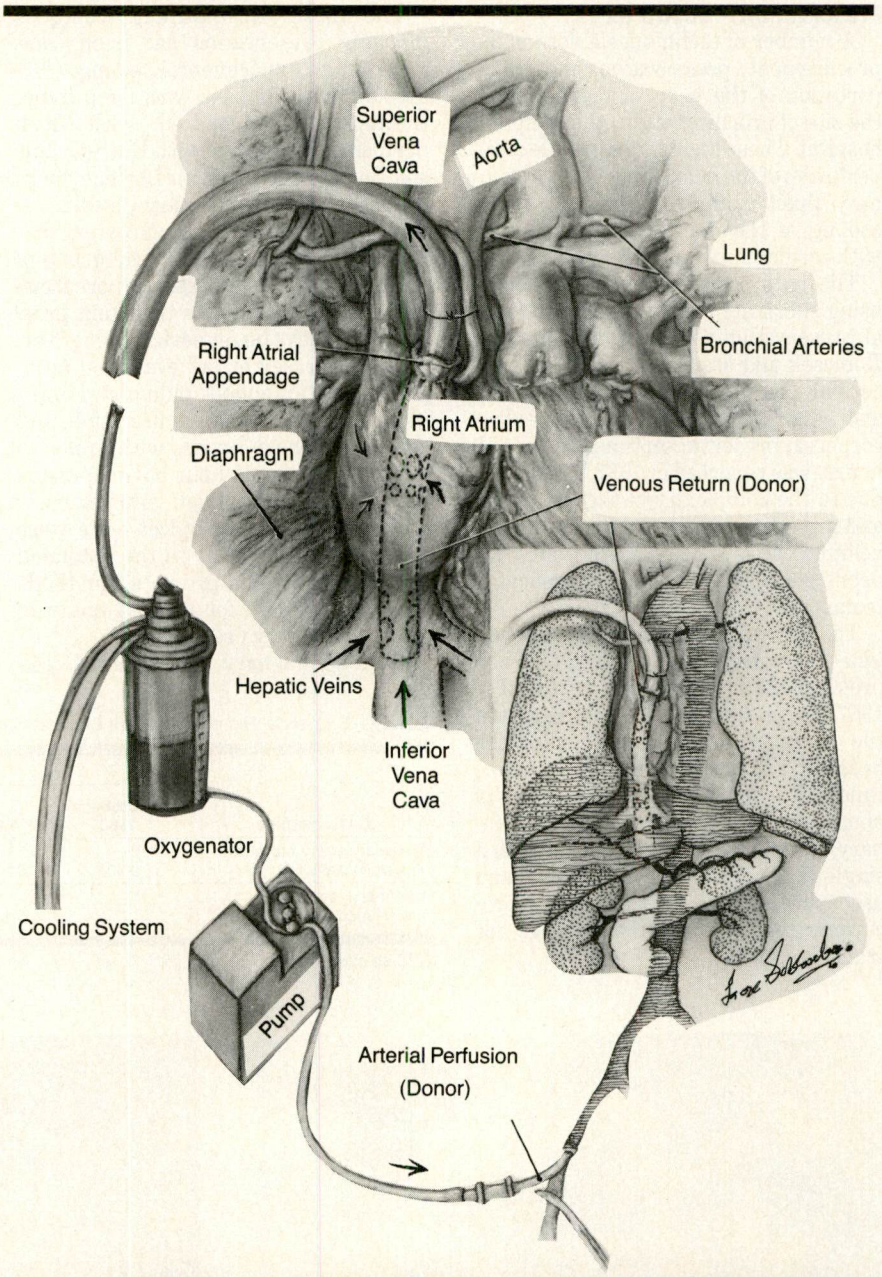

Fig 5.—Technique of cardiopulmonary bypass with profound hypothermia for multi-organ procurement (from Baumgartner et al[19]).

Other considerations when undertaking this procedure pertain to the proper evaluation of the living potential heart donor. This includes ABO compatibility, absence of a positive lymphocyte crossmatch in patients with demonstrated preformed antibody, evaluation for acute and occult infections including cytomegalovirus, hepatitis B surface antigen, herpes, and toxoplasmosis, negative human immunodeficiency virus serology, and evaluation of heart function. Heart function is determined by physical examination, chest roentgenogram, electrocardiogram, and echocardiogram or multiple gated acquisition examination. Finally, both patients must have a complete understanding of the procedure, and of course both heart-lung recipient (heart donor) and heart recipient must give informed consent.

Bilateral lung transplantation with preservation of the heart was not considered for our patient with cystic fibrosis because of a lack of experience with the bilateral transplant procedure, poor healing of the tracheal anastomosis with the bilateral procedure,[15] and the potential to use a conditioned heart for trans-

plant in a patient with elevated pulmonary vascular pressure. Satisfactory tracheal healing following combined heart-lung transplantation is attributed to preserved collateral circulation between the coronary and bronchial arteries in the subcarinal region. The Stanford group has demonstrated these coronary-bronchial collaterals to be present 1 to 6 months after combined heart-lung transplantation.[2,16]

Heterotopic transplantation as used in this report was described initially by the Capetown group in the early 1970s.[17] Although pulmonary hypertension was a primary indication for the heterotopic procedure, it was used for the majority of heart transplant recipients in the early Capetown experience. Present indications for heterotopic transplantation are increased pulmonary vascular resistance, small donor heart, potential reversibility of the cardiac malfunction in the recipient, and inadequate donor heart preservation. As the time to transplantation increases because of the limited number of donor organs, the recipient pulmonary vasculature should be reevaluated at either defined intervals or at the time of operation to determine the contemporary status of the pulmonary vasculature.

Although pulmonary hypertension has been the primary indication for the majority of heterotopic transplants performed recently, future application of this technique may be necessary to achieve maximum use of all donor hearts. Hearts that are smaller than desired for prospective recipients could be placed in the heterotopic position rather than be discarded. They would act either as interim support until a more suitably sized donor heart was available or as permanent auxiliary hearts.

Cystic fibrosis as an indication for heart-lung transplantation is not a novel idea. Patients exhibiting this disease have undergone heart-lung transplantation both in the United States and in England. Since the availability of suitable donor heart-lung blocs is severely limited, stringent selection criteria of recipients with cystic fibrosis should be applied. Only a limited number of patients will be able to benefit from the procedure. We suggest that a heart-lung recipient with cystic fibrosis also should be considered as a potential heart donor. However, in the advanced stages of disease, pulmonary failure with cor pulmonalae is not unusual, and these hearts could not be used in a domino-donor operation.[18]

Use of cardiopulmonary bypass for distant heart-lung procurement has a number of advantages. This technique also can be used for the successful procurement and transplantation of other organs including kidneys, liver, and pancreas.[19] In addition to providing a gradual diffuse cooling of all organs, it does not preclude use of further perfusion of the heart, kidneys, or liver with other crystalloid solutions. Preservation with this technique has been excellent in seven local procurements and three distant procurements (mean ischemic time, 281 ± 10 minutes) of lungs for transplant at our center. The efficacy of this technique has been documented extensively by Yacoub et al.[9] Organs harvested using this technique have shown equivalent or better function after preservation than after conventional techniques. Cardiopulmonary bypass provides excellent hemodynamic control of the donor during the harvesting procedure. It facilitates and expedites the abdominal dissection of organs during the period of cooling and exsanguination. Following cessation of cardiopulmonary bypass, the organs (cooled to 10°C to 15°C) can be harvested sequentially. With profound cooling, speed is not as important a factor as it is in conventional procurement procedures.

This particular case report illustrates many current techniques involved in cardiac transplantation and highlights advances that have occurred in transplantation during the past few years. The domino-donor transplantation operation may be one option for patients in whom the heart is not severely damaged from preexisting lung disease and for whom a heart-lung transplant might be more feasible. Lung preservation, previously a limiting factor in donor procurement, can be performed successfully by a variety of techniques, thereby potentially increasing the number of heart-lung donors. The heterotopic transplant procedure may be more widely applied to maximize the utilization of all available donor hearts. The application of the domino-donor operation, however, will be limited by the number of suitable heart-lung recipients and by availability of donor organs.

The domino-donor transplant procedure does prompt an ethical question: Does this operation put either one of the patients at increased risk, and if so, is this risk greater than that with other transplant options? The experience in the United States as well as the extensive experience by the Harefield group demonstrate the efficacy and safety of this type of procedure and suggest that the risks are no greater.

Finally, a dedicated group of individuals at the transplant center should have experience in all facets of transplantation to facilitate the successful outcome of these somewhat complicated procedures. The techniques of transplantation illustrated in this case report suggest one additional way to increase the number of donor organs and provide lifesaving transplantation to more patients.

We acknowledge all the members of The Johns Hopkins Heart and Heart-Lung Transplant Team who worked so diligently in the care of patients.

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Drug and Neurotransmitter Receptors

New Perspectives With Clinical Relevance

Solomon H. Snyder, MD

Our understanding of drug and neurotransmitter receptors has been greatly advanced by receptor binding techniques. The theme of multiple-receptor subtypes with clinical relevance is highlighted by calcium antagonist and benzodiazepine receptors. Numerous drugs may exert therapeutic and untoward effects via calcium channels. Examples include effects of loperamide hydrochloride on diarrhea, the phenothiazine thioridazine hydrochloride on cardiac and ejaculatory function, and the neuromuscular toxicity of aminoglycosides. Elevated numbers of calcium antagonist receptors in hypertrophic cardiomyopathy may be involved in the pathophysiology of this disease. Benzodiazepines act via discrete central and peripheral receptors. At central receptors, benzodiazepines facilitate the inhibitory effects of the neurotransmitter γ-aminobutyric acid. Peripheral benzodiazepine receptors are localized to mitochondria and enriched in several endocrine glands where they are influenced by therapeutic blood levels of benzodiazepines such as diazepam.

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SINCE the pioneering work of Paul Ehrlich at the turn of the century, it has been widely assumed that most drugs act by initially binding to highly specific recognition sites, designated *receptors*. For most of the 20th century, drug actions at receptors were monitored indirectly by examining effects on physiological systems like contraction of intestinal and cardiac muscle. Insights into receptor pharmacology and the development of novel drugs emerged from this type of research. For instance, diverse effects of catecholamines on cardiac muscle led to the differentiation of α- and β-adrenergic receptors and the subsequent, therapeutically important, discrimination of β_1 and β_2 receptors. However, the most extensive advances in our molecular understanding of receptors and efficient new drug design stem from the binding of reversible ligands to receptors in mammalian tissue. Successful labeling of opiate receptors in crude brain homogenates about 15 years ago led rapidly to the characterization of receptors for most of the major neurotransmitters in the brain and peripheral tissues.

The explosion of molecular-receptor research has had ramifications in a number of different areas. Our understanding of synaptic transmission has profited from the isolation of receptor proteins, their molecular cloning, and characterization of how neurotransmitter recognition at receptors is translated into alterations in membrane ion channels or second-messenger molecules. Clinical relevance of receptor research has been considerable. Careful analysis of ligand binding has led to the appreciation of multiple receptor subtypes, leading to novel drugs selective for individual subtypes. As these subtypes may be differentially distributed in various tissues, one may develop organ-selective drugs, an approach particularly effective with muscarinic-cholinergic receptors. At least five distinct muscarinic receptor subtypes have been cloned and the receptor proteins expressed in cell culture. Tissues vary in their expression of muscarinic receptor subtypes with marked differences, for instance, between the heart and the gastrointestinal tract. Accordingly, cholinergic antagonists selective for the gastrointestinal tract might relieve peptic ulcer symptoms without eliciting tachycardia at receptors in the heart. Anticholinergic drugs with this pattern of selectivity, such as pirenzipine, are being investigated. Drug screening with cloned and expressed receptor subtypes may permit the design of even more selective and effective agents.

To illustrate molecular receptor research with clinical relevance, this article will focus on two receptor systems, for calcium antagonist drugs and for benzodiazepines.

CALCIUM ANTAGONIST RECEPTORS

The three principal calcium antagonist drugs used in the United States, nifedipine, verapamil, and diltiazem hydrochloride, represent three distinct chemical classes: dihydropyridines, phenylalkylamines, and benzothiazepines, respectively. These drugs have had great clinical success in treating angina, hypertension, and other cardiovascular conditions. They were developed independently of each other prior to any awareness of drug actions at voltage-dependent calcium channels.

Calcium antagonist receptors were first labeled with tritiated dihydropyridines, though subsequently tritiated phenylalkylamine calcium antagonists

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and tritiated diltiazem have been used in receptor binding studies.[1] Evidence that the dihydropyridine binding sites represent pharmacologically relevant receptors came from investigations showing that the affinities of a wide range of dihydropyridines at the binding sites closely paralleled their potencies in influencing calcium-dependent contractions of smooth muscle. A careful examination of competition of various drugs for the tritiated dihydropyridine receptors indicated that they do not bind to identical recognition sites. Instead, there appear to be separate but interacting recognition sites for dihydropyridines, phenylalkylamines, and benzothiazepines. Initially it was not clear whether these three subtypes of calcium antagonist receptors represent three distinct protein entities or involve different recognition sites on a single protein. Studies with the purified receptor showed that all three recognition sites occur on a single-protein complex. By contrast, molecular cloning studies reveal that β_1- and β_2-adrenergic receptor proteins are distinct entities with no more similarity in amino acid sequence than occurs between β receptors and muscarinic-cholinergic receptors. The subtypes of muscarinic receptors also represent distinct proteins with different amino acid sequences.

The three subtypes of calcium antagonist drug receptors are all associated with one type of voltage-dependent calcium channel, designated the *L channel*, though others, designated *N* and *T channels*, have been identified.[2] Neurotransmitter release from both central and peripheral neurons requires opening of voltage-dependent calcium channels, which are not linked to L channels, as the major calcium antagonist drugs fail to influence neurotransmitter release. Recent evidence indicates that N calcium channels regulate neurotransmitter release. The N channel is blocked potently and selectively by a snail toxin, ω-conotoxin, which also blocks neurotransmitter release at very low concentrations.

These N channels may be responsible for toxic effects of aminoglycoside antibiotics, which elicit neuromuscular toxicity by blocking transmitter release. At therapeutically relevant concentrations, aminoglycosides inhibit the binding of radiolabeled ω-conotoxin to receptors and the relative potencies of the drugs in competing at these receptors correlate closely with their neuromuscular toxicity.[3] These findings fit with clinical observations that aminoglycoside toxicity is reversed by calcium treatment.

Since voltage-dependent calcium channels occur throughout the body, calcium antagonist drugs have been examined for influences on diverse clinical conditions. Recently we discovered a receptor for calcium antagonist drugs localized to dissociated human osteoblasts and osteoblastlike osteosarcoma cells.[4] The receptor is linked to a novel calcium channel in these bone cells. Drug effects on the calcium channel are the same as at the receptor binding sites except that dihydropyridine drug effects demonstrable in channel recordings are not apparent in binding studies. The osteoblastlike osteosarcoma cells are excellent models for osteoblast cells of intact bone as they secrete bone matrix proteins such as osteocalcin. Secretion of osteocalcin by the cultured bone cells is stimulated by the dihydropyridine calcium agonist drug BAY K 8644 and blocked by calcium antagonist drugs. This channel appears to play a role in bone remodeling in intact animals, as bone resorption in fetal rats is stimulated by BAY K 8644 and blocked in a stereoselective fashion by isomers of the calcium antagonist desmethoxyverapamil.[5] The enhanced bone resorption elicited by BAY K 8644 presumably reflects augmented osteoblast activity stemming from factors released by osteoblasts. This model resembles the pattern of bone resorption in postmenopausal, high-turnover osteoporosis. Drugs blocking these calcium channels thus might influence osteoporosis and other bone dysfunctions associated with increased resorption.

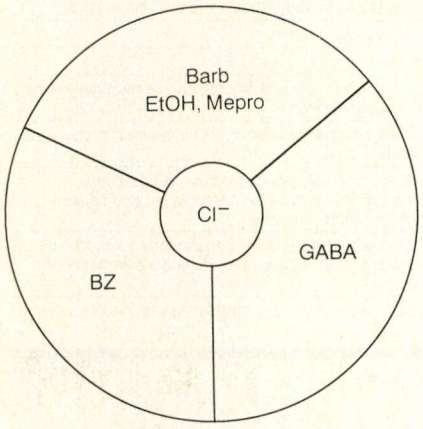
Alterations in calcium antagonist receptors may play a role in several diseases (Table). Hypertrophic cardiomyopathy involves a nondilated, hypertrophied ventricle. An inbred strain of hamsters, the Syrian cardiomyopathic hamster, displays hereditary abnormalities resembling human hypertrophic cardiomyopathy. Numbers of calcium antagonist receptors in heart, skeletal muscle, and brain tissue of these hamsters are markedly increased, while numerous other receptor sites are normal.[6] This disorder appears linked with the disease process in a causal rather than a secondary fashion, since the abnormality in calcium antagonist receptors precedes the development of cardiac hypertrophy and is apparent in extracardiac tissue. Based on the striking findings in cardiomyopathic hamsters, cardiac tissue obtained at operation from patients with hypertrophic cardiomyopathy and individuals with unrelated cardiac disease were assayed for a number of neurotransmitter receptors.[7] Calcium antagonist receptors are markedly increased in hearts of patients with hypertrophic cardiomyopathy, while other receptors are unaffected. The possibility that this abnormality represents a molecular defect associated with this disease, an autosomal dominant trait in about 50% of patients, is supported by the excellent therapeutic response of these patients to calcium antagonist drugs.

Muscular dysgenesis is a genetically determined abnormality of skeletal muscle in mice with a complete lack of excitation-contraction coupling. Animals with muscular dysgenesis display an almost total loss of the binding subunit of the dihydropyridine calcium antagonist receptor protein.[8] Correction of the molecular abnormality by replacing the missing genetic material reverses the skeletal muscle dysfunction.[9] This represents an elegant example of a receptor disease "diagnosed" and "cured" by applying molecular biologic tools to drug receptors.

The chemical structures of calcium antagonists, especially the phenylalkylamines, resemble many other clinically

Clinical, Pathophysiological, and Pharmacologic Features of Calcium Channels and Related Receptors

Drugs or Condition	Effect
Hypertrophic cardiomyopathy	
Syrian hamster model	Receptors increased in heart, brain, and skeletal muscle
Human patients	Receptors increased in atrium
Muscular dysgenesis	Dihydropyridine receptor absent
Osteoblasts	Possess calcium channels and binding sites, pharmacologically linked to bone resorption
Loperamide hydrochloride	Blocks receptor and calcium-dependent intestinal contractions at antidiarrheal doses
Thioridazine hydrochloride	Blocks receptors and calcium-dependent vas deferens contractions at doses that inhibit ejaculation and cause electrocardiographic changes
Diphenylbutylpiperidine neuroleptics	Block calcium antagonist receptors as potently as dopamine D_2 receptors; associated with relief of negative symptoms of schizophrenia
Aminoglycoside antibiotics	Block N-type calcium channels, correlating with neuromuscular toxicity



A model of the γ-aminobutyric acid (GABA) receptor. A single protein complex incorporates the chloride ion (Cl) channel and separate but interactive recognition sites for GABA; benzodiazepines (BZ); and barbiturates (Barb), ethanol (EtOH), and meprobamate (Mepro). This is the principal GABA receptor that mediates synaptic inhibition and is designated the *GABA-A receptor.*

useful drugs. In screening a large number of drugs, we obtained evidence that drugs of other classes may exert certain of their effects at calcium antagonist receptors (Table).[3]

The antipsychotic neuroleptic drugs comprise several chemical classes including the phenothiazines, butyrophenones, and diphenylbutylpiperidines. All of these drugs share the ability to block dopamine D_2 receptors potently; and the relative antipsychotic potencies of the drugs closely parallel their dopamine blocking activity, indicating that the major antipsychotic actions derive from dopamine receptor blockade. However, conventional neuroleptics, especially of the phenothiazine and butyrophenone classes, are much less effective in relieving the "negative" symptoms of schizophrenia, which involve affective withdrawal, than in treating "positive" symptoms, comprising florid hallucinations and delusions. The diphenylbutylpiperidines are unique in their ability to relieve negative symptoms of schizophrenia, enhancing social interaction and diminishing withdrawal.

Diphenylbutylpiperidines are very potent calcium antagonists of the verapamil type both at receptor binding sites and in blocking calcium-dependent contractions of smooth muscle.[3] They are about as potent as calcium antagonists. Thus, at therapeutic doses they will influence calcium antagonist receptors as well as dopamine receptors in the brain. By contrast, the phenothiazine and butyrophenone neuroleptics, which do not markedly influence negative symptoms of schizophrenia, are orders of magnitude weaker as calcium antagonists. Accordingly, the ability of diphenylbutylpiperidines to relieve negative symptoms of schizophrenia may derive from their calcium antagonist effects.

Calcium antagonist actions may also account for certain side effects of neuroleptics. The electrocardiographic changes elicited by thioridazine hydrochloride closely resemble those produced by verapamil. Thioridazine also uniquely inhibits ejaculation, presumably reflecting impaired contraction of the vas deferens. At therapeutic blood levels of thioridazine, the drug is a calcium antagonist of the verapamil type and blocks calcium-dependent contractions of the vas deferens, suggesting that its inhibition of ejaculation and cardiac side effects may represent calcium antagonist influences.[3]

Loperamide hydrochloride is a major antidiarrheal drug. Though loperamide is a potent opiate, its antidiarrheal effects are not blocked consistently by the opiate antagonist naloxone hydrochloride. When administered orally in antidiarrheal doses, loperamide is an effective calcium antagonist, acting at receptors in a verapamil-like fashion and blocking calcium-induced smooth-muscle contractions.[5] Thus, loperamide may owe all or part of its antidiarrheal therapeutic effects to calcium antagonism. Interestingly, constipation is a major side effect of verapamil therapy.

BENZODIAZEPINE RECEPTORS

Receptors that mediate the pharmacologic actions of benzodiazepines were identified by monitoring the binding to brain membranes of tritiated diazepam (Valium). In initial studies, numerous neurotransmitters did not compete for these binding sites, suggesting that the benzodiazepine receptor might have as its physiological ligand some novel neurotransmitter. More detailed studies showed that γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain, does not compete for benzodiazepine binding to diminish binding, but at low concentrations stimulates the receptor, enhancing the affinity of benzodiazepines. An abundance of evidence now indicates that the benzodiazepine receptor is a recognition site on the GABA receptor, distinct from the GABA recognition site (Figure).

For many years the relationship between actions of benzodiazepines, barbiturates, meprobamate, and ethanol had been unclear. All of these agents have sedative effects and can substitute for each other in alleviating withdrawal symptoms. However, their clinical effects differ. Abundant evidence indicates that benzodiazepines exert an antianxiety effect not manifest by barbiturates and distinct from the sedative effects that they share with ethanol and meprobamate. The purified GABA-benzodiazepine receptor protein interacts with barbiturates, meprobamate, and ethanol but at sites distinct from the benzodiazepine and the GABA recognition sites. Molecular cloning of the GABA-benzodiazepine receptor and expression of the cloned protein has clarified how GABA acts as an inhibitory neurotransmitter.[10] γ-Aminobutyric acid hyperpolarizes neurons by opening chloride ion channels that make depolarization by excitatory stimuli less probable. For years it was assumed that the GABA receptor protein was distinct from the chloride ion channel protein. Molecular cloning revealed that a single protein contains both the GABA and drug recognition sites as well as the chloride ion channel. In this way, the GABA-benzodiazepine receptor is part of a family of receptors in which recognition of the neurotransmitter directly opens an ion channel. Other receptors in which the neurotransmitter recognition site and the ion channel are part of the same protein include the nicotinic acetylcholine receptor and the glycine receptor. By contrast, receptors that act through second messengers, such as β-adrenergic and muscarinic-cholinergic receptors, have different types of protein structures that lack ion channels.

The benzodiazepine receptors just described are "central" receptors, occurring exclusively in the brain and spinal cord. An important subtype of benzodiazepine receptor, representing a distinct molecular entity, is called the "peripheral" benzodiazepine receptor. In initial studies of tritiated diazepam binding, high densities of tritiated diazepam binding sites were observed in numerous peripheral tissues.[11] However, while diazepam had similar potencies at central and peripheral receptors, other drugs differentiate the two sites. For instance, clonazepam, one of the most potent benzodiazepines in behavioral studies, is a few thousand times weaker at peripheral than central sites. On the other hand, RO5-4864, a benzodiazepine devoid of antianxiety effects, is several thousand times more potent at peripheral than central receptors.

Insights into possible functions of the peripheral benzodiazepine receptors

have come from localization studies.[12,13] Though peripheral receptors occur in a variety of tissues, they are concentrated in various glands. The adrenal gland is particularly enriched, with these receptors especially high in the zona glomerulosa of the cortex while the adrenal medulla is devoid of receptors. Within the pituitary gland peripheral receptors are highly concentrated in the intermediate and posterior lobes, but are absent in the much larger anterior lobe. Within the testes, receptors are localized to the interstitial tissue where Leydig cells produce testosterone. In the ovary, the receptors are confined to the interstitial and thecal layers that produce ovarian steroids.

At therapeutic blood levels of diazepam, the peripheral receptors should be fully occupied and presumably influence glandular function. Benzodiazepines alter the secretion of several hormones, including corticotropin, cortisol, prolactin, growth hormone, luteinizing hormone, and testosterone.[14] These effects had formerly been regarded as secondary to the central actions of benzodiazepines. More likely, these represent direct influences on the peripheral glands. Thus, diazepam inhibits aldosterone production in cultured adrenal glomerulosa cells, and the peripherally selective RO5-4864 benzodiazepine stimulates testosterone synthesis by rat testes in vitro.[13]

In the kidney, receptors are concentrated in the thick ascending portion of the loop of Henle, the distal convoluted tubules, and the collecting ducts, sites suggesting a role in water and electrolyte balance. A role of the receptors in epithelial regulation of electrolyte transport is implied by their very high densities in the choroid plexus and ependyma of the brain, the trabecular meshwork of the eye, the ciliary body of the eye, and the salivary gland.

In the brain, peripheral benzodiazepine receptors are demonstrable in selected areas such as olfactory neurons, the choroid plexus, as well as in glia. Striking increases in receptor density occur with proliferating glia and in glial brain tumors. The extraordinary enrichment of these receptors in glioblastoma may permit their imaging by positron emission tomography using benzodiazepine probes.[15]

Subcellular fractionation studies reveal that within cells, peripheral receptors occur almost exclusively in mitochondria, specifically in association with the outer membrane of mitochondria. The outer membrane of mitochondria regulates the ingress and egress of mitochondrial metabolites, a conceivable role for the receptors.

The dramatic properties of the peripheral benzodiazepine receptor suggest that it must interact with some normally occurring substance. By examining the ability of organic-tissue extracts to compete for the binding of radioligands to peripheral benzodiazepine receptors, we isolated porphyrins as the sole substance responsible for the activity of tissue extracts.[16] The exact porphyrin-influencing receptors varies with the tissue. In the spleen, the major component is hemin, presumably derived from red blood cells in the spleen, while in most other tissues protoporphyrin IX is the principal entity. Porphyrins appear to play a physiological role in association with peripheral benzodiazepine receptors for several reasons. They act in extremely low concentrations with protoporphyrin IX displaying an affinity constant of about 15 nmol. Porphyrins vary markedly in their affinities for the receptor, with the most potent porphyrins being those with known physiological activity. Moreover, the concept that porphyrins are endogenous ligands for the receptor fits with a mitochondrial localization. Thus, the initial and final steps in porphyrin biosynthesis occur in mitochondria so that the precursors of protoporphyrin IX and heme must cross mitochondrial membranes. Numerous mitochondrial proteins utilize porphyrins. Both benzodiazepines and porphyrins directly affect mitochondrial respiration.

The peripheral benzodiazepine receptors represent a receptor subtype with implication both for basic research and clinical medicine. The biologic function of the outer membrane of mitochondria has never been well characterized. The potent and selective benzodiazepines should provide probes to characterize mitochondrial physiology. Considering the widespread clinical use of benzodiazepines, there has been remarkably little investigation of their actions on peripheral organs. The fact that peripheral benzodiazepine receptors will always be occupied at therapeutic blood levels of diazepam emphasizes the importance of exploring such effects.

CONCLUSIONS

Molecular studies of drug and neurotransmitter receptors have already influenced our understanding of synaptic events in the brain, hormonal actions, and mechanisms for therapeutic and adverse effects of numerous classes of drugs. The receptor-binding techniques that permitted the identification of drug and neurotransmitter recognition sites are now utilized routinely in the pharmaceutical industry to "sculpt" novel therapeutic agents for selected targets. Finally, the tools of molecular biology, increasingly applied to receptor research, have accelerated the acquisition of new insights.

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The Molecular Biology of Medullary Thyroid Carcinoma

A Model for Cancer Development and Progression

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Medullary thyroid carcinoma (MTC) is an important human cancer for the study of molecular abnormalities that underlie initiation of neoplasia and subsequent cellular changes during tumor progression. This tumor can occur in different inherited forms, each mediated by autosomal dominant genetic events. Germline abnormalities on chromosome 10 are linked to at least one type of genetic MTC, multiple endocrine neoplasia type II. Our studies of chromosome 10 in DNA from MTC tumors failed to detect frequent loss of polymorphic DNA markers, suggesting that the genetic mechanisms involved in MTC development may be different from those for other inherited cancers such as retinoblastoma. During tumor progression of MTC, abnormalities develop in expression of the mature phenotype of the endocrine cell from which the tumor arises. In cell culture, chemical modulation or gene insertion can lead to partial correction of these defects in differentiation capacity by activating cellular signaling processes. These studies offer opportunities to dissect the molecular events that regulate endocrine cell differentiation, to determine the precise abnormalities that may underlie the initiation and tumor progression events in MTC and related cancers, and, thereby, to identify new targets for therapeutic intervention.

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DURING the past 15 years, our laboratory group has been working on the cellular and molecular biology of medullary thyroid carcinoma (MTC), a tumor of the parafollicular, calcitonin-secreting C cells of the thyroid.[1] Despite the fact that MTC is a relatively uncommon human cancer, it has properties that render it an important model for understanding the molecular steps in the genesis of neoplasia and clinically significant events in tumor progression. First, approximately 20% of patients with MTC have autosomal dominant inherited forms of the disease.[2] Second, during the course of the disease in some patients, MTC cells develop a defect in their ability to develop or maintain a mature endocrine phenotype; this abnormality correlates with clinical outcome.[3-5] In this article, we will review the progress of our laboratory efforts and those of others in defining the molecular abnormalities that contribute to tumorigenesis and tumor progression in MTC. These findings will be discussed in the context of their implications for our understanding of the molecular processes that guide normal and neoplastic cell development.

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WHAT ARE THE MECHANISMS THAT UNDERLIE INHERITANCE OF MTC?

Although the genetic abnormalities involved in familial forms of MTC have not yet been characterized, recent findings have raised important questions that may extend our understanding of the variety of molecular steps that can cause tumor formation.

The identification of a single genetic abnormality for inherited MTC is complicated by the fact that this disease is composed of at least three different clinical syndromes, each of which could result from a different genetic lesion. Most commonly, familial MTC occurs in the setting of multiple endocrine neoplasia type II (MEN II), a disorder in which patients develop not only the thyroid cancer, but also adrenal pheochromocytomas and hyperparathyroidism.[2] Less commonly, a particularly aggressive form of MTC can occur as a congenital tumor, which is also occasionally inherited as a dominant trait, in association with pheochromocytoma and more widespread neural abnormalities, including facial mucosal neuromas and abnormal ganglionic plexuses throughout the gastrointestinal tract (multiple endocrine neoplasia type III [MEN III][6]). More recently, a third form of familial MTC has been described and is characterized by an unusually late age of onset, low aggressiveness, and lack of association with other endocrine or neural lesions.[7] These different heritable clinical syndromes raise the intriguing possibility that heterogeneous genetic

mechanisms may cause the different forms of inherited MTC.

Two investigative groups that used DNA restriction fragment length polymorphism studies of lymphocyte DNA have linked the germline genetic abnormality for MEN II to the centromeric region of chromosome 10.[8,9] A more recent study preliminarily links MEN III to the same region.[10] Our ongoing collaborative studies with Y. Nakamura, MD, PhD; F. A. Wells, Jr, MD; and R. White, PhD (unpublished data, 1989) indicate that the form of inherited MTC that is not associated with other endocrine or neural lesions is probably not linked to chromosome 10. The latter finding emphasizes the heterogeneity of genetic events that can play the initial role in the formation of a human cancer, even within the same histological category.

Our past findings[11,12] and recent studies in molecular biology[13] suggest that the mechanism of tumorigenesis via the chromosome 10 lesion in MTC may be different from that proposed initially for retinoblastoma[14] and, subsequently, for several other heritable cancers.[15-22] In hereditary human cancers, loss of a "recessive tumor suppressor function" is thought to play the initial role in tumor development. This theory is based on the elegant "two hit" hypothesis of carcinogenesis developed by Knudson[14] for formation of retinoblastoma. In the familial form of retinoblastoma, the germline genetic defect (the first hit) has been traced to structural alterations of the retinoblastoma susceptibility (Rb) gene on chromosome 13.[23-26]

This abnormality is assumed to be phenotypically silent as long as the normal Rb gene allele that remains on the opposite chromosome 13 is functionally intact. During retinal development, the germline defect becomes manifest in occasional cells via loss of the remaining normal Rb gene allele. This second hit frequently occurs through gross structural changes, such as extensive chromosomal deletions or loss of the entire chromosome, that are detectable as a reduction to homozygosity for polymorphic DNA markers in involved regions of chromosome 13 (for review see references 15 and 19 through 22). Subsequent clonal tumor growth ensues from the cells that have suffered these two hits.

Aspects of the development of MTC and pheochromocytoma in MEN II and MEN III suggest that the first hit in these tumors might not be silent, as in the retinoblastoma model, but rather may confer a growth stimulus on the target thyroid C cells and adrenal chromaffin cells. Tumor development in these syndromes is preceded by a stage of generalized hyperplasia of the entire thyroid C cell[27] and adrenal chromaffin cell[28] populations; these abnormal cells are evidently precursors for eventual MTC and pheochromocytomas. The MTC lesions and pheochromocytomas evolve as multifocal clonal tumors, and each tumor comes from a different cell clone.[3,11,12] These findings firmly suggest that the initial hyperplasia reflects an abnormality of the entire target cell population. Therefore, the stimulus for this polyclonal hyperplastic growth must be encoded within germline DNA, presumably as a result of the original chromosome 10 abnormality. Later genetic events in which a few of the hyperplastic cells progress to form clonal carcinomas might involve chromosomal loci other than that harboring the germline defect on chromosome 10. One would then not necessarily expect a reduction to homozygosity of chromosome 10 in MTC.

Our recent studies of chromosome 10 regions, including those closest to the region linked to MEN II, in DNA from tumors of patients with both inherited and sporadic forms of MTC confirmed this expectation; only 2 of 16 tumors studied had reductions to homozygosity on chromosome 10 (1 from a patient with MEN II and 1 from a patient with sporadic MTC).[13] Pheochromocytomas from this patient with MEN II and his affected sister showed no structural changes of chromosome 10. Similar results for MTC are emerging from other investigators.[22] This low incidence for reduction to homozygosity of a chromosomal region genetically linked to a human cancer has also been reported for familial polyposis of the colon,[29,30] another syndrome characterized by generalized growth-related changes of the target tissue before frank tumor development.[31-33]

Failure to detect reduction to homozygosity of chromosomal regions that are linked to familial MTC (chromosome 10) and polyposis coli (chromosome 5) suggests that the two allelic hit theory of Knudson might not be operative in familial MTC and polyposis coli. It is conceivable, however, that failure to detect reduction to homozygosity might be due to a mechanism of inactivation of the normal allele function that does not involve the loss of a large segment of chromosome 10 in MTC (and chromosome 5 in polyposis coli), such as point mutations or much smaller interstitial deletions of the chromosomal region that contains the normal gene. However, the current data strongly suggest that the series of genetic events that underlie tumor formation for diseases such as familial MTC and polyposis coli are different from those for genetic tumors such as retinoblastoma. The initial steps in formation of these neoplasms might then be viewed as follows.

First, germline abnormalities, on one allele of chromosome 10 in familial MTC and chromosome 5 for polyposis coli, lead to polyclonal hyperplasia of the cell population in which eventual tumors arise. Subsequently, clonal tumors arise in the cell population at risk when genetic abnormalities ensue at chromosomal loci other than those that harbor the germline defect. As possible chromosomal locations for these subsequent genetic events, a frequent reduction to homozygosity[34] and cytogenetic abnormalities[35,36] on chromosome 1 have been described in MTC and pheochromocytoma, and frequent genetic abnormalities occur on chromosomes other than 5 in colonic polyps and carcinomas.[30,37,38] Similar multistep events may take place in genetic Wilms' tumor. In this renal cancer, which can also be preceded by generalized renal hypertrophy,[39,40] a frequent reduction to homozygosity[41-44] occurs on a chromosome not linked to the germline defect.[45,46]

Clearly, elucidation of the initial genetic events that underlie the formation of inherited MTC will teach much about the range of molecular changes that can contribute to the early stages of human cancer. Definition of the structural changes in DNA involved and the genes that they encompass will be the focus of investigation for laboratories already involved with the study of MTC and of other tumor biologists who recognize the importance of studying this endocrine cancer.

WHAT ARE THE MECHANISMS FOR TUMOR PROGRESSION OF MTC?

Once initial genetic events induce formation of neoplastic cells, a series of subsequent genetic alterations can result in progressive changes in the tumor cell populations (for review see references 47 through 50). These events can result in a block to normal maturation of the tumor cells.[51,52] In turn, these events accompany increasingly aggressive tumor growth and treatment resistance in many common forms of human cancer.[50-53]

The mechanisms of maintenance of the mature cell phenotype are not well understood as yet; but, in several systems they seem to depend, in part, on a balance of growth and differentiation events controlled by cellular processes such as those outlined in Fig 1. Growth and differentiation factors in the extracellular environment interact with cell surface receptors to activate intracellu-

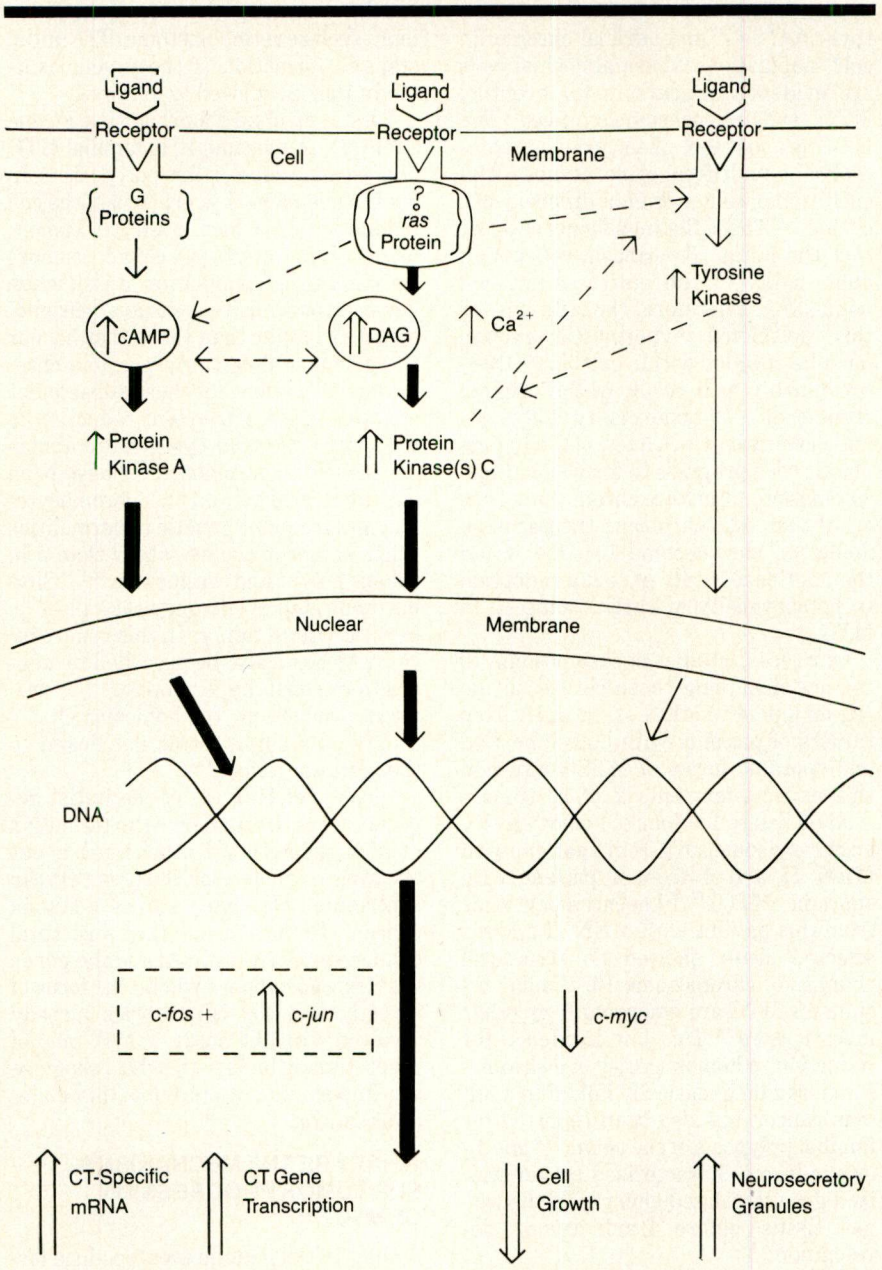

Fig 1.—Signal transduction in mammalian cells. Three of the major pathways for signal transduction from cell membrane receptors to the nucleus are portrayed schematically. In the protein kinase A system[89] (left, for example, β-adrenergic receptors[90]), binding of a ligand to its cell membrane receptor results in activation of a G protein complex. This, in turn, activates adenyl cyclase, increasing intracellular cyclic adenosine monophosphate (cAMP), which in turn activates protein kinase A. Protein kinase A phosphorylates specific proteins, some of which result in changes in gene expression; some of these changes are dependent on identified nuclear transcription factors CREB[91] and AP-2.[92] In the protein kinase C pathway[93] (center, for example, thrombin-thrombin receptor interactions[94]), ligand binding to a receptor activates a pathway of phosphoinositide breakdown, resulting in activation of protein kinase C by generation of diacylglycerol (DAG). Protein phosphorylation via the protein kinase C pathway can result in changes in gene expression; some of these changes are dependent on nuclear transcription factors c-*jun*/AP-1[85,86] and AP-2.[92] Question mark indicates that *ras* function at this step in the pathway has not been conclusively determined. In the tyrosine kinase system[95] (right, for example, insulin receptor[96] and epidermal growth factor receptor[97]), it is not yet established which nuclear transcription factors are responsible for the change in gene expression[98,99] observed. Dashed lines indicate that there is evidence for cross-communication among these pathways[93,100-103]; downward arrows, direction of pathways; and solid thick arrows, pathways we have shown to differentiate medullary thyroid carcinoma (MTC) cells. The potential for the tyrosine kinase pathway to induce MTC cell differentiation is suggested by the fact that activation of the *src* tyrosine kinase pathway has been shown to drive the differentiation of the closely related PC12 pheochromocytoma cell line.[104] CT indicates calcitonin; upward thick arrows, steps activated in each pathway; circles, steps in these pathways modulated in MTC cells[71,72,82-84]; hollow thick arrows, changes measured at the time of differentiation of MTC cells as reported herein.

lar signal-transduction pathways. In turn, these latter events influence differential patterns of activation and repression of functions that modulate cell phenotype, including the nuclear transcription factors that regulate expression of genes in a given cell. An abnormality that occurs at any point in these pathways, some of which are depicted in Fig 1, could result in abnormal growth or impaired maturation of involved cells. These abnormalities can constitute events not only for tumor initiation but also for the tumor progression patterns.

As discussed previously for studies of initial genetic changes in cancer, MTC also presents a rich opportunity to study cellular changes that occur during tumor progression and the molecular mechanisms that account for them. It is this area of investigation that has occupied the majority of our recent work with MTC. In the fully differentiated state, thyroid C cells, the normal progenitor cells for MTC, exhibit a well-characterized endocrine phenotype that includes the presence of well-formed cytoplasmic neurosecretory granules (Fig 2, top)[54,55] and abundant amounts of the small polypeptide hormone calcitonin.[27,56,57] Production of this peptide hormone in C cells is controlled not only through transcriptional activity for the calcitonin (CT) gene in these cells, but also through a tightly controlled processing pathway for the initial CT gene RNA transcript.[58,59] In normal C cells, this mRNA processing predominantly results in the production of CT-specific mRNA derived from exons 1 through 4 of the CT gene; while in other neural tissues, the processing pathway predominantly results in the production of mRNA that encodes the CT gene–related peptide from exons 1 through 3, 5, and 6. In the CT gene–related peptide mRNA, exon 4 sequences are removed from the initial RNA transcript during processing.

In patients with MTC, the tumor cells often retain most of the features of normal C cells, including abundant neurosecretory granules and abundant amounts of CT.[60-64] We and others have shown that this is especially true for patients who do well with the disease, even when local and/or distant metastases are present.[3-5,62] We have also demonstrated[3,4] and other investigators have confirmed[5] that patients who die of MTC consistently have markedly diminished or absent CT content in their primary or metastatic tumors. This observation led us to develop a cell culture model to study the differentiation control of MTC cells[65,66] and to clone various regions of the human CT gene[67] to inves-

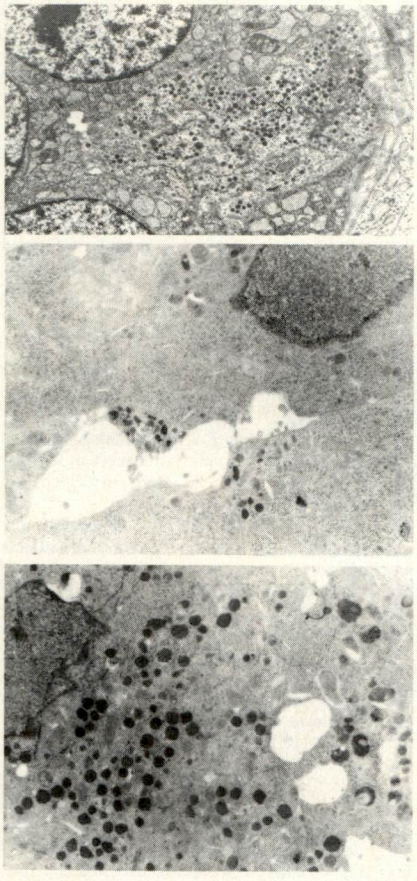

Fig 2.—Ultrastructural morphology of human C cells. Top, Normal human C cells that contain an abundant dense core of neurosecretory granules. Center, Control cells from the TT cell line of medullary thyroid carcinoma. Note the virtual absence of neurosecretory granules. Bottom, TT cells infected with HaMSV. Note numerous secretory granules in these cells that are virtually identical in number and morphology to those in the normal C cells (left). Normal cells from Chan and Conen,[54] by permission of the United States and Canadian Academy of Pathology, Augusta, Ga; and TT and TT *ras* cells from Nakagawa et al,[82] by permission of the National Academy of Sciences, Washington, DC.

tigate the molecular events that control its transcription and RNA processing in MTC cells. Since the level of CT is a significant prognostic indicator in MTC, our strategy has been to use the biology of CT gene expression as a tool to understand the cellular abnormalities that underlie the loss of maturation capacity during tumor progression for MTC.

Our cell culture model has employed the human cell line TT,[65] which was derived from a patient with the sporadic form of MTC. Like normal C cells, these tumor cells produce and secrete large amounts of CT. However, as might be expected for MTC cells derived from a patient with a very aggressive tumor, the culture line differs from normal C cells in that the cells grow in culture, have very few cytoplasmic neurosecretory granules (Fig 2, center), and the mRNA splicing for the CT gene is abnormal in that abundant mRNA species for both CT and the CT gene–related peptide are produced.[67]

To characterize differentiation abnormalities in the TT cells, we have investigated whether exogenous stimulation of some of the cell signaling processes in Fig 1 might overcome the genetic defects in the cells and result in some degree of cell maturation. This approach has provided insight into the maturation capabilities of other cancer cells, including leukemic cells and embryonal tumor cells (for review see references 52 and 68 through 70). Our first studies employed the activation of two major intracellular signaling pathways by increasing protein kinase C or A activity (Fig 1). Stimulation of each pathway independently resulted in partial differentiation of the cells[71,72] that was characterized by slowing of cell growth and increased transcription of the CT gene. However, the splicing events for the gene did not revert to the pattern more characteristic of normal C cells in that transcripts for both CT and CT gene–related peptide increased in tandem.

We reasoned that our activation of each of the previously mentioned signal-transduction pathways might be partially overriding a differentiation block in TT cells. More coordinated stimulation of these signal-transduction elements or stimulation of additional and/or stronger signal pathways more closely related to C-cell differentiation might induce a more complete differentiation response. For several reasons, we chose to test this hypothesis by inserting the viral Harvey *ras* oncogene (v-*ras*) into TT cells via infection with Harvey murine sarcoma virus. First, this virus contains a mutated homologue of the normal cellular *ras* oncogene that appears to act as a signal "coupling" protein and may play a role in the transduction of cell surface stimuli,[73-75] as depicted in Fig 1. Second, the transformation of cells by mutated *ras* genes appears to depend on activation of the same signal-transduction pathways, including protein kinase C, that we initially explored in our differentiation studies.[76,77] Finally, although mutated *ras* genes are best known to cause transformation of cells,[78] they also cause differentiation of rodent pheochromocytoma cells,[74,79,80] an endocrine tumor type closely related to MTC, and they induce germinal vesicle breakdown in *Xenopus* oocytes.[81]

Insertion and expression of the v-*ras* gene in TT cells resulted in a dramatic differentiation response characterized by slowing of cell growth, increased transcription of the CT gene, alteration of the CT gene mRNA splicing events toward those more characteristic of mature C cells, and the appearance of abundant mature cytoplasmic neurosecretory granules (Fig 2, bottom).[82] These events are associated in TT cells with stimulation of the protein kinase C pathway[83] and with increased expression[84] of the nuclear oncogene c-*jun*, which may act as a transcription factor for some genes responsive to protein kinase C–mediated signal-transduction events (Fig 1).[85,86]

Our studies of *ras* gene–induced differentiation show that the phenotypic consequences of the genetic defects in MTC cells can, at least partially, be overcome by activating a signal-transduction process at the level of the cell membrane. The *ras* oncogene may stimulate a pathway not otherwise available to the tumor cell, such that a compensatory signal overrides a defective one and results in cell maturation (Fig 1). Alternatively, the constitutive signal coupling activity of the inserted *ras* gene may bypass a more proximal defect in the normal signal-transduction pathway in the membrane of the TT cells (such as a defect in a receptor coupled to a *ras* gene protein, Fig 1) and allow maturation to proceed more normally (Fig 1). This hypothesis assumes that signal-transduction steps distal to this defect, including nuclear factors that alter gene expression, are intact in the cultured MTC cells. Exploration of these possibilities in our model system will help define the molecular abnormalities in MTC cells and thereby shed light on the regulation of normal endocrine differentiation. Furthermore, our ongoing studies to dissect the precise regions of the CT gene that are responsible for its transcriptional activation in response to these signal-transduction events will define, at the level of expression of an individual gene, how these pathways modulate the steps in expression of the endocrine cell phenotype.

In addition to their implications for understanding the biology of normal and neoplastic C cells, our studies in MTC cells also have implications for elucidating tumor progression steps in other human cancers. Endocrine cell differentiation plays a particularly important role in the spectrum of human lung cancers. Twenty-five percent of patients with this disease have the small-cell phenotype that is characterized by a variable degree of endocrine differentiation, similar to MTC. We have found that insertion of the *ras* gene into small-cell lung carcinoma cells can induce several different phenotypic responses that depend on expression levels of other on-

cogenes and the initial phenotype of the cells studied.[87,88] These effects range from differentiation of small-cell lung carcinoma cells that have endocrine properties similar to MTC[87] to tumor progression events and diminished endocrine properties in small-cell lung carcinoma cells that have amplified *myc* family genes.[88] Our studies of *ras* effects at the level of signal transduction and gene expression in MTC will augment our understanding of the factors that control tumor progression in small-cell lung carcinoma.

Finally, the ability to differentiate MTC cells in vitro suggests that some phenotypic consequences of genetic alterations in cancer cells can be overcome through manipulation of cell signaling processes. These and similar findings in other tumor cells (for review see references 52, 68, and 69) have raised hopes for the use of such manipulations in vivo for therapeutic purposes. Continued studies of the molecular controls for differentiation may identify new target points for design of "biomodifier" agents that can contribute to cancer therapy by inducing maturation of cancer cells in patients.

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A Model of Its Kind

A Century of Medicine at Johns Hopkins

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Let us hope that before the last sands have run out from beneath the feet of the years of the nineteenth century it will have become a model of its kind, and that upon the centennial of its anniversary it will be a hospital which shall still compare favorably, not only in structure and arrangement, but also in results achieved, with any other institution of like character in existence.

WITH this ringing invocation, John Shaw Billings ended his speech at the opening of The Johns Hopkins Hospital on May 7, 1889. As the individual most responsible for designing and planning the hospital, Billings was one of the key speakers. Yet his words were not mere congratulatory phrases, appropriate for an event that commemorated the end of his years of effort. In the century since the hospital's opening, Billings' hope was fulfilled, as Hopkins became a model for American medical practice, education, and research.

This model was not a composite of entirely new concepts and methods, however, but a cohesive, effective union of ideas, several of which had already been tried elsewhere. In the stimulating environment created by the early leaders of Hopkins, these ideas were merged in a novel way.

ANTECEDENTS OF THE HOPKINS MODEL

William H. Welch credited the advances in medical education made by Hopkins' predecessors:

> The state of medical education when the Johns Hopkins School was started was most favorable for the development of such a school as we had in mind. As early as 1880 there had been efforts to improve the character of the medical schools of this country. . . . By 1880, Harvard Medical School, the school at Ann Arbor and a few other medical schools had already taken steps to improve the standard.

Sweeping reforms put in place by President Charles W. Eliot at the Harvard Medical School in 1871 strengthened the curriculum and created the nation's first full-time faculty position in physiology. Six years later, the University of Pennsylvania (Philadelphia) expanded its course of instruction, added scientific subjects, and arranged them in a graded sequence. In that same year, the University of Michigan lengthened its annual session from 6 months to 9 months and added a fourth year to its medical school. By 1880, University President James B. Angell had shifted the instructional emphasis from the lecture hall to the laboratory, and the curriculum was heavily weighted toward study of the preclinical sciences.

Many of the curricular techniques employed at Hopkins were also used at other American medical schools. Beginning in 1835, for example, ward visits formed part of the instruction at the Harvard Medical School. Programs at the Medical College of Ohio in Cincinnati, the University of Michigan, and the New Orleans (La) School of Medicine also incorporated ward work for medical students into the curriculum. Furthermore, the bedside teaching turned into a routine by William Osler and William S. Halsted was already being discussed and carried out in other medical schools before the Hopkins medical school opened.

Yet Hopkins was the first medical school to make the principle of "learning by doing" a matter of stated policy—and then to carry that policy out. Other schools offered bits and pieces of it; still others recognized the importance of clinical and laboratory experience but, lacking control of a teaching hospital, were unable to execute it.

The Johns Hopkins medical school and hospital offered an unorthodox approach to the problems and responsibilities of American medicine. Its remarkableness was not diminished by the fact that isolated changes had been tried at other hospitals and medical schools. The crucial difference at Hopkins was their aggregate effect, the result of the modification of each idea by the others.

THE VISION OF JOHNS HOPKINS

The pillar of the model was the stipulation that the hospital form part of the medical school of the university, a connection specified by Johns Hopkins himself. "In all your arrangements in relation to this hospital," Johns Hopkins wrote to his trustees, "you will bear constantly in mind that it is my wish and purpose that the institution should ultimately form a part of the medical school of that university for which I have made ample provision in my will."

The man who articulated this far-reaching "wish and purpose" was a successful Baltimore merchant and banker, a Quaker who saw his fortune as a trust and believed that it should be turned to the benefit of society. Of English de-

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scent, Johns Hopkins was born at "White Hall," the family plantation in Anne Arundel County, Maryland, in 1795. But when Johns' father freed his slaves, in accordance with the beliefs of the Society of Friends, the plantation could no longer support the Hopkins family. At the age of 17, Johns was sent to Baltimore (Md) to live with his uncle, a wholesale grocer.

When his uncle denied him permission to marry his daughter (the Society of Friends did not permit marriages between first cousins), Johns Hopkins moved out of the house and established his own grocery business. Its success allowed him to accumulate enough capital to lend money, and he abandoned the grocery business and became Baltimore's leading financier.

A bachelor, Johns Hopkins was able to use his wealth for philanthropic purposes. He decided to divide his $7 million fortune into two equal parts, for the founding of a hospital and a university. In 1867, he selected trustees for the university; all but two he also appointed trustees of the hospital. The naming of these two interlocking boards was concrete evidence that Johns Hopkins wanted the hospital and the university to be closely allied.

In 1873, Johns Hopkins chose the site for the hospital, giving it to the hospital's trustees with a letter of instruction that set forth his wishes for the new institution. He specified that a home be constructed for black orphans of the city, and that the indigent sick of Baltimore be treated at the hospital without charge. A training school for nurses should also be established in conjunction with the hospital, Johns Hopkins wrote, and in addition to educating nurses, the hospital should obtain the services of physicians "of the highest character and of the greatest skill." The emphasis on excellence persisted as he directed the trustees to consult with experts in hospital design so that the institution would compare favorably with any other in existence.

No other documents signed by Johns Hopkins mention any relationship between the hospital and the university. This idea was nevertheless the key element in the success of both enterprises, with far-reaching effects on American education. More than any other specification, it determined the future of the two institutions. This highly original idea has ensured full cooperation between components of the medical institutions, and thus between the practice and the learning of medicine. It was a unique link that enabled the medical school to adopt many of the Johns Hopkins university's ideals. Like the university, the hospital and medical school emphasized the goal of advancing rather than merely transmitting knowledge.

THE CHARACTER OF THE JOHNS HOPKINS UNIVERSITY

The Johns Hopkins University, founded in 1876, was the first institution of higher learning in the United States to emphasize graduate education. Through the leadership of its first president, Daniel C. Gilman, it attracted an excellent faculty and gave them the time, the facilities, and the money to conduct research.

A spirit of unity prevailed under Gilman's leadership, not only among the faculty, but between faculty and students. Gilman referred to them as "masters and pupils . . . not two bodies but one body, a union for the purpose of acquiring and advancing knowledge." It was the fellows who bridged the traditional gap, as participants in the university's system of postgraduate education. This fellowship was the key to the new university's success as an institution dedicated to the advancement of knowledge.

The success of The Johns Hopkins University in setting a new educational standard derived from a fortunate combination of circumstances. First, there were the financial resources, a single bequest, divided equally between the university and the hospital, as large as the endowment of any other American college. There was also the university's freedom from religious and governmental control, through its status as a private, nonsectarian institution. The Johns Hopkins University was also unfettered by the limitations of tradition, free from the handicap of antiquated ideas. Its benefactor attached few specific conditions to his bequest, and it had no entrenched faculty to be replaced.

Johns Hopkins had selected the university's trustees wisely, and Gilman himself was a perspicacious choice who saw the potential for establishing a true university in Baltimore. Although three eminent university presidents—Eliot of Harvard (Cambridge, Mass), Angell of Michigan (Ann Arbor), and White of Cornell (Ithaca, NY)—recommended that the new institution offer nothing above the level of college and technological education, Gilman believed that advanced training and research were immediately feasible.

Finally, there was the temper of the times. The nation was ready in 1876 for the establishment of a new kind of school. The third quarter of the 19th century was a time of technological innovation in the United States. Americans had begun to appreciate the need for science in an industrial society. Improvements in public education were giving more and more students the background that would enable them to undertake a university education.

THE DESIGN OF THE HOSPITAL

In 1875, Francis T. King, the president of the hospital's board of trustees, invited five experts in hospital design to submit plans for hospital buildings. King asked them to address seven specific points, including methods of heating and ventilating the hospital, the location of the proposed medical school's buildings, and the merits of the "pavilion" system (detached permanent units, two or more stories tall) vs the "barracks" system (temporary, one-story structures, which could be destroyed and replaced economically). Of the five essays, that of John Shaw Billings clearly related the construction of the hospital to its philosophical underpinnings, fastening on the key point in Johns Hopkins' letter of instruction: The plan of the hospital must depend on the extent and manner in which it is to be used as an instrument of medical education and on the more or less intimate connection that it is to have with the medical school.

In addressing the trustees' specific questions, Billings' report ranged far afield from architectural details, pointing up the opportunity presented by Johns Hopkins' bequest to develop a new type of medical school. Many of his ideas echoed Gilman's: Billings advocated a high standard of admission, a 4-year course of study, and practical work in the various departments of the hospital. His plans included a first-class physiological laboratory, with ample facilities for chemical and microscopic work. Billings also stressed that the hospital must do more than care for the sick and educate medical personnel—it should promote discoveries in science and medicine and make these discoveries known for the common good. It was obvious to the hospital trustees that in Billings they would have more than an architect, and in 1875 he was employed to supervise the hospital's construction.

Billings' interest in medical education came to the foreground in 1876, when he was asked to write an article for a series entitled "A Century of American Medicine" to commemorate the nation's centennial. His conversations with Gilman and the trustees also helped to both shape and disseminate his ideas. In addition, when the university opened in 1876, Billings was appointed lecturer in the history of medicine and soon after gave a series of addresses on medical history, legislation, and education.

To Billings can be attributed many of the enduring themes of The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine. He envisioned them as the first American home of original medical research. Although the medical school's primary purpose was to educate well-trained practitioners of medicine, another of Billings' goals was to produce investigators as well, "to give the world men who can not only sail by the old charts but who can make new and better ones for the use of others."

The object of original research was not to retain these well-trained investigators at Hopkins, however. Billings intended Johns Hopkins to produce "men fitted to make research, and who will take the habit of, and the taste for inquiry which they have acquired here—into, we will hope, wider and more extensive fields of usefulness."

DELAYS IN THE OPENING OF THE HOSPITAL AND THE MEDICAL SCHOOL

Thirteen years elapsed between the opening of the university and the opening of the hospital. This delay was caused by the trustees' conservative financial approach to construction. The best hospital, one that would meet all the requirements of the new program in medical education and research, was a costly proposition. But in an example of Quaker prudence, the trustees would not touch the endowment's capital; they would spend only the annual income for hospital construction. Consequently, the building proceeded year by year, halting when each year's funds were exhausted.

Although the delay was a source of distress to all involved, the years that elapsed between the beginning of hospital construction and the admission of the first patient gave Gilman and Billings the time to establish the educational plan that would be put into effect when the medical school opened, and to begin to identify those individuals who would best fit their ideals as research professors. As Welch remarked later, "We were disappointed that the Hospital should open before the Medical School had started, but as I look back . . . this was doubtless a distinct advantage."

The Founding Faculty

Although the hospital opened in 1889, the medical school was not ready until 4 years later. But plans for the medical school had been under discussion since 1883, when the founding faculty was appointed. This group consisted of Billings, Henry Newell Martin, and Ira Remsen. Martin and Remsen were professors of biology and chemistry, respectively, at The Johns Hopkins University. Both had earned medical degrees. In a series of meetings the following year, they drew up concrete plans for the medical school, which included several novel features for the time. Admissions requirements would include knowledge of French and German as well as preparation in physics, chemistry, and biology. The curriculum would encourage research, and laboratories would be established for the study of other scientific subjects. They also decided to establish a program of fellowships, based on the system already in place in the university.

These plans languished as the years passed. Nine more years elapsed between their series of meetings and the opening of the medical school, and by then none of these three men were able to serve on the medical school's faculty.

The Original Faculty

The first active member of the medical school faculty was William H. Welch, who was appointed professor of pathology in 1884. In keeping with the idea that the hospital was part of the university, he established a laboratory in the hospital in 1885, even before it was opened for patients. This Pathological Laboratory was the first site of research in The Johns Hopkins Hospital. Here were gathered a brilliant group of young scientists for advanced study; Welch's students included William S. Halsted, Franklin P. Mall, Lewellys F. Barker, and J. Whitridge Williams—all of whom became department heads at Hopkins—as well as many others who made notable contributions elsewhere.

As the hospital buildings inched toward completion, the trustees were eager to conclude the appointment of hospital and medical school staffs. At the end of 1885, a committee of hospital and university trustees was formed to select professors of medicine and surgery. In keeping with Johns Hopkins' intention to link the hospital and the medical school, Gilman and the other trustees had devised a unique system of joint appointments. In other hospitals, several physicians alternated as chief of service, dividing the number of beds among them. In contrast, Gilman and the trustees envisioned a permanent chief of each service, who would also be professor of the respective department in the medical school.

One person thus controlled the facilities for the teaching of students, the structuring of the curriculum, the care of patients, and the organization of the research program. It was a plan with far-reaching consequences for medical education. Through this administrative arrangement, medical students easily became an integral part of the team caring for the hospital's patients, and the residency programs flourished.

This unity was cemented by the actions of the boards of trustees of the hospital and university. Although they operated independently, they had overlapping memberships, and they established several joint committees. Both boards were required to approve a chief's appointment and to share the payment of his salary equally. Chiefs of service became members of two other unique organizational entities: the Advisory Board of the medical school and the Medical Board of the hospital. Comprising department directors and administrative chiefs of the medical school and hospital, respectively, these groups advised the trustees on appointments to the staff and other matters relating to patient care, education, and research.

In 1888, William Osler was appointed professor of medicine in the medical school and physician-in-chief in the hospital; in 1890, William S. Halsted received similar appointments for the Department of Surgery. Joining Welch, Osler, and Halsted was Howard A. Kelly, who was appointed chairman of gynecology in 1890. The three directors of the clinical departments were brought from around the country. Both Osler and Kelly came from Philadelphia (Pa); Halsted had come to William H. Welch's laboratory from New York (NY).

Hopkins' policy of obtaining its medical school faculty from outside its immediate environs was a novel idea at the time. Faculty members in other medical schools were drawn almost exclusively from the pool of local physicians, who taught the preclinical sciences while continuing to practice medicine. Hospital and medical school were responsible for appointing their own staffs, and medical schools found it difficult at the time to appoint clinical professors from outside, because they would have no access to hospital beds for teaching and research. The decision at Hopkins to make appointments based on qualifications alone signaled the end of provincialism in the selection of faculty members.

The hospital's superintendent, who would be in charge of its day-to-day activities, was not appointed until shortly after the hospital officially opened. Gilman chose Henry M. Hurd, a hospital administrator, psychiatrist, and skilled editor. To run the school of nursing, Gilman appointed Isabel A. Hampton, under whose direction the school set a new educational standard for the training of nurses nationwide.

THE OPENING OF THE MEDICAL SCHOOL: THE WOMEN'S COMMITTEE CLOSES THE FINANCIAL GAP

When the hospital opened in 1889, it was unclear when—or whether—the medical school would open at all. The termination of dividend payments by the Baltimore and Ohio Railroad, whose stock represented all the university's endowment, diminished the amount of money available to the university to plan the medical school. Into the breach stepped a group of five women, four of whom were trustees' daughters: M. Carey Thomas, Mary Gwinn, Mary E. Garrett, and Elizabeth King. Thomas was also a formidable scholar who later became president of Bryn Mawr College. She led the effort to form a Women's Fund Committee in 1890 to raise the rest of the money needed to open the medical school. Subscribers included members of prominent families, First Lady Mrs Benjamin Harrison, celebrated women physicians, and women in the arts—along with hundreds of other sympathetic women nationwide. Garrett herself contributed $50 000, and in the fall of 1890 the Women's Fund Committee was able to offer the trustees $100 000. This donation came with one stipulation: women must be admitted as students on equal terms with men.

The contribution was accepted with the provision that the medical school would not open until a total of $500 000 had been obtained. By December 1892, less than $200 000 had been raised. The delay in the opening of the medical school had encouraged other schools to try to entice away members of the Hopkins faculty—one anonymous benefactor even pledged $1 million to McGill University if Osler would leave Johns Hopkins for Montreal (Canada). It was with immense relief, therefore, that the Hopkins trustees received a letter from Mary Garrett late in December, in which she offered to make up the difference between the money raised and the total required to open the medical school. From the Garrett fortune (which, ironically, derived from the earlier success of the Baltimore and Ohio Railroad), she contributed about $300 000.

Her additional gift came with its own stipulations, however. Garrett insisted that entering medical students have a bachelor's degree from a first-class college and a reading knowledge of French and German. These requirements were not the invention of the Women's Committee, but had been set forth by Welch and the founding faculty in 1884. Garrett, who had obtained a copy of the document, had supposed that these conditions were what the trustees wanted.

The faculty and trustees reacted with alarm, fearing that few students would be qualified to meet the conditions. The trustees nevertheless decided to accept the money, and the Johns Hopkins medical school became the first in America with such stringent admissions requirements. Their unprecedented character led Osler to remark to Welch that they had been lucky to get in as professors, because neither of them could have been admitted as students.

With Garrett's gift, funds were available to obtain professors of pharmacology, anatomy, and physiology, a task delegated to Welch. Welch turned to the first generation of students at The Johns Hopkins University: His choice in anatomy was Franklin P. Mall, one of his own fellows, who had collaborated with Halsted; and his choices for pharmacology and physiology, William Henry Howell and John Jacob Abel, were students of Henry Newell Martin. These faculty members had a qualification virtually unknown to American medicine: their proven ability as investigators. Most had studied in Germany, a center of research in the 1880s, and they brought back one of the most profound influences of German medicine on America: the university ideal.

At Hopkins, this idea was promulgated first by Gilman. When The Johns Hopkins University opened in 1876, Gilman shaped it into the first modern university in this country—the first to adopt the European idea of graduate university education in a research-oriented environment. His ideas about the university ideal had crystallized by the time he arrived at Hopkins. Gilman had spent almost 4 years as president of the University of California (first in Oakland, then Berkeley); he had also been a professor at Yale's Sheffield Scientific School and secretary of the school's executive committee. During his tenure at Yale, the school developed its pioneering biology course for prospective medical students. In addition, Gilman had spent a winter at the University of Berlin (Germany), where he absorbed the ideas that he would later incorporate into The Johns Hopkins University.

The university ideal was thus extended from the university to the new medical school. The ideal emphasized the importance of research and required all faculty members to be investigators. The professors at the medical school were thus capable not only of teaching what was known but of developing new knowledge. Well-equipped laboratories were provided in the preclinical sciences—facilities rare in other medical schools—along with sources for the dissemination of results. The journals created at Johns Hopkins for this purpose were among the first such publications in the United States. In sum, the trustees of the new university medical school created the conditions that allowed the university ideal to flourish, and eventually to become the model for all medical schools.

The opening of the medical school in October 1893 was announced the preceding February. Word spread in the intervening months, and on October 2, sixteen applicants brought their credentials for Welch's perusal. All 16 were admitted (some provisionally), and 2 more were enrolled a few days later. The first class of The Johns Hopkins University School of Medicine thus comprised 18 students, 3 of whom were women.

THE PRECLINICAL YEARS

During their first 2 years of medical school—the so-called preclinical years—the students were immersed in rigorous, if informal, courses taught by the professors of anatomy, physiology, pharmacology, pathology, and physiological chemistry. The atmosphere was exciting: So knowledgeable were these professors that they used the standard textbooks only as a point of departure. In the classroom, students found themselves listening to investigators who were conducting pathbreaking research.

This emphasis on laboratory work even for beginning medical students was the hallmark of the school's policy of "learning by doing," a curricular feature that set the medical school apart from other medical schools of the time. Gilman and Billings' intention to encourage research implied adherence to this particular method of education: The student would have to acquire knowledge rather than passively receive it. The curriculum should not be too crowded, Welch said, so that the student could read, exercise, and digest knowledge. Instead of filling the students' hours with required subjects, Welch asked, What is the irreducible minimum in a subject without which one cannot let the student get his degree?

THE CLINICAL YEARS

By 1895, the first class of students had reached the clinical years. Although most other schools relied on lectures as the primary method of instruction in the final 2 years, courses at Hopkins continued to emphasize student participation. Highlights of the clinical years were Osler's clinic (for third-year students) and clinical clerkship (for fourth-year stu-

dents). Both involved students heavily in the daily routines of the hospital. This was Osler's "natural method of teaching," as he called it, in which "the student began with the patient, continued with the patient, ended his studies with the patient, using books and lectures as tools, means to an end." For the clinical years, Osler made the hospital the laboratory of the medical school, and the students were a part of the team caring for the patients. By taking careful histories of their patients' illnesses, performing thorough physical examinations, conducting the routine laboratory tests, following the moment by moment course of their patients' conditions, and making suggestions regarding management, they learned about disease and therapy through personal experience, not through mere textbook description.

Osler himself identified this innovation in teaching as the best idea to emerge from Johns Hopkins:

> By far the greatest work of The Johns Hopkins Hospital has been the demonstration to the profession of the United States and to the public of this country of how medical students should be instructed in their art. I place it first because it was the most needed lesson, I place it first because it has done the most good as a stimulating example, and I place it first because never before in the history of this country have medical students lived and worked in a hospital as part of its machinery, as an essential part of the work of the wards.

What made the clinical clerkship possible was, once again, the unique link between the hospital and the medical school. Most hospitals were staffed by local practitioners, who controlled staff privileges and policies, and teaching was not generally considered a part of a hospital's responsibilities. Most medical schools lacked the authority to place students on wards as clinical clerks, and permission of hospital boards was frequently difficult to obtain. At Johns Hopkins, in contrast, this connection gave the hospital the professional services of the teachers in the medical school while providing the medical school with advantages for clinical training unexcelled at the time.

In surgery, too, students participated in "learning by doing." One of the most innovative teaching devices was introduced by Halsted in 1895 and later expanded by Cushing: the course in experimental surgery. In the Hunterian Laboratory, students performed operations on anesthetized dogs using aseptic techniques. The revolutionary feature of the course was its simulation of surgery on a hospitalized patient. Students noted the "patient's" history, kept an anesthesia chart, wrote operative and postoperative notes, and performed a complete postmortem examination. Working on living, anesthetized animals required students to learn and observe the principles of scientific surgery.

Self-education under guidance was the goal of this new brand of medical education, and the faculty believed that it should be available to every student. This was the American achievement in medical education: the application of democratic principles to the training of physicians. In England, France, and Germany, the majority of students were not permitted to obtain firsthand experience in the laboratories and on the wards. The unique idea in American medicine, in contrast, was that the ideal medical education should be available to every medical student, not to just a few. Osler believed that a solid foundation was necessary for *all* medical students who wanted to become competent practitioners, not just for those who would become teachers and investigators.

THE RESIDENCY SYSTEM

The hospital's first interns—11 men and 1 woman—were chosen from among the 15 members of the first graduating class of the Johns Hopkins medical school, who received their degrees on June 15, 1897. From 1889 to 1898, the hospital had to acquire its residents from elsewhere. Once graduates of the Hopkins medical school became available, however, they filled many, but not all, of the residency positions. The chiefs of service also wanted to take advantage of the best minds from other medical centers besides their own.

It was Osler who introduced residency training at Hopkins. His system permitted a physician to spend an indefinite number of years living in the hospital to complete his specialized training. Hopkins medical residents remained for so long that during his 16 years at Johns Hopkins, Osler trained only five chief resident physicians. The first resident, appointed at the hospital's opening in 1889, was Henry A. Lafleur. His successor, William S. Thayer, was second in command of the hospital for the next 7 years. Medical educators have singled out these graded residencies as another important advance. This system melded the needs of patients with the needs of medical education. What patients lost in privacy they gained in the quality of care, as they were observed by a hierarchy of physicians rather than by a single physician.

THE RISE OF CLINICAL SCIENCE

In 1905, William Osler accepted the Regius Professorship of Medicine at Oxford (England) University. Welch had resigned as dean in 1898, and Osler succeeded him. Osler spent only 1 year in the deanship before stepping down, weary with the responsibility of running both the entire school and its Department of Medicine. Although Osler's departure removed the most influential member of the clinical group, by 1905 the course of the hospital and medical school had been set, and he left behind a strong, flexible institution.

Osler was a master clinician and diagnostician, and he believed that experimental work should be the primary responsibility of the preclinical science departments. At the same time, he was a proponent of the new medicine, devoted to the idea that observation and statistical analysis to develop new clinical knowledge should supplement work on the wards. As an old-style naturalist-observer, he neither undertook nor vigorously promoted studies of the fundamental nature of disease.

Osler's successor as chairman of the Department of Medicine was a new type of clinician. Lewellys F. Barker was trained in the basic sciences, coming to Johns Hopkins from a professorship of anatomy. He was instrumental in bringing laboratory investigation into clinical medicine, first at Hopkins and, by extension, throughout American medicine.

Barker organized three research divisions within the Department of Medicine to provide his staff with opportunities for investigation. Barker's laboratories were unique because they were established for this specific purpose. They were the start of a movement that changed the character of university clinics in the United States and helped to create the scientific base of modern medical practice.

The Physiological Division was the first of Barker's three facilities, opening in 1905. Its purpose was the study of individual cases of disease from the standpoint of function. In charge of the division was Arthur D. Hirschfelder, a 1903 graduate of the Hopkins medical school, who concentrated on disturbances of the heart and circulation. The Biological Division opened the following year, under the direction of Rufus I. Cole. Cole remained at Hopkins until 1910, when he became the first medical director, and the first full-time clinician, of the Hospital of the Rockefeller Institute. The Chemical Division also opened in 1906. It was supervised by Carl Voegtlin, who later became the first director of the National Cancer Institute.

These three laboratories were the site of pathbreaking investigations. They diversified Hopkins' approach to

the study of disease and provided facilities for the training of young physicians interested in clinical methods of scientific investigation.

Few additional innovations were applied to the organization and operation of the Johns Hopkins hospital and medical school until 1914, when full-time professorships were inaugurated in the clinical departments.

FULL-TIME PROFESSORSHIPS

The "full-time" system specified that physicians and scientists in a university school of medicine should devote their entire professional lives to the work of the university. The clinicians among them should not accept fees from private patients. Instead, the university should be the primary source of income for its faculty, and it should pay them well. This system was intended to free professors for teaching and investigative work.

The Preclinical Sciences

Although in 1893 a few full-time preclinical chairs existed in medical schools nationwide, Johns Hopkins was the first medical school in the United States to place all of its preclinical departments on a full-time basis. These were lean years for the preclinical sciences, years in which well-trained investigators were few, and those who were well trained had either inadequate facilities to work with or no place to go. As Welch wrote, "I was often asked in Germany how it is that no scientific work in medicine is done in this country, how it is that so many good men who do well in Germany and show evident talent there are never heard of and never do any good work when they come back here. The answer is that there is no opportunity for, no appreciation of, no demand for that kind of work, here."

American investigators trained in German laboratories were returning to seek academic positions at home. The time was ripe in 1893, therefore, to replace practicing physicians in preclinical departments with salaried teachers and investigators. Knowledge in the basic sciences was expanding, and Welch was one who believed that the full-time system would open the way more freely for academic careers: "That is, if young men who do good scientific work, who publish valuable results of original investigation, and who acquire a reputation among those who are competent to judge them, could look forward with some reasonable assurance to securing positions in our leading medical schools."

Welch's hopes were realized, as this innovative policy set new standards for instruction in the preclinical sciences across the country. By 1910, enough positions were available in medical schools to accommodate most of the qualified scientists in the United States.

The Clinical Sciences

By the turn of the century, the preclinical sciences had prospered, but the clinical sciences were still undeveloped. The success of the full-time system in the preclinical sciences at Johns Hopkins encouraged the professors in those fields—particularly Welch and Mall—to consider implementing it in the clinical departments. But it was Lewellys F. Barker who in a 1902 address to Hopkins alumni, "Medicine and the Universities," made the question of full-time professorships a national issue overnight. Although Barker believed that the services of part-time clinicians were also necessary, he thought that the greatest need was for full-time physicians and surgeons trained in physiology and pathology, who, after careful observation in the wards and over the operating table, would submit the ideas there gleaned to experimental study in laboratories adjacent to the wards.

But the clinical faculty themselves had serious doubts. Osler in particular resisted the idea. He feared that the full-time system would produce "clinical prigs," physicians isolated from the local profession and thus from the surrounding medical community of practicing physicians; that these full-time faculty would be out of touch with the world of clinical practice—the world in which their young residents would eventually have to live; and worst of all, that under this system the practice of medicine might eventually be taught by laboratory investigators without clinical experience.

Accustomed to augmenting their medical school salaries with fees from private patients, clinicians were loath to eliminate this source of income. Even Barker fell prey to the difficulties inherent in implementing the system he espoused. He accepted the professorship of medicine at Hopkins with the hope that it would be a full-time position, but sufficient endowment was not available to support his salary. By the time funds were available, Barker had built up such a large clinical practice (and such an elaborate way of life) that he could no longer consider a smaller income.

The money to place the clinical departments on a full-time basis came from the Rockefeller Foundation's General Education Board, whose representative, Abraham Flexner, had identified the Hopkins medical school as the outstanding medical school in America. In 1910, Flexner had produced his famous report for the Carnegie Foundation, which fueled the movement for change already under way. His report was notable for its scathing indictment of American medical education: of the 150 medical schools then in existence, he had lukewarm praise for only 5. But of Johns Hopkins he said, "This was the first medical school in America of the genuine university type. . . . It has finally cleared up the problem of standards and ideals."

Flexner came to the attention of John D. Rockefeller and his adviser, Frederick T. Gates, after the publication of his report. "What would you do," asked Gates, "if you had a million dollars with which to make a start in the work of reorganizing medical education?" Flexner replied, "I should give it to Dr. Welch."

Welch had been negotiating with the Rockefeller Foundation for funds to extend the full-time system to the clinical departments since 1910, when the Hospital of the Rockefeller Institute (New York, NY) opened with a staff of full-time clinicians. Flexner was on the scene the next year as an emissary of the General Education Board. But it took 3 more years for Welch to win the support of the Hopkins faculty. Not until 1913 did he have sufficient backing at home to ask the General Education Board for aid. Then, assisted by a $1.5 million grant from the board, Hopkins placed its departments of medicine, surgery, and pediatrics on a full-time basis. This was another turning point in American medicine.

The plan went into effect immediately in the Department of Surgery, and John Howland, the chairman of the new Department of Pediatrics, also accepted the arrangement. Barker, however, resigned the chairmanship of medicine because he was unwilling to accept a full-time post. His successor was Theodore C. Janeway, who in 1914 became the first full-time professor of medicine. As funds became available, additional clinical chairs were made full-time: obstetrics in 1918, psychiatry in 1923, and ophthalmology in 1925.

It is important to emphasize that the full-time system in the clinical departments applied only to a few members of the staff. The rest of the clinical faculty remained on a part-time basis. This diversity was beneficial to the medical school and the hospital: The very existence of the plan pressured all clinical professors to value research, and the presence of part-time associates maintained private practice as an important element.

The system of full-time clinical pro-

fessorships at Hopkins led to rapid change nationwide, when the General Education Board used Hopkins as a model to introduce similar arrangements at other medical schools. Although national acceptance was not easily won and some schools delayed for many years, most medical schools eventually adopted some version of the full-time principle.

THE EXTENSION OF THE MODEL: THE EXPORT OF PHYSICIANS

The early leaders of the hospital and medical school had the satisfaction of recognizing the attainments of the institution they had shaped. By 1914, the 25th anniversary of the hospital's opening, all the features of the model were in place. By this time, too, the hospital's vitality was apparent: Its endowment, the value of its physical plant, its bed capacity, and the number of outpatient visits had all increased substantially since its opening. Growth in the medical school could also be measured by the number of men and women it had sent out to populate other medical schools nationwide.

Some had been fellows (in the preclinical fields) or residents (in the clinical sciences) at Hopkins, graduate students who bridged the gap between faculty and medical students. Of the 17 faculty members and fellows who had studied with Franklin P. Mall, for example, 11 became professors of anatomy. On the clinical side, 11 of Halsted's 17 chief residents instituted training programs of their own—programs that produced the next generation of resident surgeons trained in the Halsted tradition, who in turn trained the third generation.

When the Rockefeller Foundation provided funds to establish new medical schools based on the Hopkins model, Hopkins graduates were brought to the new schools as deans and faculty members. These schools included Washington University in St Louis (Mo), Vanderbilt University (Nashville, Tenn), the University of Rochester (NY). Duke University (Durham, NC) was the most complete Hopkins colony: Of the original faculty of the schools of medicine, nursing, and health services at Duke, 30 of 46 members had trained at Hopkins.

THE IMPLICATION OF THE MODEL'S SUCCESS

The specific execution of Johns Hopkins' general idea reflected a unified vision, extending from the founder through the faculty, residents, and students. Those who implemented the plan were not simply following directives; their belief in the principles underlying the hospital and medical school unified all who worked and studied there. The resulting harmony, the sense of collegiality that remains to this day, was remarked upon by Alan Gregg at the commemoration of Welch's 100th birthday:

> I suggest that something extraordinarily precious comes out of the close but entirely free association of really superior people. To this emergent quality I give the name—the heritage of excellence, mostly because it lasts so long and because it never comes from, nor appeals to, mediocrities . . . . What Welch and his colleagues did and believed and wrote is not as important now—nor anywhere near as important—as the heritage of excellence their contacts with each other have left us.

The success of the Hopkins migration helped to transform American medicine, and what was put forth as a model is now firmly entrenched. Today, we take for granted the ideals promulgated by Gilman, Billings, Welch, Osler, and the rest of the Hopkins founders as commonplace aspects of academic medicine—an acceptance that may be Hopkins' greatest contribution.

The spread of these ideals diffused the uniqueness of the Johns Hopkins medical school and hospital. As its graduates helped to create other strong schools, Hopkins became one of many. The historian Richard Shryock points out the paradox: The fact that Hopkins training is no longer as distinctive as it was 100 years ago suggests the hospital and medical school's greatest achievement. Viewed from this perspective, he writes, the loss of its once unique position becomes a persuasive measure of its enormous success.

For background material, we have made extensive use of Alan M. Chesney, *The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine*, 3 vols (Baltimore, Md: The Johns Hopkins Press; 1943, 1958, 1963); Kenneth M. Ludmerer, *Learning to Heal: The Development of American Medical Education* (New York, NY: Basic Books Inc Publishers; 1985); and Richard Shryock, *The Unique Influence of The Johns Hopkins University on American Medicine* (Copenhagen, Denmark: Munksgaard International Publishers Ltd; 1953). This synopsis was adapted from the two-volume history, *A Model of Its Kind*, recently published by The Johns Hopkins University Press.

Current Concepts in Brain Resuscitation

Mark C. Rogers, MD, Jeffrey R. Kirsch, MD

WHILE the initial impetus for intensive care 20 years ago grew out of major advances in cardiac and pulmonary care, the last decade has seen a tremendous interest in neurological intensive care. Several factors have combined to stimulate this interest. First, as intensivists provided better care to sicker patients with cardiac and pulmonary disease, critically ill patients survived more often and a review of their long-term complications noted a significant frequency of neurological problems. Next, as an outgrowth of the Vietnam War, techniques for rapid evacuation of casualties were used to improve treatment for traffic accident victims in the United States. The result was large numbers of hospitalized patients with head injury. Neurosurgical techniques designed to treat head-injured patients, including intracranial pressure monitoring,[1] became commonplace in tertiary care hospitals. Pharmacologic and physiological treatment for cerebral edema, developed for patients with head injury, was used in medical patients with conditions ranging from Reye's syndrome[2] to near drowning.[3] As a result, neurological intensive care became a legitimate area of focus in critical care medicine.

Initially, there appeared to be little hope that anything could be done except to minimize the effects of brain edema and increased intracranial pressure by the vigorous use of diuretics,[4] the practice of elective intubation and hyperventilation,[5] and the frequent use of intracranial pressure monitoring.[6,7] These therapies have all been directed at limiting the secondary effects of a neurological insult in a way analogous to the treatment of pulmonary edema after myocardial infarction. They treat the complications of a process rather than the process itself. More recently, therapies have been developed that are designed specifically to limit or even to prevent the primary brain injury seen after a neurological insult. This therapy is analogous to the prevention of permanent myocardial damage following a coronary occlusion by the rapid administration of thrombolytic agents. The principle of the therapy is that permanent injury to an organ can be prevented, even after a physiological insult, by rapid reversal of the physiological process. In neurological intensive care, this area of research is generally known as cerebral resuscitation and has met with mixed success. This article will review theories or therapeutic strategies under which this work has proceeded, as well as the success of both research and clinical efforts in this field (Table 1).

ALTERATIONS IN BRAIN METABOLISM AND THE USE OF BARBITURATES

For many years, it has been known that anesthetics, including barbiturates, lower cerebral metabolism. Based on this principle, animal studies were done in the 1960s that seemed to demonstrate that barbiturates could prolong the period that animals could endure hypoxia without neurological insult.[8-10] These early studies were simple, crude experiments, often involving the timing of a rodent's survival in a bell jar from which oxygen had been removed. Nevertheless, these experiments prompted various investigators to suggest that a neurological insult results in a period of diminished cerebral blood flow and that treatment with barbiturates might diminish cerebral metabolic demand and thus limit, if not prevent, neurological injury.

Beginning in the early 1970s, literally thousands of articles were published in the field. Among the most influential was the work of Bleyaert et al,[11] who showed in a hypotensive ischemic monkey model that thiopental given after the insult could improve neurological outcome as measured by a neurological deficit score. Furthermore, these results were obtained with thiopental administered as late as 1 hour after the neurological insult. In retrospect, there were real problems with these data. First, the authors had very small group sizes (as low as five), along with a group of controls on whom data had been published previously and who, therefore, did not appear to be concurrent with the experimental animals. Also, large numbers of animals had to be excluded because of premature death or deviations from protocol. As an example, 9 of 19 controls and 16 of 43 animals given thiopental were excluded in the study by Bleyaert et al.[11] Furthermore, it appeared that animals treated with 120 mg/kg of thiopental would have improved outcomes if treated 1 hour after injury, but not if treated only 1/2 hour after injury. This curious finding was never fully addressed because of the enormous excitement and clinical interest generated by the work.

Soon barbiturates were being tried in patients following virtually all global neurological insults. Going way beyond

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Table 1.—Therapeutic Strategies in Cerebral Resuscitation

Agent	Specific Property Suggested to Improve Neurological Function
Barbiturates	Decrease cerebral metabolism
Calcium blocking agents	Abolish no-reflow phenomenon due to cerebral vasospasm
Free radical scavengers	Decrease reperfusion injury
Neurotransmitter blockade	Abolish neuronal damage from excessive excitotoxins

their documented property of acutely lowering intracranial pressure,[12] barbiturates were given to produce coma in order to lower cerebral metabolism and, thereby, to provide cerebral resuscitation. Treatment protocols for barbiturate coma were used in patients with near drowning,[3] head injury,[13] Reye's syndrome,[14] serious bacterial meningitis,[15] hepatic encephalopathy,[16] cardiac arrest,[17] and a host of other conditions. For several years this treatment was generally accepted, and then the concepts began to unravel.

First, the original suggestion for the use of barbiturates for brain protection was based on the premise that barbiturates would lower cerebral metabolism more than they would lower cerebral blood flow. When the relationship between cerebral blood flow and cerebral metabolism was examined, however, there was no specific property of barbiturates that would lower metabolism selectively.[18] Any decrease in metabolism produced by barbiturates is accompanied by a corresponding decrease in blood flow. As a result, the concept that it is possible to give barbiturates to lower cerebral metabolism selectively until it is equilibrated to a low but fixed cerebral blood flow is not valid.

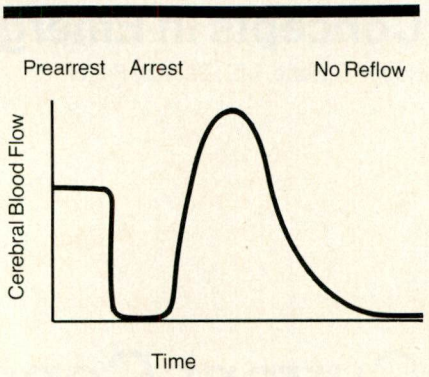
Next, while neurological outcome in patients treated with barbiturate coma was originally assumed to be improved, more careful analysis failed to document these assumptions. As an example, after a tremendous interest in barbiturate therapy for near drowning, a major clinical group in this area discovered its results were no better with barbiturate coma than without it.[19,20] Similar limitations arose in patients with Reye's syndrome.[14] When a major international study[21] done on neurological outcome following cardiac arrest in patients with and without barbiturate treatment failed to show any difference in outcome, many intensivists began to limit the use of barbiturate coma. Finally, concern over the lack of clinical utility prompted a reexamination of the original experiments. When the authors of the original experimental studies failed to replicate their results,[22] the whole justification for barbiturate coma for global cerebral ischemia became uncertain.

At present, barbiturates generally are accepted for limited use to treat increased intracranial pressure. Occasionally, repeated administration inadvertently will result in coma, but the coma itself is not a desired therapeutic end point. Other uses for barbiturates in the setting of regional cerebral ischemia,[23] including use during cardiopulmonary bypass to prevent focal neurological complications,[24] remain controversial.[25] Nevertheless, for global cerebral ischemia, the benefit of the use of barbiturate coma does not appear to justify the risk. The documented hemodynamic instability provided by barbiturates, including their potential to increase myocardial infarct size,[26] makes them a potentially dangerous drug to use in large doses in critically ill patients without an absolutely clear-cut indication.

THE NO-REFLOW PHENOMENON AND CALCIUM BLOCKING AGENTS

Experimental studies on cerebral blood flow following cardiac arrest or following occlusion of cerebral arteries all show a characteristic pattern of response (Figure). When cerebral blood flow is restored following a prolonged interruption, it develops a characteristic hyperemic response. Cerebral blood flow rebounds much higher than control. Next, there is a gradual decrease in flow again until there is virtually no flow. This lack of ability to sustain cerebral blood after a significant period of flow interruption is referred to as the "no-reflow" phenomenon.

It is clear that reversal of the no-reflow phenomenon might be associated with an improved neurological outcome. Furthermore, at the time that intensivists were interested in this field, neurosurgeons were involved in work on a similar problem.[27] For years, it had been recognized that when a stroke occurs, neurological damage is more generalized than that which would be expected from more limited interruption of blood flow in the affected vessel. The reason is that, following a cerebral hemorrhage, blood in the subarachnoid space produces a more generalized cerebral vasospasm.[27] In isolated tissue bath preparations, whole blood can provoke cerebral artery constriction[28] and, in these experiments, cerebral vasospasm can be



The temporary interruption of cerebral blood flow produces a transient hyperemic response followed by a gradual decline in cerebral blood flow called the no-reflow phenomenon.

reversed by calcium blocking agents. As a result, in the past several years neurosurgeons have been evaluating calcium blocking agents clinically to treat cerebral vasospasm. Similar studies have been conducted on the possible role of calcium blocking agents in reversing the no-reflow phenomenon,[29-34] because of the possibility that this phenomenon also might be due to cerebral vasospasm.

This area has also met with mixed success. Early reports of success of these agents met with concerns about technical errors in the experiments.[34] Alternatively, different groups were getting different results with the same agents.[29-32] With the introduction of nimodipine, however, it became clear that it was possible to get a reproducible improvement in cerebral blood flow following global cerebral ischemia.[33,34] This improvement was initially believed to be due to the ability of nimodipine to alter the no-reflow phenomenon. Once again, there was initial enthusiasm, but a more thoughtful analysis has, to date, limited the clinical use of nimodipine for cerebral resuscitation.

Nimodipine has not yet gotten extensive clinical use for cerebral resuscitation because the experimental data do not as yet justify widespread clinical use. While nimodipine will improve cerebral blood flow after global cerebral ischemia, it is a statistically significant but small improvement.[33,34] In animals treated with nimodipine before or after global cerebral ischemia, cerebral blood flow rarely is above 30% to 35% of control values.[33,34] As a result, while statistically significant, these studies may be clinically irrelevant in global cerebral ischemia, since these levels of cerebral blood flow will not sustain normal brain function. Furthermore, most studies

that do show an improved cerebral blood flow do not show an improved cerebral metabolic rate.[33,34] Cerebral metabolism, as distinguished from cerebral blood flow, does not appear to improve dramatically if animals with global cerebral ischemia are treated with calcium blocking agents.

Before completely eliminating calcium blocking agents, however, it is important to note that they still may have a role to play. They still may improve neurological outcome following global ischemia[38] by an unknown mechanism that may be related to intracellular calcium accumulation producing neuronal injury. As such, it is possible that there still may be a role for calcium blocking agents in global cerebral ischemia, but only as part of a more comprehensive therapy yet to be developed. Controlled clinical trials of these agents are ongoing, but results are not yet available as of the writing of this review. The potential role of calcium and its interaction with free radicals is discussed below.

Table 2.—Vertebrate Excitatory Amino Acid Receptor Subtypes*

	Pharmacologic Characteristics†			
Type	Agonist	Competitive Antagonist	Noncompetitive Antagonist	Allosteric Agonist
NMDA	NMDA	CPP	MK-801	Glycine
	Aspartate	D-AP5	PCP	...
	Ibotenate	D-AP7	SKF10047	...
		2-APH	Mg^{2+}	...
Quisqualate‡	AMPA	...	...	...
	Quisqualate	...	...	...
	L-glutamate	...	...	...
Kainate	Kainate	...	...	...
	Domoate	...	...	...
	L-glutamate	...	...	...
L-AP4		L-AP4[b]	...	...
		L-SOP	...	...

*Adapted from Cotman and Iversen.[60]

†NMDA indicates *N*-methyl-D-aspartate; CPP, 3-3(2-carboxypiperazine-4-*yl*)propyl-1-phosphonate MK-801, (+)-5-methyl-10,11 dihydro-5H-dibenzo [a, d] cyclohepten-5,10-imine maleate; D-AP5, D-2-amino-5-phosphonovalerate; PCP, phencyclidine hydrochloride; D-AP7, D-2-amino-7-phosphonoheptanoate; SKF10047, *n*-allylnormetazocine; 2-APH, 2-amino-7-phosphonoheptanoic acid; Mg, magnesium; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; L-AP4, L-2-amino-4-phosphonobutyrate; L-SOP, L-serine-O-phosphate.

‡No selective antagonists yet available, but γ-D-glutamyl aminomethyl sulphonate and 1-(*p*-chlorobenzoyl)-piperazine-2,3-dicarboxylate show some selectivity for K and Q vs NMDA.

FREE RADICALS

In the last several years, it has become apparent that at least some of the injury that occurs in any organ following interruption of blood flow occurs during the period of reperfusion rather than during the period of ischemia. It is commonly believed that this reperfusion injury is related to free radical damage.[35] Free radicals are molecules or molecular fragments that have an unpaired electron in the outer orbit. Common oxygen-derived free radicals include diatomic oxygen, the superoxide radical, the hydroxyl radical, the hydroperoxy radical, the alkoxy radical, and the peroxy radical. Since these substances have a single free electron, they are very reactive and may interact with lipid membranes and DNA to produce cellular damage. As a result, the body has a complex defense system that involves use of endogenous antioxidants, free radical scavengers, and perioxidases.[35]

When this system is overwhelmed, as is believed to happen during the period of reperfusion following an episode of ischemia, significant cellular damage can result. In brief, oxygen free radicals react with superoxide dismutase to form hydrogen peroxide. Next, the hydrogen peroxide reacts with metal chelates to form the hydroxyl radical. This radical provokes lipid perioxidation, which, in turn, can generate a chain reaction producing widespread cellular injury.[35] Furthermore, cellular damage can be exacerbated by calcium since, during ischemia, there is calcium influx. During reperfusion, free radicals can interact with calcium-triggered formation of arachidonic acid and lead to accumulation of prostaglandins, thromboxane, and leukotrienes.[36-38] There are now multiple organs in which the role of free radicals has been demonstrated in ischemic tissue damage. Among these are the gastrointestinal tract,[39,40] the myocardium,[41-43] and the nervous system.[44-47]

To date, there are no human studies evaluating the use of free radical scavengers in improving neurological outcome following an ischemic injury. Animal models have been used, however, and have shown some evidence of success. The use of allopurinol, if given before global ischemia, has been shown to improve neurological outcome and to decrease biochemical markers of brain injury.[48] The mechanism is believed to be related to the ability of allopurinol to block xanthine oxidase–generated production of free radicals, which occur during oxidative metabolism of adenosine by-products. The allopurinol in these studies has been given in advance of the insult so that it has sufficient time to cross the blood-brain barrier. Evidence also exists that superoxide dismutase, an endogenous free radical scavenger, improves cortical blood flow and metabolism after focal cerebral injury.[49] Similar results have been found in animals subjected to temporary spinal cord ischemia.[50] This effect is enhanced when the superoxide dismutase is linked to polyethylene glycol to enhance transmission of the agent across the blood-brain barrier.[51] The beneficial effects of superoxide dismustase, as measured by improved cortical evoked potentials, may also be enhanced when combined with deferoxamine.[52] This may involve the ability of deferoxamine to inhibit the conversion of hydrogen peroxide to the hydroxyl radical. However, it is the superoxide dismutase that appears to be the major contributor, since deferoxamine by itself does not improve neurological outcome, even though it may improve the overall survival rate.[53,54] Catalase, another agent that inhibits the production of superoxide radicals, has also been shown to limit infarct size in rats exposed to focal ischemia when the catalase is administered linked to polyethylene glycol.[55] Finally, other superoxide radical scavengers such as α-tocopherol,[56] dimethyl sulfoxide,[57,58] and mannitol[59] have been shown to result in some neurological improvement in a range of animal models.

The net result of all of these studies is an intense interest in this field. To date, however, no human data are available and the animal research can best be described as exciting, if not yet wholly convincing. Further work must be done before the proper role of a specific superoxide radical scavenger can be recommended for treatment of a specific neurological injury.

EXCITATORY NEUROTRANSMITTERS, EXCITOTOXINS, AND RECEPTOR BLOCKERS

Specific amino acids, particularly L-glutamate and L-aspartate, appear to be the main excitatory neurotransmitters in the brain.[60] In the last 30 years, it has been found that there are at least four subtypes of these excitatory amino acid neurotransmitters, as well as a variety of competitive and noncompetitive antagonists (Table 2). Over this same

time, various diseases have been shown to be related to these neurotransmitters. In animals, for instance, neurotransmitters that produce excitation of neurons can cause focal degeneration if injected into the brain in excess.[61] The observation that cytopathological changes occur in postsynaptic structures in a manner consistent with the neuroexcitatory amino acid excess resulted in the development of the term *excitotoxin*.[62,63] This term is used to explain how neurotransmitters such as glutamate and aspartate can both excite cells in a normal fashion and also produce neuronal death when these substances are present in excess. This excessive excitation by excitatory neurotransmitters has also been suggested as responsible for neuronal loss in cerebral palsy, Alzheimer's disease, Huntington's disease, and other chronic degenerative disorders.[61] More recently, excess neurotransmitters have been shown to be important in status epilepticus.[61,64-67]

While there are four receptors as shown in Table 2, much of the attention for possible clinical use has focused on the *N*-methyl-D-aspartate (NMDA) class of glutamate receptor and its pharmacologic antagonists. The interest has been based on extension of the evidence developed for status epilepticus. Not only do excitatory amino acid antagonists protect against chemically induced seizures,[68,69] they are potent against sound-induced seizures,[70] as well as against seizures induced by kainate.[71] Some of these compounds, including 2-amino-7-phosphonoheptanoic acid, are as potent anticonvulsants as are benzodiazepines.[72] Researchers now believe that ischemia may result in massive release of excitatory neurotransmitters that cause neurological injury independent of the direct damage produced by the initial ischemic insult. As a result, the administration of NMDA-receptor blockers is now being evaluated as a way of providing cerebral resuscitation following ischemia.

The use of NMDA antagonists has been limited by the fact that the blood-brain barrier prevents the penetration of most of these compounds into the brain in sufficient quantities to obtain the high concentrations of agent needed to be effective.[61] Studies on agents such as 2-amino-7-phosphonoheptanoic acid (Table 2) have used focal injection or brain microdialysis to evaluate areas of the brain that may benefit from use of NMDA antagonists. More recently, this area has been advanced with studies using (+)-5-methyl-10,11 dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate (Table 2), a noncompetitive NMDA antagonist that is readily able to cross the blood-brain barrier.[70] In general, since the release of excitatory neurotransmitters occurs rapidly after an ischemic episode and these substances disappear rapidly during reperfusion,[73] it would be most useful to administer these agents prior to a global cerebral ischemic event. In fact, this has been demonstrated to be true, since preischemic administration of NMDA-receptor antagonists does result in diminished brain injury.[70] On the other hand, this is not likely to be a clinically relevant model, since medical management is not available prior to most global cerebral ischemic events because these events most often are unexpected and occur out of hospital. Nevertheless, the same principles can be applied in focal cerebral ischemia, since these injuries produce both an area of direct injury and a penumbra at risk for the development of further injury. Excitatory neurotransmitter receptor blockade should limit the damage ischemia produces in the penumbra, even if given after the ischemic event. In certain studies, (+)-5-methyl-10,11 dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine maleate has been shown to reduce infarct size following focal ischemia from middle artery occlusion, even when given 2 hours after the occlusion.[74] This research needs further development, however, as might be anticipated for a mode of therapy that is as new as is the whole area of treatment with NMDA blockers. Possible extension of this research into global cerebral ischemia and brain resuscitation protocols for humans may be years away.

SUMMARY

The area of cerebral resuscitation has become an exciting area of research in critical care medicine. It is a complicated field, however, which has seen attempts to protect the brain using a single therapy such as barbiturates ultimately disappoint investigators in the field. It is likely that much more work needs to be done in understanding the intracellular metabolic and biochemical effects of ischemia before therapies can be designed that are likely to be effective. This work might ultimately require knowledge of how ischemia or hypoxia interrupt cellular RNA and DNA machinery before these effective therapies can be developed. Before we are discouraged by the difficulty of the task, however, it is useful to review how much progress has been made in understanding the pathophysiology of ischemic brain injury in the past decade, so that we may be challenged to continue our efforts in this exciting area of critical care medicine.

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Evaluation and Percutaneous Management of Atherosclerotic Peripheral Vascular Disease

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ATHEROSCLEROTIC peripheral vascular disease (PVD) of the lower extremities deprives a person of the ability to exercise to their satisfaction, later of the ability to perform the activities of their daily life, and finally of their legs themselves. Peripheral vascular disease has long been managed by the vascular surgeon utilizing endarterectomy and peripheral arterial bypass.[1-4] These surgical techniques have been shown to be effective in relieving symptoms and to be durable with the passage of time. Postoperative morbidity, rising health care costs, and refinement of percutaneous catheter technology have led to the development and use of nonsurgical modalities for the management of PVD.[5] Patient acceptance of nonsurgical, percutaneous procedures such as percutaneous transluminal balloon angioplasty (PTA) is high.[6] Increased utilization of these procedures has led to improved techniques and adjuncts to therapy, as well as more critical review of long-term results. This article will review the evaluation and nonoperative management of PVD, with an emphasis on the newer modalities of management presently being investigated.

INITIAL PATIENT EVALUATION

Patients with PVD usually present to their physicians with exertional pain in their feet, calf, thigh, or buttocks. Heaviness or numbness in these regions is less commonly reported. It is important to ascertain how long patients have had the symptoms, how far they can walk before the onset of pain, how much the symptoms interfere with their daily activities, and, finally, if they are having symptoms suggestive of tissue ischemia, such as pain at rest or a nonhealing ulcer. Physical examination will help to localize the arterial stenoses and will help to distinguish arterial disease from neurological, venous, or other abnormalities.[7] Doppler measurement of ankle blood pressure will provide additional data on the severity of the arterial disease. A useful ratio is a comparison of the ankle pressure, to the brachial arm pressure, or ankle-brachial index. A normal ratio is 1.0 or greater.[8-10]

MANAGEMENT APPROACH

Patients with minimal symptoms that do not interfere with their life-style are best treated conservatively. A consistent exercise program, walking 1 to 3 miles daily as tolerated, can be very effective in improving collateral circulation with relief of symptoms. Patients with more severe, life-style–altering claudication who have had symptoms for less than 2 months are also given a trial of walking. A significant percentage (50%) of them will develop sufficient collateral flow around their arterial disease to relieve their symptoms without further intervention.[11] Cessation of smoking, by limiting progression of the disease process, may also allow sufficient collateral formation to relieve symptoms. Patients who have chronic symptoms, have failed a walking program, or have symptoms suggesting an acute occlusive event are studied by angiography. The arteriogram defines the location of the arterial stenosis or occlusion, its extent, the collateral vessels present, and the level of arterial reconstitution distal to the obstruction. These factors influence the type of percutaneous intervention offered to the patient.

PATHOLOGY

Atherosclerotic arterial plaque is a mosaic of components including lipid deposits, fibrous tissue, cellular hyperplasia, and calcium.[12-14] The plaque may be eccentric or may narrow the lumen concentrically. It may be focal, diffuse, or intermittent. The lesion may grow slowly or may rapidly occlude the lumen owing to hemorrhage within the plaque or thrombus formation across the area of narrowing. The latter most often occurs in a setting of slow arterial flow or actual stasis. With rapid onset of vascular occlusion, collateral flow does not have time to form, resulting in acute symptoms with possible ischemic change.

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PERCUTANEOUS TRANSLUMINAL BALLOON ANGIOPLASTY

First described by Dotter and Judkins in 1964,[15] PTA is the mainstay of nonoperative arterial recanalization.[16] This modality gained popularity in the United States with the development of the double-lumen balloon angioplasty catheter by Gruntzig and Hopff in 1974.[17,18] The foremost technical necessity in PTA is the ability to maneuver a guide wire across the area of stenosis or occlusion. An inability to do this has resulted in a technical failure rate for iliac and femoral PTA of 15% to 50%.[19-26] Recent catheter and guide-wire modifications have markedly decreased this problem. Balloon inflation causes a "controlled injury" to the vessel wall, increasing the luminal diameter.[12-14] This occurs by "cracking" the diseased intima and media, separating it and the plaque. Healing, with normal fibrous tissue deposition, maintains the lumen in the expanded state. Patients receive platelet inhibitors (aspirin, 125 mg/d, and dipyridamole, 75 mg three times per day) to prevent acute clotting across the thrombogenic-exposed intimal and medial surfaces. Heparin and nitrates are given during the procedure to accomplish the same purpose.[27,28]

Complications of PTA can be divided into those related to the arterial puncture, such as groin hematoma formation, which though possibly requiring blood transfusion seldom have significant long-term sequelae, and those associated with the dilation procedure itself. The latter include subintimal guide-wire passage, which often terminates the study but rarely causes other difficulty; distal embolization, which though rare, may necessitate thrombolytic therapy or embolectomy; and vessel occlusion, which may be due to arterial dissection, acute thrombosis, or raising occlusive intimal flaps as a result of balloon dilation. Vascular occlusion is usually managed by vascular bypass surgery, unless thrombus can be lysed percutaneously. Allergic reactions to contrast media are treated symptomatically with diphenhydramine hydrochloride, steroids, and epinephrine. Contrast overload can lead to transient renal failure. Permanently decreased renal function following contrast administration is seen preponderantly in patients with prior renal failure and diabetes. Adequate hydration has proved to be the best preventive. Significant complications, defined as those requiring operative management or transfusion or resulting in permanent renal failure, are seen in 1% to 8% of cases.[20,22,29-38] A 3% to 15% rate is noted for all complications.[19,29-31,33,36,38-40]

Table 1.—Aortic Dilation

Source	N	Primary Success, %	Follow-Up (Mean)	Follow-Up Success, %	Comments
Tegtmeyer et al[44]	32	91	1 mo–4.5 y (14 mo)	75	3 redilated
Charlebois et al[43]	14	100	1 mo–5 y (16 mo)	100	. . .
Morag et al[42]	14	93	1-5 y (3 y)	92	. . .
Johnston et al[41]	17	. . .	3 y	70	. . .

Table 2.—Iliac Artery Dilation

Source	N	Primary Success, %	Follow-Up (Mean)	Follow-Up Success, %	Comments
Colapinto et al[53]	66	78	4 y	78 of primary	All occlusions
Mortarjeme et al[35]	66	84 stenoses	2 y	100 of primary	. . .
		33 occlusions		100 of primary	
Waltman[33]	100	97	3 y	92	. . .
Zeitler[49]	88	. . .	5 y	61	. . .
Spence et al[48]	160	93	3 y	80	. . .
Olbert et al[50]	40	84	3 y	67	. . .
Schneider et al[37]	200	93	5 y	85	. . .
Borozan et al[51]	22	73	3 y	28	. . .
Kadir et al[38]	141	96	3 y	89	. . .
Zeitler et al[36]	782	85	5 y	50	80% for claudication
Gallino et al[29]	153	95	5 y	83	. . .
Knight et al[47]	. . .	. . .	3 y	58	. . .
Sampson et al[45]	69	88	4 y	78 of primary	. . .
van Andel et al[40]	194	96	7 y	90	. . .
Colapinto et al[34]	112	. . .	2 y	86	. . .
Fletcher et al[21]	26	92	4 y	40	. . .
Korogi and Takahashi[23]	6	83	3 mo–2 y (1 y)	100 of primary	All occlusions
Daniell et al[52]	15	53	1-3 y (2 y)	100 of primary	All occlusions
Graziani[22]	18	44	4 y	22 of total	All occlusions
Johnston et al[41]	598	. . .	5 y	55 of total	. . .
Morag et al[42]	14	93	1-5 y (3 y)	92	. . .
Rubinstein et al[20]	26	70	4 y	76 of primary	. . .
Wilms et al[46]	15	93	3 mo–4 y	80	Intraoperative

Table 3.—Femoropopliteal Artery Dilation

Source	N	Primary Success, %	Follow-Up	Follow-Up Success, %	Comments
Greenfield[30]	79	87	3 y	84	. . .
Zeitler[49]	1916	74	2.5 y	55	Limb salvage, Dotter technique
Martin et al[26]	46	76	2 y	57	Occlusions
Spence et al[48]	119	84	3 y	70	. . .
van Andel[56]	. . .	. . .	2 y	84	Stenoses
Olbert et al[50]	197	69	4 y	49	. . .
Schneider et al[37]	682	88	5 y	68	. . .
Waltman et al[57]	98	86	3 y	75	. . .
Borozan et al[51]	30	64	3 y	18	. . .
Probst et al[55]	57	. . .	2 y	70	F/U angiogram
Gallino et al[29]	329	97	5 y	58	. . .
Sampson et al[45]	89	92	4 y	50	Limb salvage
Krepel et al[32]	164	93 stenoses	5 y	70	. . .
		58 occlusions	10 y	45	. . .
Fletcher et al[21]	44	91	4 y	58	. . .
Graziani[22]	67	82	4 y	66	. . .
Johnston et al[41]	284	. . .	5 y	40	Good runoff, 55%
Murray et al[24]	177	82	4.5 y	62	. . .
Wilms et al[46]	20	90	1 mo–4 y	70	Intraoperative
Milford et al[25]	27	74	2 y	47	Limb salvage
Tonnesen et al[31]	50	70	3 y	43	Retrograde popliteal

Table 4.—Tibial Artery Dilation

Source	N	Primary Success, %	Follow-Up	Follow-Up Success, %	Comments
Sprayregen et al[59]	6	83	1.5 y	40	. . .
Starck et al[58]	42	85	. . .	. . .	. . .
Wilms et al[46]	5	80	1 mo–1 y	40	Intraoperative
Schwarten and Cutcliff[39]	131	100 stenoses, 88 occlusions	2 y	86	. . .

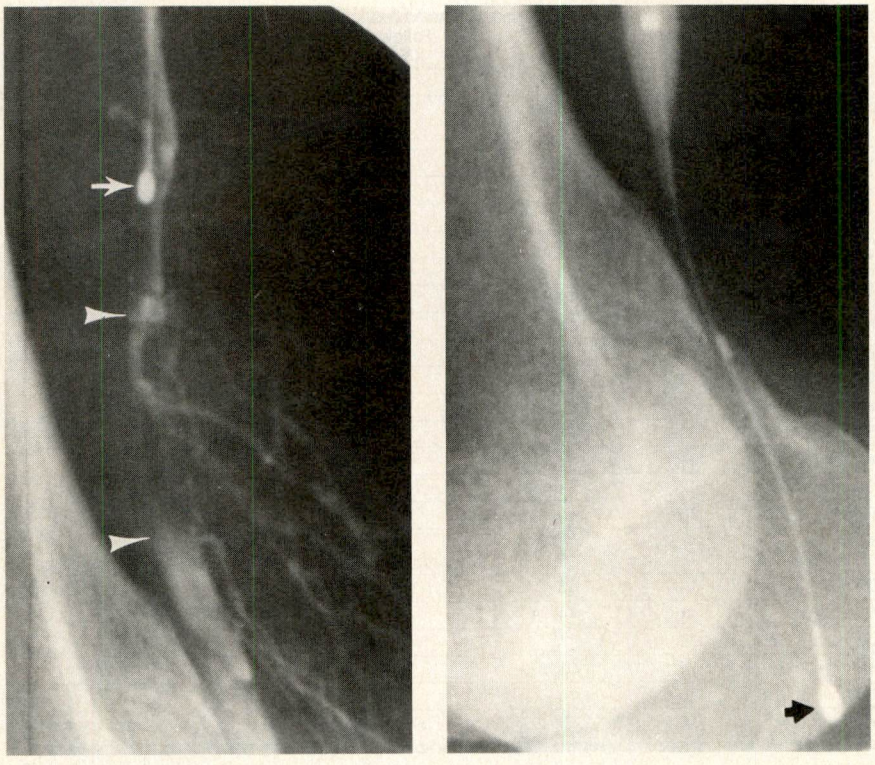

Fig 1.—Left, Obstructed superficial femoral artery–popliteal segment in a 55-year-old man with life-style–altering claudication. A 2.0-mm laser probe (arrow) at distal superficial femoral artery occlusion (arrowheads) as demonstrated by contrast injected through introducer sheath. Right, Once laser probe (arrow) is through the obstruction, a 6-mm angioplasty balloon is inserted over the laser fiber to dilate the artery.

LONG-TERM PTA RESULTS

Percutaneous transluminal angioplasty has been performed for a sufficient number of years that the long-term results are now available for review (Tables 1 through 4). Aortic dilation, often using a two-balloon "kissing" technique, provides a primary success rate of 90% to 100% with a 3-year patency rate of 70% to 100%.[41-44] Iliac dilation is often divided into procedures performed for stenosis vs occlusion. For all lesions, a primary success rate of 84% to 95% can be expected. Follow-up study for 3 to 7 years shows a continued patency rate of 40% to 90%, with the vast majority of studies showing approximately 80% patency at this time.* Both the primary and long-term success rates for iliac occlusions are much lower, ranging between 33% and 83% for primary success with 75% to 100% of these remaining patent at 2- to 4-year follow-up.[20,22,23,52,54] Femoral angioplasty has a primary success rate of 70% to 85%. Follow-up study for 3 to 5 years shows continued patency in 45% to 75%, with most studies averaging 50% to 70% patency.† Though only limited experience with tibial angioplasty is reported, primary success can be expected in 85% of cases. One- to 2-year patency rates range from 40% to 85%.[39,46,58,59] Redilation of failed angioplasty sites is well reported and seems to have the same primary success rate as PTA performed for the first time.[24,44,60]

*References 20-22, 29, 33-38, 40-42, 45-53.

†References 21, 22, 24, 25, 29-32, 37, 41, 45, 46, 48-51, 55-57.

FACTORS AFFECTING PATENCY IN PTA

The factors that affect the long-term patency of vessels that have undergone balloon angioplasty have been well described. Similar to vascular bypass grafting, adequate inflow to the dilated segment and outflow from it are essential.[2,3,36,41,55,61-63]

Similarly, the extent of symptoms relates directly to the overall success of angioplasty and bypass grafting.[25,36,45,61] Patients with ischemic symptoms, in whom therapy is being provided for limb salvage, will have a lower success rate than patients treated for claudication. This is because much more extensive disease can be expected in the former group, who already have inadequate collateral circulation to maintain limb viability. In patients with ischemic ulcers, a short-term increase in distal blood flow is often sufficient to allow ulcer healing and limb salvage. Even with late vessel or graft occlusion, unless a second insult occurs to the limb, recurrent ulceration and ischemia are often avoided.[24,25,45,49]

Certain additional variables in the success of PTA are directly related to the plaque morphology. These variables are not seen with operative arterial grafting as the entire diseased segment is bypassed. The length of an arterial stenosis or occlusion is the first important variable. Long-segment stenoses (>10 cm) indicate extensive atherosclerotic disease and PTA in such femoral arteries has been disappointing. We have noted a 67% patency rate at 56 months for femoral stenosis less than 7 cm, by which time all stenoses longer than this had reoccluded.[24]

Occlusions are not as easily categorized. An occlusion may consist of a long segment of severely atherosclerotic vessel, for which PTA results similar to those seen with long-segment stenoses can be expected. More often, an occlusion represents a short segment of high-grade plaque formation that, owing to stasis, has occluded. Thrombus then forms either proximal or distal to the plaque until a major collateral branch is reached. This serves to provide outflow to the distal vessel collaterals or inflow from the proximal vessel collaterals. By lysing the thrombotic segment with urokinase (Abbokinase, Abbott Laboratories, Chicago, Ill) or other fibrinolytic agents, the underlying short-segment stenosis or occlusion can be uncovered. Angioplasty of this area will yield similar results to those seen with initial short-segment lesions.[54,64-67]

Eccentric plaque formation and calcified plaque are two additional pathological features that decrease the efficacy of

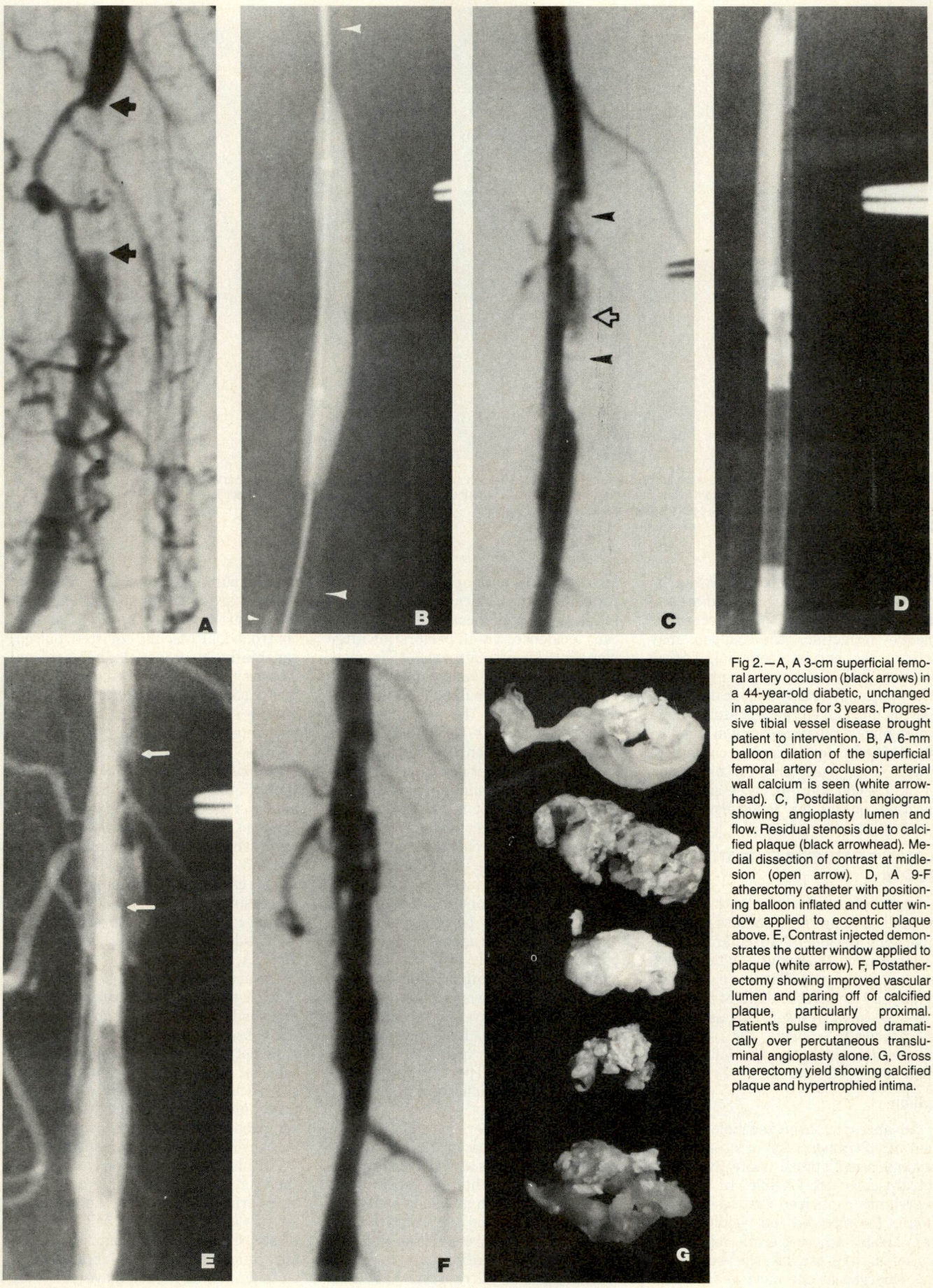

Fig 2.—A, A 3-cm superficial femoral artery occlusion (black arrows) in a 44-year-old diabetic, unchanged in appearance for 3 years. Progressive tibial vessel disease brought patient to intervention. B, A 6-mm balloon dilation of the superficial femoral artery occlusion; arterial wall calcium is seen (white arrowhead). C, Postdilation angiogram showing angioplasty lumen and flow. Residual stenosis due to calcified plaque (black arrowhead). Medial dissection of contrast at midlesion (open arrow). D, A 9-F atherectomy catheter with positioning balloon inflated and cutter window applied to eccentric plaque above. E, Contrast injected demonstrates the cutter window applied to plaque (white arrow). F, Postatherectomy showing improved vascular lumen and paring off of calcified plaque, particularly proximal. Patient's pulse improved dramatically over percutaneous transluminal angioplasty alone. G, Gross atherectomy yield showing calcified plaque and hypertrophied intima.

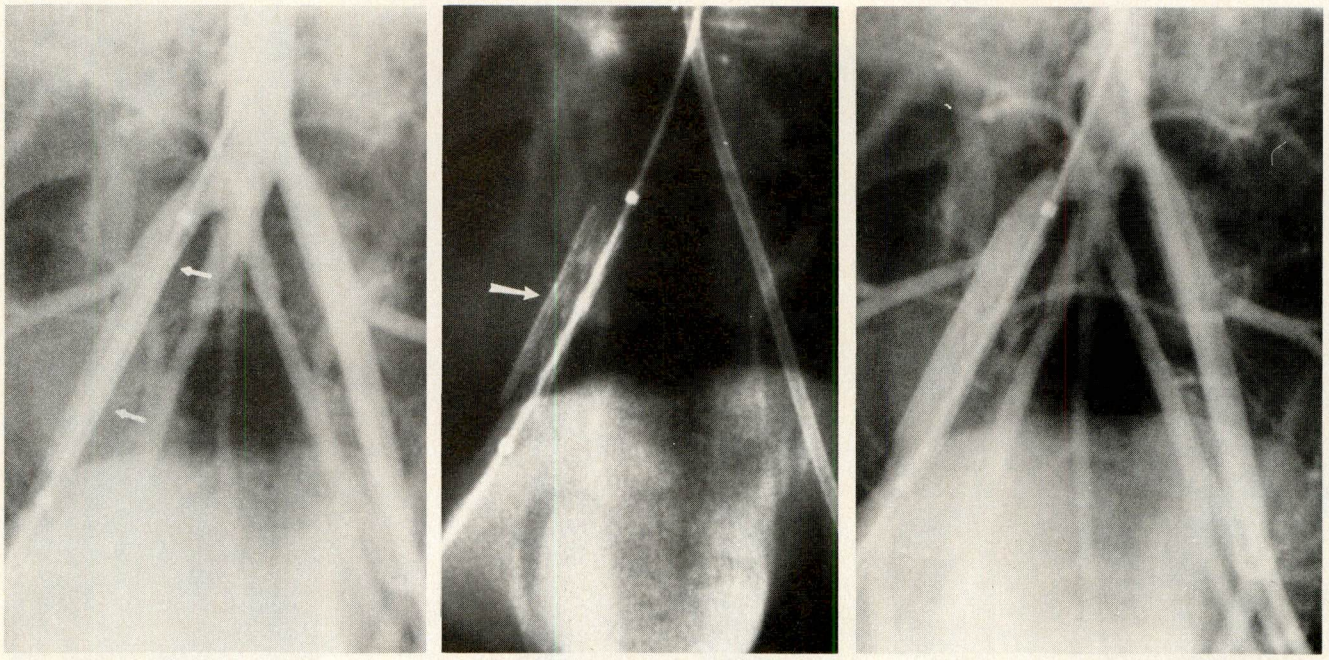

Fig 3.—Left, Intravascular stent (arrows) loaded on a balloon angioplasty catheter placed in the external iliac artery of a swine. Center, Stent inflated (arrows). Balloon catheter remains through stent. Right, Contrast injections following stent insertion showing a patent external iliac artery and branch.

PTA.[55] Balloon angioplasty works by creating a fissure in a diseased area of intima and media. With eccentric plaque formation, the balloon may stretch the normal, compliant vessel wall that is elastic enough to spring back into position following balloon deflation, leaving unchanged the eccentric plaque impinging on the vessel lumen. Similarly, calcified plaque may be too hard to crack, never permitting full expansion of the balloon. Both of these situations portend poorly for long-term vessel patency.

NONOPERATIVE ALTERNATIVES TO PTA

In an effort to increase both primary as well as long-term success rates in managing peripheral vascular disease, several new therapeutic alternatives are being explored. These are designed to increase the technical ability to cross the stenoses and occlusions as well as to physically remove the offending plaque, decreasing the possibility of late restenosis.

Laser

Advances in laser technology have permitted transmission of laser energy through small optical fibers that make intravascular use feasible. In vitro research has confirmed that laser radiation in the infrared and visible ranges can ablate atherosclerotic plaque.[68-73] Based on these studies, the argon laser has emerged as the most widely used energy source with open-fiber vascular recanalization. Clinical and experimental studies have documented a significant incidence of wall perforation after bare-fiber laser treatment.[68-73] The metal-capped fiber, or *laser probe*, was developed to avoid the likelihood of arterial perforation.[74-78] The metallic cap is mounted on a 300- to 600-μm quartz fiber, depending on the metal probe size, and uses either an argon or neodymium:yttrium-aluminum-garnet energy source. The hot metal probe seeks the path of least resistance, which is the vascular residual channel surrounded by plaque (Fig 1). Eccentric plaque, particularly that which is calcified, may force the laser probe into the arterial wall and result in perforation. In our experience, as well as that of others, the perforations readily seal.[79,80] The most significant remaining problem associated with perforation is inability to regain access to the native vessel lumen for continued therapy. Recent versions of the hot-tip laser, which follow a guide wire or have a small port for direct emission of laser radiation, were designed to avoid this problem.

High-energy lasers have been shown to vaporize atherosclerotic plaque but are prone to arterial wall perforation. Open-ended, nonthermal lasers have been modified with a balloon-centering device and dispersed light beam from an argon energy source, decreasing the likelihood of perforation.[81]

Intravascular ultrasound has been used to automatically trigger the laser pulse at areas of intimal thickening using "smart laser" technology. Manually controlled, ultrasound-assisted, pulsed, tunable dye lasers are also being tested. These systems attempt to decrease the perforation rate by limiting the amount of laser energy the normal arterial wall encounters.

Once the lesion is crossed, an angioplasty catheter can be advanced through the small irregular laser channel for subsequent balloon dilation (Fig 1, right). The angioplasty is essential to establish a satisfactory lumen; however, the current guide-wire tracking probes can be passed through the lesion successive times so that additional plaque can be removed, possibly creating an adequate lumen without the need for PTA.

An argument for plaque removal is that postdilation restenosis may be diminished. Some initial reports support this observation.[55] Unfortunately, we have not had this experience with the thermal laser probe. Evaluation of 47 superficial femoral artery angioplasty procedures managed with use of the laser probe for total occlusion shows a patency rate of 29% at 12 months.

At this time, it is too early to predict the eventual impact of laser devices on long-term vessel patency and particularly as an alternative to balloon angioplasty. Controlled randomized studies are difficult to establish clinically and suitable animal models have yet to be

developed. Comparative data on therapeutic efficacy of a particular modality are hard to interpret given the complexity of the lesions being treated and the simplistic angiographic criteria used to describe them.

Atherectomy

Restenosis following balloon angioplasty has some correlation with the degree of residual narrowing of the vessel following maximal dilation.[55] The notion of removing plaque from the treated artery to reduce the likelihood of recurrence has led to the development of the atherectomy catheter (Fig 2). The Simpson atherectomy catheter, now approved by the Food and Drug Administration, can be inserted percutaneously for management of arterial atherosclerotic stenoses and occlusions.[82-85] The atherectomy portion of the Simpson catheter consists of a steel cylinder with a longitudinal opening on one side and a low-pressure balloon on the other. When the balloon is inflated, it presses the opposite face of the cylinder against the diseased intima. The atherosclerotic plaque that protrudes into the window is shaved free by a central rotating cutter as it is advanced across the cylinder opening. The atherectomized debris is compacted in a distal collecting chamber. The entire assembly is withdrawn when the collection chamber is full of atherosclerotic plaque and the samples are removed. The catheter can then be reinserted through an indwelling arterial introducer sheath, usually in the common femoral artery, and further lesion debulking can be performed. The leading distal tip of the atherectomy catheter has a small, flexible guide wire that is used to maneuver through stenotic lesions. Atherectomized samples (Fig 2) are evaluated microscopically. Portions of intima, internal elastic lamina, and media are often seen in the average specimen. Percutaneous catheter atherectomy has, in our experience, been a reliable method of reestablishing normal blood flow through stenotic and occluded segments of superficial femoral arteries. Subintimal and medial vessel-wall dissection, intraluminal debris, and residual plaque, often seen on angiography following PTA, have not been seen following atherectomy.

The Simpson atherectomy catheter has been approved for use in the United States for less than 1 year. Therefore, only preliminary results are available. We have had a 95% primary success rate treating iliac and superficial femoral artery stenoses, without distal embolization or vessel occlusion. Follow-up is too short to be meaningful. Others have reported a restenosis rate of 9% at 6-month follow-up for femoral atherectomy. In this series of 144 patients, a 4% complication rate was seen, with distal embolization, vascular thrombosis, and false aneurysm formation at the puncture site being the most serious problems encountered (Barry Katzen, MD, Donald Schwarten, MD, Arina van Breda, MD, William Cutliff, MD, Kenneth Rholl, MD, John Simpson, MD, unpublished data, February 1988).

Stents

A third method of managing PVD is to percutaneously place an intravascular graft, or *stent*, across a stenotic region (Fig 3). By acting as a scaffold, the intravascular stent may allow primary recanalization of long-segment, eccentric, and calcified stenoses and may prevent recurrent stenoses in these high-risk lesions.[86-91] Initial laboratory and clinical trials with several stainless steel–alloy intravascular stents have shown that they quickly become endothelialized, preventing the thrombosis often seen with surgical grafts.[87,89] This neointima also appears to retard plaque formation at the stented site, decreasing the probability of restenosis. While only initial data are presently available, intravascular stents may play a significant role in the percutaneous management of PVD not amenable to balloon dilation.

CONCLUSION

It is apparent from the long-term results discussed herein that balloon angioplasty has stood the test of time for the management of peripheral vascular disease. As with all treatment modalities, a variety of factors effect the long-term results of balloon angioplasty. For short-segment concentric iliac and femoral artery stenoses or occlusions, PTA represents the optimal mode of nonoperative therapy. Other modalities such as lasers, atherectomy catheters, and intravascular stents may play a significant role in managing those lesions not adequately dealt with by the balloon. Time will tell which of these new technologies proves most beneficial in which situations. Certainly though, this is an exciting, rapidly progressing time in the nonoperative management of atherosclerotic peripheral vascular disease.

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Charlene Breedlove, MA, *Section Editor*

Forty Years of Medical Genetics

Victor A. McKusick, MD

I AM often asked why I shifted from cardiology to medical genetics; I did not. In fact my activities in the two fields developed in parallel; it was a matter of phasing out cardiology and phasing in medical genetics. Indeed, my first published piece of clinical investigation was on a genetic topic, the syndrome of spots and polyps (1949), and my first book was *Heritable Disorders of Connective Tissue* (first published in 1956). In 1952 when I completed house-staff training there was no clinical discipline of medical genetics and no formal training program. So I trained in cardiology, which brought my attention to the Marfan syndrome because of the conspicuous cardiological complications.

In the early 1950s, for 5 years after completing the chief residency at Johns Hopkins in Baltimore, Md, I was a junior faculty person. I pursued the analysis of heart sounds and murmurs by a method called *spectral phonocardiography* and, at the same time, studied the Marfan syndrome and related conditions that could be interpreted as generalized and hereditary disorders of connective tissue.[1]

Medical genetics was institutionalized at Johns Hopkins on July 1, 1957, when Dr A. McGehee Harvey, chairman of the Department of Medicine, established a division of medical genetics in his department. When he asked me to direct the multifaceted chronic disease clinic established by Dr J. Earle Moore, I set the condition that I be permitted to develop a division of medical genetics and a strong genetic aspect in the Moore Clinic program.

At the same time the division of medical genetics was started near the shores of Chesapeake Bay, a similar division was founded in a young school on Puget Sound. Robert Williams asked Arno Moltulsky, a hematologist, to head the Seattle program. Arno and I both probably felt more comfortable pushing into the unknown by reason of having backgrounds in an established subspecialty.

I can claim to be an autodidact in genetics. My interest in the subject was first sparked by a stimulating teacher at Tufts College in Medford, Mass, Prof Paul A. Warren. Near the end of my internship I encountered a patient with intestinal polyps and melanin spots of the buccal mucosa, lips, and digits. Four more patients came along in fairly quick succession, and I heard through the grapevine that Harold Jeghers had cases in Boston. About that time Jeghers went to Washington, DC, as the first full-time professor of medicine at Georgetown University. As a resident, I made a practice of traveling to Washington, DC, to write up these cases for publication with Jeghers.[2]

A major fringe benefit of this work was the contact it gave me with geneticist Bentley Glass, professor of biology at The Johns Hopkins University. I sought his advice in interpreting the family data, and he remained a mentor and colleague for 15 years, until he left Baltimore. I also must acknowledge a large debt to Curt Stern, partly for his monumental textbook of human genetics and particularly for his brief but powerfully influential visiting professorship in January 1959. During that month, Stern gave 12 lectures to a packed house in the main auditorium of The Johns Hopkins Hospital. There were never fewer than five or six department chairmen on hand. Although not a physician, he made the significance of genetics to medicine vividly evident. By close associations during the 4 weeks he lived in the hospital, he made a deep impression on the fellows, students, and faculty. He was a gentle person who had been associated with most of the great figures of European and American genetics in the period after 1920. He was also one of the many splendid lecturers in genetics from a golden age of classic genetics. A memorable series of lecture films with Theodosius Dobzhansky, L. C. Dunn, George Beadle, James Crow, Joshua Lederberg, Hermann Muller, and many others, including Stern, was made about that time and it is still a marvelous archive.

Associations With the Jackson Laboratory

Much of the foundation for my work in medical genetics, and much valuable tutelage, came from my associations for almost 30 years with the Jackson Laboratory, Bar Harbor, Me. The founder of the laboratory, C. C. Little, was a student of William E. Castle, the professional father of mammalian genetics (and the biologic father of William B. Castle). Elizabeth Shull Russell, also on the staff, was a student of Sewell Wright, who in turn was a student of W. E. Castle. The body of knowledge they had gathered on the genetics of the mouse was highly valuable to my development. The way the association with the Jackson Laboratory came about is an interesting story.

A main research interest of mine, in addition to heritable disorders of connective tissue, continues to be genetic linkage and chromosome mapping. I was intrigued by the elegance of mapping, in drosophila in particular and in other organisms such as maize. My first application for a National Institutes of Health grant to study linkage in humans was submitted in the

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fall of 1958. A few years previously, some autosomal linkages had been described, eg, between one form of elliptocytosis and Rh blood type. Dr Robin Bannerman, who was with me, had a collection of elliptocytosis families to study and we also proposed to study linkage in the Marfan syndrome, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and some other disorders.

The project site visit for that grant application had an important by-product. One of the visitors was Earl Green, director of the Jackson Laboratory. Knowing that I come from Maine, he invited me to visit the laboratory, which I did in July 1959. During that visit the idea arose to have a summer course in medical genetics "to teach the teachers," particularly the faculty of medical and other professional schools, in a setting where advantage could be taken of the mouse models and the great depth of knowledge in mammalian genetics available at the laboratory. The course was initiated in the summer of 1960 as a joint venture of The Johns Hopkins University and the Jackson Laboratory, with funding from the March of Dimes. In one form or another, the "Short Course" has continued annually since that time. In 1989, the 30th annual course will be given; since the Jackson Laboratory will be 60 years old in 1989, the Short Course will have been in existence during half its life span.

The course, which lasts 2 weeks, began as "Short Course in Medical Genetics." On alternate years, between 1967 and 1977, it was predominantly a mouse course and was called "Short Course in Experimental Mammalian Genetics." Since 1977 it has been a combined course called "Short Course in Medical and Experimental Mammalian Genetics." The present course title reflects the remarkable degree to which mouse genetics and human genetics have converged, thanks to the development of somatic cell genetics and molecular genetic methods used in the study of both species. So similar are the approaches to studying the two species that the existence of two separate courses is no longer justified.

The March of Dimes has supported the Bar Harbor course throughout its 30-year history—the longest grant in the 50-year history of that foundation. In the spring of 1959 I had been appointed to the Medical Advisory Board of the March of Dimes, which had extended its purview from poliomyelitis to birth defects. Later that year, when the idea of the course was conceived, I went directly to Basil O'Connor and to Dr Tom Rivers, vice president for medical affairs, and got their agreement to support the course. In 1966, when the question arose whether the March of Dimes would also support the "mouse course," as it had the medical genetics course, I approached Basil O'Connor, the autocratic president of the foundation, with some diffidence, expecting an answer in the negative. But he said, "Why not? What reason do they study those mice if it isn't to understand birth defects?"

The success of the Bar Harbor course stimulated the creation of a 1-week European equivalent, first held in Sestri Levante on the Ligurian coast of Italy in April 1988. It promises to be an annual success also, although it has a long way to go to match the record of the Bar Harbor course.

Chromosomal Mapping

Linkage (for chromosome mapping) was an effective research theme for a developing division of medical genetics. To define inborn errors of metabolism and the carrier state and to identify linkage markers, one needed to have biochemical genetics; one needed cytogenetics for reasons that are perhaps obvious; one also needed immunogenetics for the definition of linkage markers; one needed mathematical genetics and population genetics for the linkage analysis; and finally, one needed clinical genetics for proper study of the families and the disease phenotypes.

Our most successful linkage endeavors were (1) the estimation of the interval between the color-blindness loci and the G6PD locus on the X chromosome in the early 1960s (with Ian Porter) and (2) the mapping of the first gene assigned to a specific non–sex chromosome: Duffy blood group locus to chromosome 1 in 1968 (with Roger Donahue and others). In 1963, my associate S. H. Boyer, with others, used the principle of linkage disequilibrium to conclude that two hemoglobin loci, δ and β, are very tightly linked. Furthermore, with John Graham of Chapel Hill, NC, he showed that the locus for classic hemophilia is very close to the locus for G6PD. Very tight linkage of adenylate kinase to the nail-patella syndrome was also demonstrated, a fact that should prove useful to molecular geneticists in isolating the gene for the nail-patella syndrome by reverse genetics.

My interest in human-gene mapping led to a collaboration with Dr Frank Ruddle at Yale in establishing international human gene–mapping workshops that have met annually or biannually to give the aficionados an opportunity to collate information on the gene map. Since 1971, I have kept up a human gene–map newsletter; whereas one page sufficed at the beginning, now the chromosome gene list is 100 closely printed pages.

The gene-map listing has become an integral part of *Mendelian Inheritance in Man*, the catalogs of inherited traits, normal and pathological, that I started about 1960. The first catalog, that of X-linked disorders and traits, was assembled when I was studying the X chromosome to find out what genetic information it carried. The list of X-linked disorders was like a photographic negative from which one could create a positive picture of the genetic constitution of the X chromosome. When I started studying the Amish in late 1962, I initiated a catalog of autosomal recessive traits; in those inbred groups, we expected to find "new" recessive traits and needed to know the old ones. For the sake of completeness the autosomal dominant catalog was added in 1964. Also in that year, the catalogs were put on computer to facilitate updating and indexing. The eight published editions, 1966 through 1988, were all computer based—a first for a publication in this format.

Mendelian Inheritance in Man aims to be a comprehensive gene encyclopedia, with one uniquely numbered entry per gene locus. At the beginning, and indeed until relatively recently, genes could be identified only on the basis of mendelizing phenotypes. Increasingly in the last few years, genes have been cloned, sequenced, and mapped and their expression studied in vitro. When this has been achieved, the gene is listed in the catalogs, even though no mendelian variation related to the gene has been identified.

For almost 2 years *Mendelian Inheritance in Man* has been also available on-line, where it is continuously updated. Information added today in Baltimore is available worldwide tomorrow.

Studies of the Amish

In 1962 in an article in a drug company "throwaway" journal about a Lancaster County, Pa, family practitioner, Dr David Krusen, I read that "achondroplasia is unusually frequent among the Amish." With that, my interest in the Amish was stimulated. Soon after, I was introduced again to the Amish when, as a member of the faculty advisory committee for the Johns Hopkins Press, I saw the manuscript of John Hostetler's *Amish Society*. I immediately recognized this as a marvelous opportunity for study. I teamed up with Hostetler for this purpose and undertook to study dwarfism as the first project.

I suspected that it was not really achondroplasia that was present in the Amish because that condition is a dominant,

and recessive conditions, not dominants, are expected to be unusually frequent in inbred groups such as the Amish. It turned out that there are two frequent forms of dwarfism in the Lancaster County Amish, both recessive. One was a previously described disorder called the Ellis–van Creveld syndrome, or six-fingered dwarfism, of which 50 reports of cases had been published by 1964. In that year, in one fell swoop we doubled the number of reported cases.

The other form of dwarfism was a previously undefined entity that we called cartilage-hair hypoplasia. This condition occurs in Amish communities throughout the country. Like the Ellis–van Creveld syndrome, it is not limited to the Amish; it was merely easier to recognize among the Amish because of the large number of cases. Indeed, cartilage-hair hypoplasia is the cause of short stature in actor Billy Barty and in Pat Bilon, who played E. T. in the movie of that name. It turns out that cartilage-hair hypoplasia is also very frequent in Finland, probably because the demographic history of the Finnish population bears some similarities to that of the Amish. The mutation in the Finns almost certainly arose independently of that in the Amish.

The Amish studies met with as much success as they did in part because of John Hostetler, who enjoyed a good rapport with these people, and because I went to them as a physician prepared to help them with their health problems. The Amish projects, which continue to this day, have been great fun, simply because the people are so interesting to work with. They can be exasperatingly stubborn, but on the whole are always fair. And they have a sense of humor, too. On one occasion my wife and I, with one of our children, went to spend a weekend with an Amish family in Mifflin County, Pa. On arriving we were ushered into the sitting room by the white-bearded Amish patriarch. Anne went to sit down in a rocking chair and, hesitating, said, "Is this your chair, Mr Detwiler?" to which he replied with a twinkle, "They are all my chairs."

The Years at Johns Hopkins

I have been blessed by a marvelous variety of exciting topics on which to work and an institution of great depth and breadth in which to work. I have been at Johns Hopkins uninterruptedly for more than 46 years and a member of the faculty continuously since 1947. I have not even taken a sabbatical. Such a sessile career is unusual in academic medicine, which, as a rule, leads to a nomadic existence. The sessile career has been possible because Johns Hopkins is, figuratively and literally, at a crossroads. It is located on the trade routes, let us say, and it has been possible for me to pitch my tent beside the road and find out what goes on in far-off Cathay without ever traveling there myself.

Just as my clinical genetics research was facilitated by being in a large general hospital, introducing genetics into the mainstream of clinical medicine was also made easier by being so situated. Especially when studying pleiotropic conditions such as the Marfan syndrome and other heritable disorders of connective tissue, being at a large general hospital was a great asset. Patients in pediatrics, ophthalmology, dermatology, cardiology, and other specialties were useful in defining the full range of the clinical picture.

But it is also true that one cannot always sit within a hospital, even one with as strong a drawing influence as Johns Hopkins, and get the information one needs. It is necessary to get out into the homes and examine multiple family members and go to likely sources in search of new cases that come to the attention of specialists or social services, including cases not likely to find their way to the hospital. Only in this way can one define the full range of a given condition's severity or even know its true familial nature.

Homocystinuria illustrates these last points. In 1964, I learned from Charles Dent, of London, England, who visited Hopkins to give the Thayer Lectures, that this inborn error of metabolism closely simulates the Marfan syndrome, both having dislocated lenses and many of the same skeletal features. He also told me about the frightful thrombotic episodes in some of these patients. I was immediately reminded of three sibs who appeared to have the Marfan syndrome, but had unaffected parents, suggesting recessive inheritance (Marfan syndrome is a dominant). They also had thrombotic episodes that were fatal by age 20 in two of them. While Dent was still in Baltimore, I was able to demonstrate, by the same cyanide nitroprusside test used routinely for cystine in urine, that the surviving sister had homocystinuria. Shortly thereafter Neil Schimke and I initiated a nationwide search for cases by having urine samples submitted from patients with ectopia lentis, identified in large eye clinics around the country. As a result, in 1965 we published a study of a series of 20 families with 38 affected persons.[3] This mode of ascertainment demonstrated that patients with homocystinuria are not all mentally retarded as previously supposed; at least two of our patients have PhD degrees. The first cases reported had been found in the course of a urine chromatography screening in institutions for the mentally retarded in Northern Ireland; naturally all patients described were mentally retarded.

Historical Writing

As stated, my first clinical investigation, published with Jeghers, was on polyps and spots. This also led to my earliest (actually second) historical piece, a long clinical biography of Jonathan Hutchinson,[4] who in 1896 described identical twins with what we now know as the Peutz-Jeghers syndrome. The biography was based in part on Hutchinson's voluminous writings and in part on his large collection of clinical illustrations acquired for The Johns Hopkins Medical School by Sir William Osler after Hutchinson's death in 1913.

History has always interested me greatly. In a sense, genetics is history. The history of our species is written in the human genome. The best way to get "on top" of a subject is to know how the field got to its present state. The initial chapter in *Cardiovascular Sound in Health and Disease* (1958) is a long discussion of the history of cardiac auscultation and the study of heart sounds and murmurs. The first specific reference to heart sounds that I found was in a posthumous publication of Robert Hooke, discoverer of the law of elasticity.

My work in the analysis of heart sounds by sound spectrography—"spectral phonocardiography"—stimulated me to write a biographical essay on the engineer Osborne Reynolds, whose *Reynolds number* defined the conditions of transition from laminar flow to turbulent flow, which are also the conditions for generating heart murmurs or vascular bruits.[5] Genetic studies led me to write biographical essays on Walter S. Sutton, the Kansas farm boy who wrote an early article proposing the chromosomal basis of mendelism,[6] and on Marcella O'Grady Boveri, the Boston-born, Massachusetts Institute of Technology–educated biologist who married her professor in Würzburg, Germany, and made his chromosome theory of cancer known to the English-speaking world by translating his monograph on the subject.[7]

Genetic Nosology

The work that has most absorbed my interest and energies throughout my career can be labeled *genetic nosology*—the delineation of discrete genetic entities. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes*, first published in 1966 and now in its eighth edition, with a continuously updated online version available worldwide, really is an encyclopedic expression of this interest in genetic nosology. The March of

Dimes–supported conferences on birth defects held annually at Johns Hopkins from 1968 to 1972 and called "Clinical Delineation of Birth Defects," served the same purpose.

The Amish studies had a large nosologic aspect. Their inbreeding, large families, and "tight" sociological characteristics made for increased visibility of ordinarily rare autosomal recessive disorders. In addition to cartilage-hair hypoplasia, about a dozen "new" genetic entities were delineated on the basis of the Amish studies. One of these was the hydrometrocolpos syndrome in which transverse vaginal septum is combined with polydactyly and, in some patients, congenital heart malformation. Two affected sisters were found in Lancaster County, Pa, and two others in an Amish community in Geauga County, Ohio. We could show that the four parents of the two affected sibships shared common ancestors. In collaboration with C. Everett Koop, then head of pediatric surgery at Children's Hospital of Philadelphia, Pa; Roger B. Scott, gynecologic surgeon at Babies and Children's Hospital in Cleveland, Ohio; and Robert L. Bauer, general practitioner in Intercourse, Pa, I reported hydrometrocolpos as a mendelian recessive disorder, in 1964. It was for Robert Kaufman, a former student of mine, to point out that polydactyly and cardiac malformation are occasional pleiotropic manifestations of the gene responsible for the hydrometrocolpos.

In addition to the Amish population, my laboratories for genetic nosology have been the clinic and the library. Genetic nosology was something that I could continue during the years (1973 to 1985) that I was chairman of the Department of Medicine and physician-in-chief of The Johns Hopkins Hospital.

I am finding that it is an advantage in nosology not only to work in a large general hospital but also to have long tenure in that hospital. For example, in the early 1950s, Frank Ellis and Harry Robinson, dermatologists at Johns Hopkins, diagnosed cutis laxa in a 3½-year-old girl. I studied her at age 16; she then looked 20 years older than her mother. Recently, I saw her again at age 36. The hypertension she has had for 10 to 15 years turns out to be secondary to fibromuscular dysplasia of the renal arteries bilaterally; she has the same condition in her carotid arteries. A nonsmoker, she has pulmonary bullae. I presume that in this instance arterial fibromuscular dysplasia is a consequence of the heritable disorder of connective tissue. Shortly before seeing this patient, I saw a 1-year-old child with cutis laxa and multiple peripheral pulmonary arterial stenoses. I can, of course, cite many other examples of the value of long-term follow-up study.

It is a source of great pleasure to me that clinical genetics has achieved full professional status, with its own certifying board (founded in 1980) and the other accoutrements of a genuine clinical subspecialty. I would not have predicted this, indeed did not predict it as late as 1974.[8] It seemed to me then that clinical genetics would be an activity confined mainly to a few academic and regional medical centers that could support large groups of specialists in medical genetics (cytogeneticists, biochemical geneticists, genetic counselors, and so on). These institutions, it seemed to me, have ways to regulate a discipline such as this and monitor performance, making "boards" unnecessary. Such was not the judgment of my colleagues, however. It is still true that most genetic services will be provided by groups because of the need for diverse expertise.

Even more than witnessing the professionalization of clinical genetics, I am delighted to see the extent to which basic genetics has been woven into the fabric of clinical medicine. Mapping genes on chromosomes is the modern anatomy, and knowledge in this area is providing a neo-Vesalian basis for all of medicine.[9]

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Patrick A. Murphy, MD, *Section Editor*

Blastomycosis

Patrick A. Murphy, MD

CASE PRESENTATION

—Sidney Yoon, MD

A 53-YEAR-OLD white man presented to The Johns Hopkins Hospital, Baltimore, Md, with erythematous lesions on his nose, ear, and palate. He was well until March 1987, when he developed a painful palatal lesion that made it so difficult to swallow that he lost 9 kg. Three months later a lesion developed on his nose that caused intermittent epistaxis, and after another 3 months a lesion developed behind his right ear.

For editorial comment see p 3164.

All three lesions persisted and enlarged slowly. Biopsy samples were believed to be nondiagnostic but suggestive of epithelioma. Bacterial cultures of the biopsy samples were negative. He denied fever, chills, chest pain, productive cough, headaches, and changes in his bowel habits. He recently noted nocturia and dribbling of urine.

His medical and family histories were noncontributory. He worked for the Maryland State Highway Administration for 20 years as a grass trimmer, weeder, and tidier of highways along the Eastern Shore. He smoked two to three packs of cigarettes per day for 40 years.

Physical examination revealed a thin, white man in no distress. Vital signs were normal and he was afebrile. There was a verrucous lesion behind the right ear that was 2.5 cm in diameter, with central clearing and an active raised edge. A second lesion on his right nostril was invading the nasal cavity. Pressure on both of these caused the appearance of small beads of pus (Fig 1). The palatal lesion had been removed by biopsy, and only an ulcer remained. The chest showed a persistent area of dullness to percussion and crepitations in the right upper lobe. The prostate was smoothly enlarged and nontender. Results of the rest of the examination were normal.

The clinical diagnosis was disseminated blastomycosis with a pulmonary primary lesion and at least three separate skin lesions. It was suspected that the infection also had spread to the prostate. There was no clinical evidence of central nervous system involvement.

Laboratory data were notable for a white blood cell count of 15.7×10^9/L, with a differential cell count of 0.09 band forms and 0.57 polymorphonuclear cells. The chest roentgenogram showed bilateral upper-lobe interstitial infiltrates, which were more pronounced on the right side. Results of routine serum chemistry analyses including alkaline phosphatase, urinalysis, and electrocardiogram were unremarkable.

Biopsy samples of the nasal lesion and the lesion behind the right ear revealed great numbers of yeasts morphologically consistent with *Blastomyces dermatitidis*. These were visible on hematoxylin-eosin–stained sections as well as on potassium hydroxide and methenamine-silver preparations. The previous biopsy samples were obtained and showed identical yeasts. Subsequently, *Blastomyces* was cultured from the nasal lesion. Cultures of sputum and urine were negative for fungus. The prostate was examined by a urologist and by ultrasound. It showed only benign hypertrophy. A lumbar puncture and a computed tomograph of the head with contrast were both negative. He therefore was discharged taking ketoconazole, 400 mg/d, and was followed up as an outpatient.

The patient tolerated the medication well; the lesions on the palate and behind the right ear cleared up and the chest roentgenogram improved. However, the nasal lesion persisted and, after 4 months of therapy with 400 mg/d of ketoconazole, expressed pus contained numerous yeasts; culture again showed growth of *Blastomyces*. The dose of ketoconazole was doubled and the nasal lesion healed slowly. The patient will be treated with 800 mg/d of ketoconazole for a total of 12 months, assuming he continues to tolerate it.

DISCUSSION

Clinical Picture in This Patient

The verrucous hyperplasia and microabscess formation displayed by this man's skin lesions were so characteristic of blastomycosis that no other disease was considered seriously. He had persistent crepitations in the right upper lobe that could not be cleared by coughing. Chest roentgenogram showed fine interstitial infiltrates in both upper lobes, with no evidence of hilar adenopathy. This appearance is nondiagnostic but is consistent with a tuberculous or fungal infection and specifically with the diagnosis of blastomycosis. No biopsy or bronchoscopy was done, but the infiltrates and the abnormal physical signs vanished after therapy with ketoconazole, and it seems reasonable to suppose that they represented a primary pulmonary infection with *B dermatitidis*. We did not pursue a tissue diagnosis of the pulmonary infiltrates because it seemed unlikely that a man would have *Blastomyces* in the nose and tubercle bacilli in the lung.

Blastomycosis frequently involves

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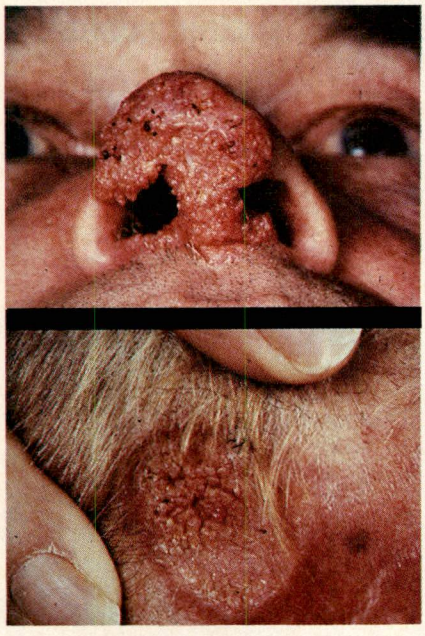

Fig 1.—Two skin lesions typical of blastomycosis. Note the epithelial hypertrophy and microabscess formation.

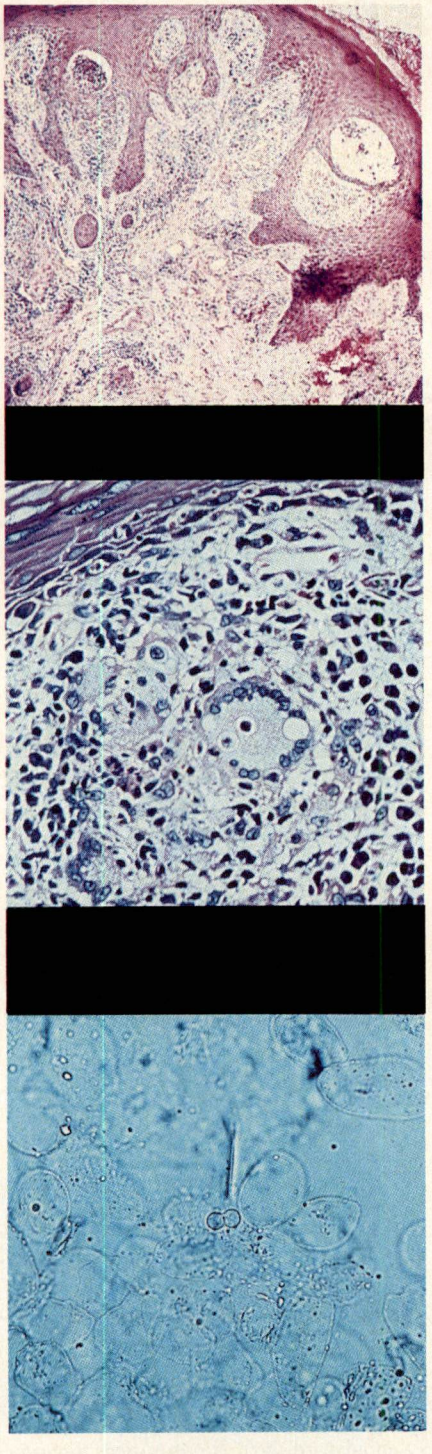

Fig 2.—Three microscopic preparations from the patient's nose. Top, Epithelial hypertrophy, microabscesses in the epidermis, and granulomatous inflammation in the dermis are shown (hematoxylin-eosin, original magnification ×100). Middle, High-power view of a dermal granuloma; the giant cell contains yeasts, and several others are visible in the surrounding tissue (hematoxylin-eosin, original magnification ×400). Bottom, Potassium hydroxide preparation of pus from the patient's nose. A refractile yeast with a broad-based bud can be seen among epithelial cells (×400).

the prostate and epididymis, and our patient did complain of urinary symptoms at only 53 years of age. However, we were unable to find the organism in urine or prostatic fluid, and there was no evidence of inflammation on either physical or ultrasound examination. We concluded that he simply had an unusually early onset of benign prostatic hypertrophy. Since symptoms have persisted, that opinion probably was correct.

Figure 1 shows two of the skin lesions. His nose was his predominant complaint, and a tremendous heaping up of the epidermis can be seen. The lesion stood up from the skin and was studded with miliary abscesses. Pressure on the nose made pus ooze from multiple points. The lesion spread up inside the nose on the nasal septum. One reason for doing a computed tomographic scan of the head of this patient was that sometimes *Blastomyces* tunnels up inside the nose and involve the nasal sinuses, with considerable bony destruction and deformity. In fact, he was examined by an ear, nose, and throat surgeon, and no evidence of such extension was found. The lesion behind the ear showed a red advancing edge and verrucous epithelial hyperplasia in the middle, with fissuring and abscess formation. The hair was white in this area because the patient had been using hydrogen peroxide to treat the lesion.

Definitive evidence of blastomycosis was obtained from the nasal biopsy samples. These showed a marked degree of epithelial hyperplasia, hyperkeratosis, and microabscess formation in the epidermis. The dermis showed giant cells surrounded by epithelioid histiocytes and chronic inflammation. These findings are typical of dermal and epidermal involvement by *Blastomyces*. Even on the hematoxylin-eosin stains, some of the giant cells could be seen to contain yeasts. Methenamine-silver stains and potassium hydroxide preparations showed large yeasts, 5 to 10 μm in diameter, with the broad-based bud formation diagnostic for *B dermatitidis* (Fig 2). The diagnosis was established firmly by growing the organisms.

Central nervous system involvement was an issue in this man. His Mini Mental State score was only 23 or 24 of a possible 30, and we were unsure if that was because of blastomycosis involving his nervous system or if it was a long-term condition. His job suggested that his level of cortical function had never been high. He had been in a severe accident at age 9 years, had been unconscious for 3 weeks, and was not released from the hospital for 9 months. It seems likely that the defect was long-term and related to a head injury in childhood rather than anything to do with *Blastomyces*.

Historical Perspective

This illness was described in this hospital by T. Caspar Gilchrist, MD, who was appointed professor of dermatology when he was 34 years old and served the institution for 36 years. For the whole of that time he did not receive a salary, and the total budget of the Department of Dermatology never exceeded $500 a year. He could be gruff and sarcastic, and the medical students lived in fear of his sharp tongue. However, they packed his outpatient clinics because he was by consent the best teacher of clinical dermatology in the hospital. Dr Gilchrist's first patient had blastomycosis of the hand and was written up in the 1894 *The Johns Hopkins Hospital Reports*. However, the fullest account of the new disease was given by Gilchrist and Stokes in the 1898 *Journal of Experimental Medicine*. Their patient was

a 33-year-old man who had a skin disease for 11 years characterized by slow progression, an active edge, and healing and scarring in the center. It involved the face, with severe deformity. He was sent to Dr Gilchrist by William S. Halsted, MD, as a case of skin tuberculosis. Dr Gilchrist performed a biopsy on the lesion and showed that no tubercle bacilli could be seen, but yeast forms were present. He injected tissue into guinea pigs and showed that they neither developed lesions nor died of tuberculosis. He injected tissue into a variety of other animals and demonstrated that they did develop lesions but that the lesions contained the same yeasts that were visible in material from the patient. He observed that the organism grew as a yeast in the patient but as a mold on a culture plate. The only thing he did not have available was a treatment. He thought the prognosis would be good because the disease was of such long duration, but the patient was unavailable for follow-up and we do not know what happened to him. From what we now know about disseminated blastomycosis, it seems unlikely that he did well.

One did not take pictures in Dr Gilchrist's day, but he illustrated his histological findings with beautiful drawings that are worth viewing in their original form. He noted the tremendous pseudoepitheliomatous hyperplasia but stressed that the basement membrane remained intact. He saw the giant cells and the yeasts within them, but noted that caseation was rather uncommon, in contrast to tuberculosis. He distinguished *Blastomyces* from *Candida* because of the former's large size and broad-based bud. Finally, he drew pictures of the mold form that the yeast assumed in culture. This is one of the few articles still worth reading 90 years after its publication.[1]

Epidemiology

In general, the distribution of blastomycosis in the United States follows the great river valleys of Mississippi, Missouri, and Ohio. However, the edge of the distribution crosses the Appalachians into Maryland and reaches over the Eastern Shore to Salisbury, Md, where the patient had lived since age 9 years. The usual model for fungus diseases is that the fungus lives in the environment somewhere and has a life that is entirely independent of people or animals. However, its spores are airborne and are breathed by humans and animals. In a proportion of those infected, disease develops.

Blastomycosis probably follows this model, but evidence of this is incomplete. It has been difficult to show that *Blastomyces* grows anywhere in the environment. If you take *Blastomyces* in either the yeast or the mycelial form and put it onto soil it dies. There is strong epidemiologic evidence for environmental sources because point-source epidemics are observed. For example, a farmer and his dogs went hunting in a local wood in Arkansas and the farmer and six of eight dogs developed blastomycosis. There was no other case in the farmer's family or among farm workers, so presumably they had been exposed to something in the wood.[2] Generally speaking, even when point-source epidemics have occurred, it has not been possible to isolate *Blastomyces* from the place where the epidemic was presumed to originate. However, most patients have outdoor occupations, frequently near water. Blastomycosis is common in dogs, and an analysis of dog blastomycosis in Wisconsin showed that three fourths of the infected animals lived within 500 m of a body of water.

Three epidemics of human blastomycosis in Wisconsin have been associated with environmental isolation of the organism. Two small epidemics were associated with riverbanks and rotting wood.[3] A large point-source epidemic involved 89 children and 10 adults who were camping in the woods near a beaver pond.[4] The more adventurous children walked out to the beaver lodge, and the most adventurous danced on top of it and threw sticks around. The closer they were to the beaver lodge and the more physically active they were the more likely they were to develop blastomycosis. No one who did not go to the beaver pond developed illness. *Blastomyces* was cultured from the lodge and from rotting wood around the site. From the available information, it seems likely that *Blastomyces* grows in rotting wood at a low pH, especially after heavy rain and if the temperature is high.

The other reason we have trouble with the epidemiology of blastomycosis is that we have no good test for diagnosing infected but asymptomatic cases. For histoplasmosis or coccidioidomycosis, we have skin tests that in general are excellent and show us that there are large numbers of people who live in the endemic areas for those fungi who are infected but never develop the disease. We have no such knowledge in blastomycosis. It is possible that the fungus is rare but virulent for man and that most infected people develop disease. However, there probably are cases of blastomycosis that improve spontaneously. In the beaver dam epidemic, 26 children had symptoms of an acute pulmonary syndrome that probably was caused by *Blastomyces* and another 11 had abnormal chest roentgenograms. Nine children actually had *Blastomyces* identified by culture in the sputum and were treated. Thirty-nine people, 17 symptomatic and 22 asymptomatic, had positive antibody or lymphocyte activation tests and probably were infected. The 39 patients with negative cultures were not treated, and all recovered. This is the principal evidence for the idea that just as with histoplasmosis and coccidioidomycosis, there is an acute pulmonary blastomycosis syndrome that generally improves even if untreated.

Blastomycosis is not common in immunosuppressed people; most patients who have it, like this man, are perfectly normal. We do not know whether the failure to see blastomycosis as an opportunistic infection simply is because there are not many infected people or because of other reasons.

Clinical Picture in General

Most patients with the chronic form of blastomycosis present as ours did, without a recognized acute episode of pneumonia. The clinical symptoms can arise either from the lung or from a peripheral site after spreading to the bloodstream. Several large series have been published that discuss the frequency of various types of organ involvement.[5] Although probably 100% of patients have pulmonary disease, it can be of any degree of severity. About 80% of patients have skin involvement, about half have involvement of bones and joints, about one fourth of men have involvement of the reproductive system (involvement of the female reproductive system is unusual), and about 5% have involvement of the nervous system. In contrast to tuberculosis, renal and lymph node involvement are rare.

Two common types of pulmonary involvement are nodule formation and massive consolidation, both suggestive of lung cancer. It is not unusual for a mass to be removed from the lung under the impression that it is a carcinoma only to have *Blastomyces* isolated or seen in the middle of it.

The skin disease in most patients is as Gilchrist described. A rare form of cutaneous blastomycosis is seen in pathologists or veterinarians who inoculate themselves with *Blastomyces* from patients or dogs. They get a skin lesion and local lymphadenopathy that look like inoculation tuberculosis. In the past, such lesions often healed spontaneously, though nowadays they probably would be treated.

The bone disease usually is asymptomatic and frequently is diagnosed

when a roentgenogram shows round, punched-out lesions at the ends of long bones. It also might present as a joint disease, typically involving a single joint and with a great deal of ligamentous destruction. Even if the infection is controlled with antimycotic treatment, some kind of surgical procedure may be necessary to stabilize or immobilize the joint. We did not do a skeletal survey on this patient because he was not complaining of any bone symptoms and because the discovery of symptomless bone lesions would not have affected his therapy.

The most common type of brain involvement in blastomycosis is cerebral abscess, but meningitis also is seen. We did both a computed tomographic scan and a lumbar puncture in this man because when it comes to treatment, the presence or absence of brain involvement determines whether you must use amphotericin B or whether you can use ketoconazole.

Laboratory Diagnosis

The only certain way of diagnosing blastomycosis is to grow the organism from tissue. Less satisfactory is to see typical yeasts in tissue sections. There is a blastomycin skin test reagent, but it is positive in fewer than half of proved cases and it cross-reacts extensively with other fungi such as *Histoplasma capsulatum*. The same applies to the complement fixation and the immunodiffusion tests that are freely available. Not only do they cross-react with histoplasmosis, but they are positive in only a small proportion of blastomycosis cases proved by culture.[6] Better tests are being developed, and two of them were used in the epidemic that originated from the beaver dam. One was an enzyme-linked immunosorbent assay for antibody to *Blastomyces* antigen A; the other measured activation of peripheral blood lymphocytes by *Blastomyces* antigen.[7] Both tests were specific for blastomycosis and both were positive about 80% of the time in proved cases. The enzyme-linked immunosorbent assay probably will become available commercially in the near future.

Treatment

As I stated previously, there is a syndrome of acute pulmonary blastomycosis that improves spontaneously and does not require therapy. However, we have no good way of predicting a happy outcome, and in the past most patients with proved blastomycosis have died. This is true even for apparently isolated pulmonary nodules removed as carcinomas and found to contain *Blastomyces*. When one removes fungomas of other etiologies, it is probably all right not to treat the patient if there is no evidence of disease anywhere else. Patients with blastomycosis who have not been treated have re-presented with progressive pulmonary or systemic disease. We know that chronically infected patients like the man reported herein or Gilchrist's patient do badly: the mortality of disseminated blastomycosis before therapy was available was 92% at 5 years. I think the safest thing at the moment is to assume that if *Blastomyces* is isolated from a patient it should be treated.

The standard treatment until recently has been amphotericin B, and it has been a large dose both in terms of daily rate and of the total amount given. There is evidence now that ketoconazole is equally effective for all forms of the disease except brain abscesses and meningitis.[8] One has to use large doses for a long time. Although the literature on ketoconazole therapy is recent, so that follow-up is relatively short, it seems likely that many cases will be manageable either with ketoconazole or with one of the new congeners that are under development like fluconazole or itraconazole. Data from two articles that discuss ketoconazole therapy are aggregated in the Table. With 800 mg/d of ketoconazole, 100% of extraneural blastomycosis was cured, with follow-up ranging between 1 and 3 years. With 400 mg/d of ketoconazole, the cure rate was 80% but side effects were minimal. The 800-mg dose was associated with a considerable degree of toxic reactions. Almost half the patients had anorexia, nausea, or vomiting, one third had a rash or pruritus, and one fourth had manifestations of endocrine dysfunction such as impotence, gynecomastia, or menstrual disturbances. Many were unable to continue taking the high dose. Surgery usually is not necessary for blastomycosis, although it might be required for joint destruction or facial deformity.

Results of Treatment of Blastomycosis With Low- and High-Dose Ketoconazole for at Least 6 Months[9,10]

Result	No. of Patients	
	400-mg/d Dose	800-mg/d Dose
Cured	60	32
Persistent infection	4	0
Relapse after therapy	6	0

To summarize, if the patient has only extraneural blastomycosis, I advise the use of ketoconazole at a daily dose of 400 mg. The dose always can be raised later if the disease does not respond, and amphotericin B can be substituted if it proves to be necessary. This is a chronic, slow-moving disease, and nothing is going to happen overnight, so there is plenty of time for reconsideration. The man reported herein proved to be resistant to therapy with 400 mg/d of ketoconazole but seems to be responding well to 800 mg/d.

I am grateful for the editorial assistance of Genevieve Losonsky, MD.

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The Synergistic Triangle

The first century of Johns Hopkins Medicine has been spectacularly successful. People, ideas, and new techniques all flowed from the new institution and changed medicine and medical education throughout the world. The celebration of the centennial stimulates us to look back, identify the reasons for that success, and make sure they are incorporated into planning for our next century.

I believe the key to the success of The Johns Hopkins Medical Institutions has been a synergistic balance of research, teaching, and patient care. We think of these three activities as forming a triangle, and this triangle provides the strength and stability essential for all our endeavors. The dean's job is to ensure that all three sides of the triangle grow at the same rate. There are, and have always been, forces in the environment that tend to stimulate the growth of one or the other of the three sides. For example, there was a time in the 1960s when research grew rapidly and patient care and teaching suffered. More recently, the demands of patient care have increased and research and teaching have been threatened.

The first and most fundamental role of the dean in maintaining balance is in the selection of people to fill important leadership posts. The dean must oversee the choice of department directors who are committed, in their own recruiting, to keeping the triangle equilateral. It has been argued that there are few people today who combine the qualities of a great teacher, a leader in the science of medicine, and a top-notch clinician. This may be true, but it does not mean that today's leaders are lesser persons than their predecessors. The field of medicine has expanded beyond the ability of even the best to excel in every area. Nevertheless, department directors can ensure that teaching, research, and patient care are all equally strong in the department, if not in each individual.

The dean can also maintain symmetry by shifting resources from one area to another to meet the needs of the time. For example, Johns Hopkins has an enviable record of being among the top few medical schools in the amount of competitive research funding received from the National Institutes of Health. However, we are running short of space and face the possibility of being forced to turn down research grants because we do not have laboratories in which to conduct the research. This could, in short order, result in the departure of our best faculty and lead to a decline in the quality of research. There are no longer any federal funds for research construction, so funds must be found elsewhere. Fortunately, the synergy of our three principal activities has sustained us, for we have been able to use funds generated by our successful clinical practice, along with philanthropic support, for the construction of a new research building. The clinical departments will be able to use space in this new building as a powerful inducement in recruiting new faculty. So, this new building, financed in part by clinical revenues, will not only boost our research program but will also enhance our ability to maintain the high quality of our faculty.

Much of the early distinction of Hopkins Medical School arose from the then uniquely intimate relationship between the university and the hospital. Incorporation of students into the day-to-day work of the hospital not only trained the students well but also contributed to the vigor of the place. The intellectual architect of The Johns Hopkins Medical Institutions, John Shaw Billings, put it well 100 years ago, in 1889, when he said, "The clinical teacher must do his best; keen eyes will note every error in diagnosis, every failure in results of treatment; moreover, the very act of teaching clarifies and crystallizes his own knowledge." In the same address, Billings went on to say, "the sick in a hospital where medical instruction is given receive more constant, careful and thoughtful attention than those in a hospital where no such instruction is given." Faculty are still attracted here because it is a *teaching* institution, and they relish the stimulation provided by bright, creative students.

Unlike research and patient care, which are subject to outside pressures and build a momentum of their own, teaching is kept vigorous only by our own constant attention. Furthermore, the quality of teaching is not as easily measured as research productivity and clinical activity. We conduct course evaluations each year based on students' questionnaires to assess teaching, but students' evaluations are not enough and often tend to reward the most popular teacher, rather than the best. To supplement the students' appraisal, we have added a professors' award given by a committee of professors who evaluate a teacher's performance. We must be constantly alert to ensure that faculty teach what students need to know and not what they, the faculty, want to teach because of their special interests. Teaching must also be recognized as one of the most important criteria for promotion.

The quality of the educational process depends not only on teachers but also on students. Therefore, efforts to support educational programs also include strategies to attract students with broad interests and talents—for example, our decision to drop the Medical College Admissions Test as an entrance requirement and our FlexMed admission program. The FlexMed program is especially significant in that it permits students to take an extra year or 2 after college to broaden their experience and education before entering medical school.

In 1889, John Shaw Billings spoke of the importance of research when he stated that the mission of the new institution was to "give to the world men who cannot only sail by old charts, but who can make new and better ones for the use of others." (Billings can be forgiven for failing to foresee in 1889 that the new institution could give the world both men and women with this ability.) The "better charts" that Billings spoke of are the product of creative people, and the support of talented young people in pursuit of their own research projects is one of our proudest traditions. Recently, however, competition and regulation pushed junior faculty to see more patients and, hence, they had less time in their lives for science. Research began to lose ground in clinical departments, and patient care was receiving disproportionate emphasis.

To ensure a continuing supply of clinicians with research interests and experience, we established the Clinician Scientist Program. We set up an internal peer review system to select junior faculty for awards of up to $50 000 a year for 2 years to provide time for them to develop projects and seek

ongoing support from the National Institutes of Health or other sources. More than 80% of the 50 recipients have done just that and established themselves as competent investigators in ophthalmology, cardiology, immunology, oncology, endocrinology, and genetics. The program was started with $2.5 million from the clinical practice reserves, but another $2.5 million has been raised from external sources. Thus, money earned by the clinical departments has been reinvested in their own future viability by supporting the development of leaders for tomorrow. The shift of resources from the clinical to the research side of the triangle has made it possible for us to invest in buildings and people for the future and, thus, increase the strength of the whole system.

We must also reinvest in clinical practice. As practice patterns shift to outpatient settings, we must provide appropriate facilities not only to maintain our competitive position in providing patient services, but also to ensure that we have access to such settings for training our students. Thus, we have joined with the hospital to create an ambulatory-care building—an investment in the future of clinical practice and teaching that will preserve the symmetry of the triangle that has made The Johns Hopkins Medical Institutions so strong.

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Medical Grand Rounds at Hopkins

With this issue, THE JOURNAL commences publication of selected case discussions from medical grand rounds at The Johns Hopkins Hospital, Baltimore, Md.[1] Case discussions as a form of teaching began with William Osler and have continued at Hopkins.[2] Osler performed rounds in the clinic on patients he had never seen before; he took a history and did a physical examination on the spot, and he said whatever he wished about them, drawing on his immense personal experience and his encyclopedic knowledge of the literature in three languages. Usually what Osler had to say was remarkably shrewd. Of course, he was in a somewhat privileged position: if Osler said the diagnosis was typhoid, no intern was going to quibble about the negative Widal's reaction.

See also p 3159.

With time, people who could discuss anything at a moment's notice became scarce, and rounds changed. The venue was moved from the clinic to an auditorium, the time became Saturday morning, and the cases discussed were inpatients rather than outpatients. Each patient was presented by a house officer and discussed by a faculty member. While the house officer had memorized every detail of the case, the history was edited heavily, and no presentation ever exceeded 5 minutes. The goal was to teach young physicians how to organize and present the pertinent aspects of the case in a logical and expeditious fashion. The patient was always present and sometimes was asked to corroborate or expand on what the house officer said.

The discussant was now a faculty member who had been involved personally in the care of the patient, and the discussion focused on a particular clinical aspect of the case at hand. Occasionally, a distinguished visitor would be invited to discuss a case, but that was rare. Most discussants were members of the Department of Medicine, but it was not uncommon for cases to be discussed by neurologists, psychiatrists, dermatologists, or surgeons. The discussants were under considerable pressure. They usually were informed of their responsibility on Wednesday evening; thus, they had Thursday to consult the literature, organize their talk, and prepare slides. The photography department needed Friday to make the slides, although in emergencies they could produce them at an hour's notice, and at least one discussant began his talk 5 minutes before the slides arrived in the projection booth. Discussants were strictly limited to 20 minutes, and at 18 minutes the chairman would ostentatiously begin to consult his watch.

The audience was composed of all the faculty members of the Department of Medicine as well as virtually all the members of the medical house staff. The only excuse for a house officer to miss rounds was to have a patient with cardiac arrest. The audience numbered in the hundreds, filling the steeply banked seats of Hurd Hall and overflowing into the balconies and the entrance hall. Once the discussion was finished, the audience members were free to ask any question that occurred to them. No quarter was given or expected, and the question-and-answer periods were sometimes quite acrimonious.

Grand rounds have evolved further now, but they retain more than a trace of their origins. Three patients are presented and discussed during a 1½-hour period on Saturday mornings. These are teaching exercises given for the benefit of young physicians by faculty members who have been involved personally in the care of the patient. They are clinically oriented and address specific aspects of the case. Occasionally, but not always, patients are present to help make a specific point. The auditorium is larger, the audience still numbers in the hundreds, and physicians from the community often attend. Cases for discussion are selected by the chairman of the Department of Medicine in concert with the four assistant chiefs of service. The main criterion for inclusion is clinical interest; no attempt is made to cover the whole field of medicine over the course of a year or any other period. Cases are still presented from memory by residents, who are still expected to (and do) know the most arcane details about their patients. The time pressure has been reduced, as both resident and discussant usually get about 2 weeks' notice, although emergency performances by either are not unknown.

These case discussions are offered for what they are: records of what a particular physician thought was worth saying about one of his/her patients. They are not encyclopedic; no one can cover everything in 20 minutes. They are enjoyed by the people who hear them and are believed to deserve a wider audience. They represent a special feature of Hopkins medicine: patient-oriented discussions by thorough and scholarly physicians. Perhaps this is not too far from William Osler's original rounds.

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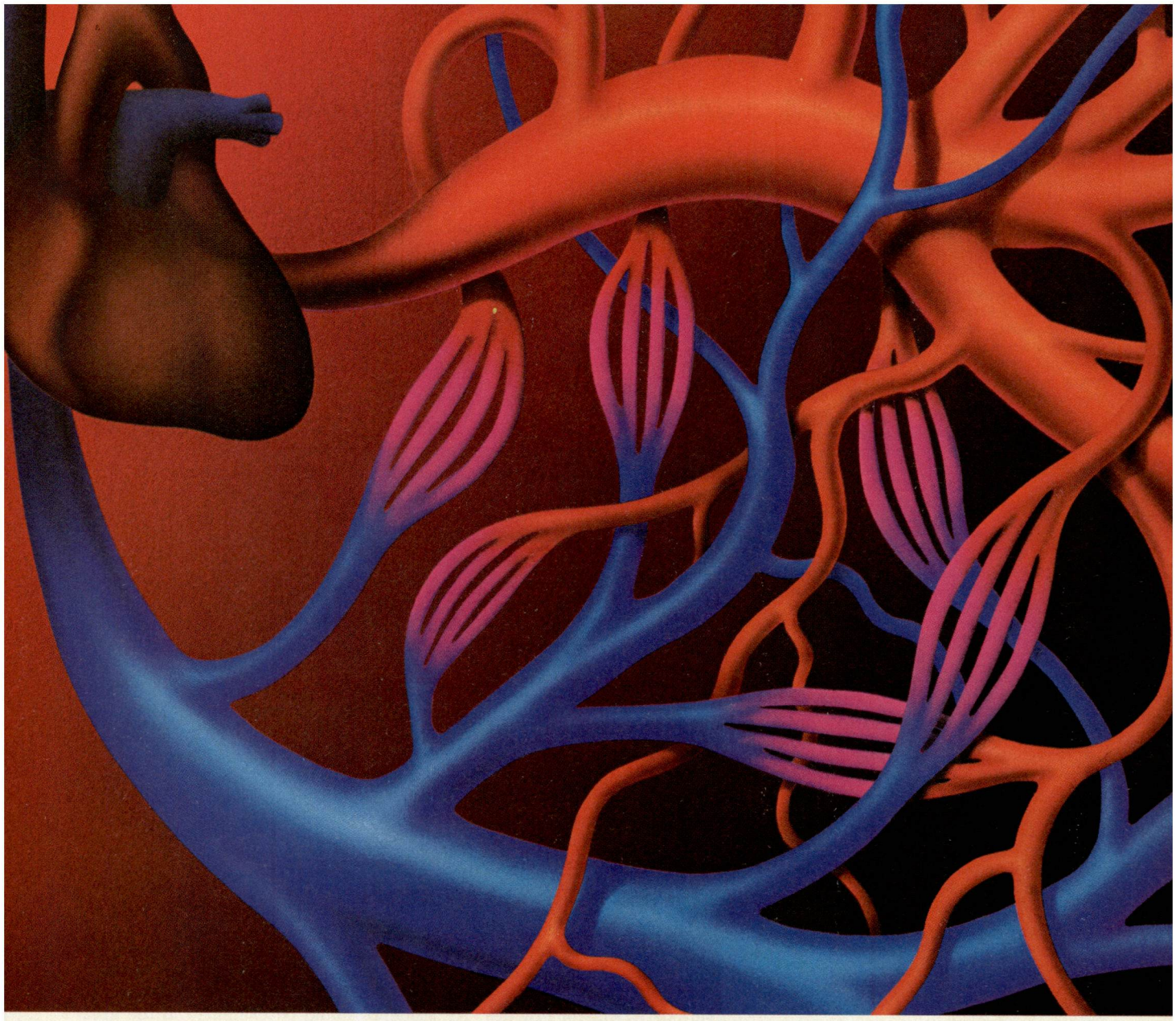

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LICENSE TO PRACTICE. . . .

BY WILLIAM OSLER, M.D.,
PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE.

In connection with the license to practice, there are, it seems to me, three courses open: 1. A continuance in the plan at present, widely prevailing, which makes the college the judge of the fitness of the candidate; and State supervision is only so far exercised that the diplomas are *vised*, and registered, if from legally incorporated schools. 2. The appointment by the State or by parties so deputed of a board of examiners which shall, irrespective of diplomas examine all candidates for the license. 3. The organization of the entire profession in each State into an electorate which shall send representatives to a central parliament, having full control of all questions relating to medical education, examination and registration. . . .

Theoretically, there can be no question (particularly in democratic communities) that a State board should be elective, not appointed by the Governor or the societies. An elective board is in reality a medical parliament, which should take cognizance of all matters relating to medical education, and, perhaps, though of this I am not so sure, of questions of public health within the State. The assembly districts or other territorial divisions which might be made, would send one, or perhaps two, representatives to the board (depending upon the professional population in each district). The electors would be constituted by all practitioners irrespective of schools, which had registered at a certain date. A man who had practiced, even without a diploma, for a certain time would, under these circumstances, have to be recognized and permitted to register.

. . . The necessary expense would be met—first, by the fees paid by the candidates for examination; secondly, by a small annual tax levied upon all registered practitioners. . . .

The first important function of the board would be the regulation of the minimum standard of education required in entering the profession. It is perfectly legitimate that the profession should say, through its representatives, what should be the qualifications of a candidate who desires to enter upon the study of medicine. In law this holds good; why should it not be so with us. . . .

The examination and registration of candidates would constitute the most important function of the board. . . .

There need not be any difficulty in the existing differences between the various schools of practice. All students would be examined in the great primary divisions, anatomy, physiology and chemistry, and so also in pathology and morbid anatomy, in obstetrics and in operative gynecology and in medical jurisprudence.

. . . I am free to confess that this scheme may, to some, seem Utopian, but I am firmly convinced that the majority of those who hear me to-day will live to see State Boards organized on this, or upon a modified plan.

Opposition will be strongest on the one hand from the schools, which look askance at any measure likely to interfere with their prerogatives, and on the other hand the members of the homeopathic and eclectic fraternity, not unnaturally, dread lest in any such arrangement a full measure of justice should not be meted them.

. . . If we are truly anxious to deal fairly with them in a matter, not relating so much to our own as to the interests of the public, I am quite sure that we shall find them ready and willing to join hands in such a laudable work. Nor must we talk to them of concessions, but acknowledge plainly their rights, which before the law are the same as our own.

To move surely we must move slowly, but firmly and fearlessly, confident in the justness of our claims on behalf of the profession and of the public, and animated solely with a desire to secure to the humblest citizen of this great country in the day of his tribulation and in the hour of his need, a skill worthy of the enlightened humanity which we profess, and of the noble calling in which we have the honor to serve.

(*JAMA*. 1889;12:649-654)

Edited by Annette Flanagin, RN, MA, Assistant to the Editor, and Micaela Sullivan-Fowler.

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Before prescribing Seldane® (terfenadine), please see Brief Summary of Prescribing Information, which appears on the reverse side.

Only SELDANE provides fast, unsurpassed relief[1-5] that lets patients stay alert[1,6,7] so they can perform at their best

Seldane® (terfenadine) 60 mg Tablets

BRIEF SUMMARY

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Seldane (terfenadine) is available as tablets for oral administration. Each tablet contains 60 mg terfenadine. Tablets also contain, as inactive ingredients: corn starch, gelatin, lactose, magnesium stearate, and sodium bicarbonate.

INDICATIONS AND USAGE

Seldane is indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

CONTRAINDICATIONS

Seldane is contraindicated in patients with a known hypersensitivity to terfenadine or any of its ingredients.

PRECAUTIONS

Information for patients

Patients taking Seldane should receive the following information and instructions. Antihistamines are prescribed to reduce allergic symptoms. Patients should be questioned about pregnancy or lactation before starting Seldane therapy, since the drug should be used in pregnancy or lactation only if the potential benefit justifies the potential risk to fetus or baby. Patients should be instructed to take Seldane only as needed and not to exceed the prescribed dose. Patients should also be instructed to store this medication in a tightly closed container in a cool, dry place, away from heat or direct sunlight, and away from children.

Carcinogenesis, mutagenesis, impairment of fertility

Oral doses of terfenadine, corresponding to 63 times the recommended human daily dose, in mice for 18 months or in rats for 24 months, revealed no evidence of tumorigenicity. Microbial and micronucleus test assays with terfenadine have revealed no evidence of mutagenesis.

Reproduction and fertility studies in rats showed no effects on male or female fertility at oral doses of up to 21 times the human daily dose. At 63 times the human daily dose there was a small but significant reduction in implants and at 125 times the human daily dose reduced implants and increased post-implantation losses were observed, which were judged to be secondary to maternal toxicity.

Pregnancy Category C

There was no evidence of animal teratogenicity. Reproduction studies have been performed in rats at doses 63 times and 125 times the human daily dose and have revealed decreased pup weight gain and survival when terfenadine was administered throughout pregnancy and lactation. There are no adequate and well-controlled studies in pregnant women. Seldane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Seldane is not recommended for nursing women. The drug has caused decreased pup weight gain and survival in rats given doses 63 times and 125 times the human daily dose throughout pregnancy and lactation. Effects on pups exposed to Seldane only during lactation are not known, and there are no adequate and well-controlled studies in women during lactation.

Pediatric use

Safety and effectiveness of Seldane in children below the age of 12 years have not been established.

General

Consideration should be given to potential anticholinergic (drying) effects in patients with lower airway disease, including asthma.

ADVERSE REACTIONS

Experience from clinical studies, including both controlled and uncontrolled studies involving more than 2,400 patients who received Seldane, provides information on adverse experience incidence for periods of a few days up to six months. The usual dose in these studies was 60 mg twice daily, but in a small number of patients, the dose was as low as 20 mg twice a day, or as high as 600 mg daily.

In controlled clinical studies using the recommended dose of 60 mg b.i.d., the incidence of reported adverse effects in patients receiving Seldane was similar to that reported in patients receiving placebo. (See Table below.)

ADVERSE EVENTS REPORTED IN CLINICAL TRIALS

Adverse Event	Percent of Patients Reporting				
	Controlled Studies*			All Clinical Studies**	
	Seldane N=781	Placebo N=665	Control N=626***	Seldane N=2462	Placebo N=1478
Central Nervous System					
Drowsiness	9.0	8.1	18.1	8.5	8.2
Headache	6.3	7.4	3.8	15.8	11.2
Fatigue	2.9	0.9	5.8	4.5	3.0
Dizziness	1.4	1.1	1.0	1.5	1.2
Nervousness	0.9	0.2	0.6	1.7	1.0
Weakness	0.9	0.6	0.2	0.6	0.5
Appetite Increase	0.6	0.0	0.0	0.5	0.0
Gastrointestinal System					
Gastrointestinal Distress (Abdominal distress, Nausea, Vomiting, Change in Bowel habits)	4.6	3.0	2.7	7.6	5.4
Eye, Ear, Nose, and Throat					
Dry Mouth/ Nose/Throat	2.3	1.8	3.5	4.8	3.1
Cough	0.9	0.2	0.5	2.5	1.7
Sore Throat	0.5	0.3	0.5	3.2	1.6
Epistaxis	0.0	0.8	0.2	0.7	0.4
Skin					
Eruption (including rash and urticaria) or itching	1.0	1.7	1.4	1.6	2.0

*Duration of treatment in "CONTROLLED STUDIES" was usually 7-14 DAYS.

**Duration of treatment in "ALL CLINICAL STUDIES" was up to 6 months.

***CONTROL DRUGS: Chlorpheniramine (291 patients), d-Chlorpheniramine (189 patients), Clemastine (146 patients)

In addition to the more frequent side effects reported in clinical trials (See Table), adverse effects have been reported at a lower incidence in clinical trials and/or spontaneously during marketing of Seldane that warrant listing as possibly associated with drug administration. These include: alopecia, (hair loss or thinning), anaphylaxis, angioedema, arrhythmia (including ventricular tachyarrhythmia), bronchospasm, confusion, depression, galactorrhea, hypotension, insomnia, menstrual disorders (including dysmenorrhea), musculoskeletal symptoms, nightmares, palpitation, paresthesia, photosensitivity, prolonged QT interval, seizures, sweating, syncope, tachycardia, tremor, urinary frequency, and visual disturbances. In clinical trials, several instances of mild, or in one case, moderate transaminase elevations were seen in patients receiving Seldane. Mild elevations were also seen in placebo treated patients. Marketing experiences include isolated reports of jaundice, cholestatic hepatitis, and hepatitis; in most cases available information is incomplete. In neither the clinical trials nor marketing experience is a causal relationship of liver abnormalities to Seldane use clear.

OVERDOSAGE

Information concerning possible overdosage and its treatment appears in Full Prescribing Information.

DOSAGE AND ADMINISTRATION

The usual dosage for adults and children 12 years and older is 60 mg (1 tablet) twice daily.

Product Information as of June, 1988 Y352D

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

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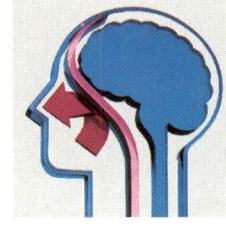
(terfenadine) 60 mg tablets BID for seasonal allergic rhinitis



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*Based upon worldwide prescription and distribution information (1986-1988)—data on file.

References: 1. Data on file, MERRELL DOW PHARMACEUTICALS INC., Cincinnati, Ohio 45215. **2.** Kemp JP, Buckley CE, Gershwin ME, et al: Multicenter, double-blind, placebo-controlled trial of terfenadine in seasonal allergic rhinitis and conjunctivitis. Ann Allergy 1985;54:502-509. **3.** Backhouse CI, Brewster BS, Lockhart JDF, et al: Terfenadine in allergic rhinitis. A comparative trial of a new antihistamine versus chlorpheniramine and placebo. Practitioner 1982;226:347-348, 351. **4.** Buckley CE, Buchman E, Falliers CJ, et al: Terfenadine treatment of fall hay fever. Ann Allergy 1988;60:123-128. **5.** Melillo G, D'Amato G, Zanussi C, et al: A multicentre controlled trial of terfenadine, dexchlorpheniramine, and placebo in allergic rhinitis. Arzneim-Forsch/Drug Res 1982;32:1202-1203. **6.** Fink M, Irwin P: CNS effects of the antihistamines diphenhydramine and terfenadine (RMI 9918). Pharmakopsychiat 1979;12:35-44. **7.** Roehrs TA, Tietz EI, Zorick FJ, et al: Daytime sleepiness and antihistamines. Sleep 1984;7:137-141.

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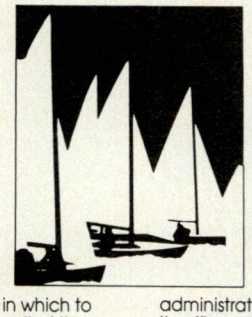

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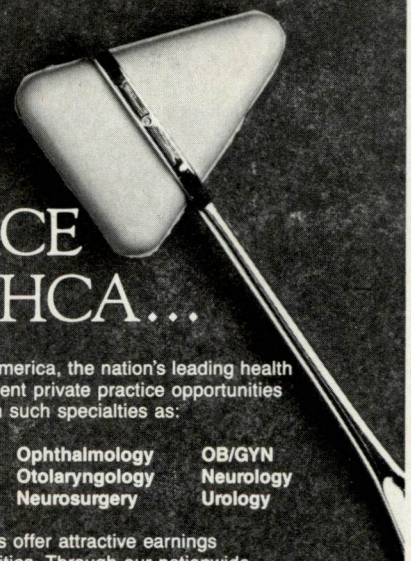

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JAMA Reference Directories

Because of space considerations, the Organizations of Medical Interest, State Medical Associations/Examinations and Licensure, and Meetings Outside the United States reference directories appear only once per volume, twice a year. Issue dates were January 13, 20, and 27, respectively, and will be July 14, 21, and 28, respectively. Deadlines for receipt of copy for January was October 10, 17, and 24, respectively, and for July will be April 13, 20, and 27, respectively. Meetings in the United States are published in the first issue of each month. AMA Officials will still be published semiannually following the AMA Annual and Interim House of Delegates meetings. Listings marked by a star (*) contain information added since the previous scheduled appearance of that directory. Display of exhibits is indicated by [E]. An activity for members only is indicated by [M]. Meetings that are open to the public are indicated by [O]. Scientific and business meetings are indicated by [S] and [B]. Languages are noted if English is not one of the official languages. Readers are urged to notify *JAMA* Reference Directories promptly of any omissions or inaccuracies.

Please note, only *meetings* of medical interest appear in these directories. Continuing medical education programs, activities, and *courses* appear twice a year (July and January) in a Continuing Education Opportunities section printed in *JAMA*. Direct notices of these continuing medical education programs, activities, and courses to the CME unit, AMA headquarters. Such activities are not listed in these directories.

The American Medical Association does not review or evaluate the quality of meetings listed and neither endorses nor approves their scientific content or educational value. The Association reserves the right to decline any meeting announcement at its sole discretion.

The following gives the latest issue in which a particular Directory appeared:
Meetings in the United States—May 5
Organizations of Medical Interest—January 13
State Medical Associations—January 20
Examinations and Licensure—January 20
Meetings Outside the United States—January 27
AMA Officials—April 3

Meetings in the United States

American Medical Association, Exec Vice Pres: James H. Sammons, MD, 535 N Dearborn St, Chicago, IL 60610.

Meetings
1989: Annual—Chicago, June 18-22
Interim—Honolulu, December 3-6
1990: Annual—Chicago, June 24-28
Interim—Orlando, December 2-5

June 1989

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American Academy of Cosmetic Surgery, Century Plaza Hotel, *Los Angeles*, Calif, June 23-25. Info: Exec Dir, C. J. McMann, 159 E Live Oak Ave, Arcadia, CA 91006; (818)447-1579.

American Academy of Pediatrics, Cloister Hotel, *Sea Island*, Ga, June 22-25. Info: W. C. Mankin, 4059 Land O'Lakes Dr, NE, Atlanta, GA 30342; (404)237-3922.

American Association of Neuropathologists, Plaza of the Americas, *Dallas*, June 15-18. Info: Sec-Treas, R. R. Heffner, Jr, MD, Erie County Medical Center, Buffalo, NY 14215; (716)898-3117.

***American Association for the Study of Headache (annual),** Westin Copley Place, *Boston*, Mass, June 16-18. Info: Exec Dir, W. Raymond Dion, 616 S El Camino Real, San Clemente, CA 92672; (714)498-1846.

American Medical Association Auxiliary, Inc, Drake, *Chicago*, Ill, June 18-21. Info: H. J. Lewis, 535 N Dearborn St, Chicago, IL 60610; (312)645-4470.

American Orthopedic Society for Sports Medicine, Grand Traverse Resort, *Traverse City*, Mich, June 19-22. Info: Exec Dir, S. J. Hill, 70 W Hubbard, #202, Chicago, IL 60610. (312)644-2623.

American Rheumatism Association Scientific Meeting (53rd), Cincinnati Convention Center, *Cincinnati*, June 13-17. Info: American Rheumatism Association, 17 Executive Park Dr, NE, Ste 480, Atlanta, GA 30329; (404)633-3777

American Sleep Disorders Association, Omni Shoreham, *Washington*, DC, June 21-25. Info: Exec Dir, C. C. Westbrook, 604 Second St SW, Rochester, MN 55902; (507)287-6006.

Drug Information Association, Marriott, *Boston*, Mass, June 19-22. Info: Admin Dir, T. W. Teal, PO Box 3113, Maple Glen, PA 19002; (215)628-2288.

Endocrine Society (71st), Washington Convention and Trade Center, *Seattle*, Wash, June 21-24. Info: Exec Dir, S. Hunt, Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814; (301)571-1802.

Environmental Health Conference, sponsored by the Center for Environmental Health and Injury Control of the Centers for Disease Control, the Agency for Toxic Substances and Disease Registry, and the Association of State and Territorial Health Officials, St Anthony Inter-Contintental Hotel, *San Antonio*, TX, June 20-23. Info: L. Webb, CDC (404)488-4700; or J. Andrews, MD, CDC (404)488-4682; or P. McCumiskey, ATSDR (404)488-4682.

***Flying Physicians Association (35th),** King & Prince Hotel, St Simon's Island, Ga, June 25-30. Info: Admin Asst, Carol Laurie, CPS, PO Box 17841, Kansas City, MO 64134; (816)763-7336.

***The Genetics Society of American (58th),** Atlanta Hilton & Towers Hotel, *Atlanta*, Ga, June 30-July 2. Info: Asst Pub Mgr, Eileen Cahill, GSA, Administrative Office, 9650 Rockville Pike, Bethesda, MD 20814; (301)571-1852.

International Conference on Preventive Cardiology (2nd), sponsored by the American Heart Association's Council on Epidemiology, *Washington*, DC, June 18-22. Info: Secretariat, 2nd International Conference on Preventive Cardiology, 9650 Rockville Pike, Bethesda, MD 20814.

Society of Nuclear Medicine, *St Louis*, June 13-16. Info: Exec Dir, H. L. Ernstthal, JD, 136 Madison Ave, New York, NY 10016; (212)889-0717.

***Society for Vascular Surgery,** Hilton, *New York*, NY, June 20-21. Info: N. R. Hertzer, MD, Cleveland Clinic, 9500 Euclid Ave, Cleveland OH 44106; (216)444-5705.

Ukrainian Medical Association of North America, *New York*, June 26-July 2. Info: Pres, W. Marchuk, MD, 40 S Clay, Hinsdale, IL; (312)323-6970.

July

American In-Vitro Allergy/Immunology, San Diego Marriott Hotel & Marina, *San Diego*, Calif, July 21-22. Info: Admin, B. Kahler, 229 Parking Way, PO Box 459, Lake Jackson, TX 77566; (409)297-8964 or (409)297-7089.

American Veterinary Medical Association, Peabody, *Orlando*, Fla, July 15-20. Info: Exec Vice Pres, R. Dommert, 930 N Meacham Rd, Schaumburg, IL 60196; (312)605-8070.

Association of Pakistani Physicians, Dearborn Hyatt Regency, *Chicago*, Ill, July 6-9. Info: Sec, M. A. Khan, 1301 Copperfield, Joliet, IL 60432; (312)968-8585 or (312)968-8606.

***Association of Philippine Physicians in America,** Omni International, *St Louis*, Mo, July 28-30. Info: Exec Dir, R. Santos, MD, 8344 Traford Lane, Unit C, Springfield, VA 22024; (703)569-6532.

Korean Medical Association of America, Hilton, *New York*, NY, July 2-5. Info: Sec-Gen, B. H. Shin, Korean Medical Association, 162 Deer Run, Watchung, NJ 07060; (201)755-5622.

National Medical and Dental Association, Tara Hyannis, *Hyannis*, Mass, July 26-30. Info: Exec Dir, R. S. Dziejma, 72-41 Grand Ave, Maspeth, NY 11378; (718)478-3333.

August

American Association of Medical Society Executives, Marriott, *San Diego*, Calif, August 2-6. Info: Exec Dir, R. Krieger, CAE, 1 East Erie, Chicago, IL 60611; (312)280-7265.

American Orthopaedic Foot and Ankle Society, The Lodge, *Sun Valley*, Idaho, August 3-6. Info: Exec Sec, A. Napolilli, 222 S Prospect Ave, Park Ridge, IL 60068; (312)698-1626.

American Society for Pharmacology and Experimental Therapeutics, Salt Palace, *Salt Lake City*, Utah, August 13-17. Info: Exec Officer, K. A. Croker, ASPET, 9650 Rockville Pike, Bethesda, MD 20814; (301)530-7060.

***Association of Medical Illustrators,** The Fairmont, *Dallas*, Tex, August 11-16. Info: Exec Dir, M. H. Henry, AMI, 2692 Huguenot Springs Rd, Midlothian, VA 23113; (804)794-2908.

International Conference on Emergency Health Care Development, *Washington*, DC, August 15-18. Info: EHC Conference, MCD International , 1742 "R" St, NW, Washington, DC 20009; (202)462-1920.

International Symposium on Lipofuscin and Ceroid Pigments—1989 (3rd), *Maui*, Hawaii, Aug 20-23. Info: E. A. Porta, MD, Dept Path, School of Med, University of Hawaii, 1960 East-West Rd, Honolulu, HI 96822; (808)948-8845.

***International Conference on Emergency Health Care Development (ICEHCD),** Hyatt-Regency Hotel, Crystal City at National Airport, *Washington*, DC, August 15-18. Info: ICEHCD, MCDI, 1742 R St, NW, Washington, DC 20009; (202)462-1920.

Midwest Surgical Association, American Club, *Kohler*, Wis, August 13-16. Info: Sec, G.V. Aranha, 2160 S First Ave, Maywood, IL 60153; (312)531-4596.

Ohio State University 26th Urology Outing, sponsored by the Division of Urology, Deer Creek State Park, *Sterling*, Ohio, August 18-20. Info: J. R. Drago, MD, Ohio State University, 456 W 10th Ave, 4841A, Columbus, OH 43210.

September

American Academy of Cosmetic Surgery along with the American Society of Liposuction Surgery, *Houston*, Tex, September 7-10. Info: Exec Dir, C. J. McMann AACS, 159 E Live Oak Ave, Suite 204, Arcadia, CA 91006; (818)447-1579.

American Academy of Facial Plastic and Reconstructive Surgery, Hilton, *New Orleans*, La, September 21-23. Info: L. VanBremen, PhD, CAE, 1101 Vermont Ave NW, Suite 404, Washington, DC 20005; (202)842-4500.

American Acadmey of Family Physicians, Bonaventure Hotel, *Los Angeles*, Calif, September 18-21. Info: Exec Vice Pres, R. Graham, 8880 Ward Pkwy, Kansas City, MO 64114; (816) 333-9700.

American Academy of Otolaryngic Allergy, New Orleans Convention Center, *New Orleans*, La, September 21-23. Info: Exec Dir, D. J. Clark, AAOA, 1101 Vermont Ave, NW, #303, Washington, DC 20005; (202)682-0456.

American Academy of Otolaryngology-Head and Neck Surgery (93rd), New Orleans Hilton, *New Orleans*, La, September 24-28. Info: J. C. Goldstein, 1101 Vermont Ave, Suite 302, Washington, DC 20005; (202)289-4607.

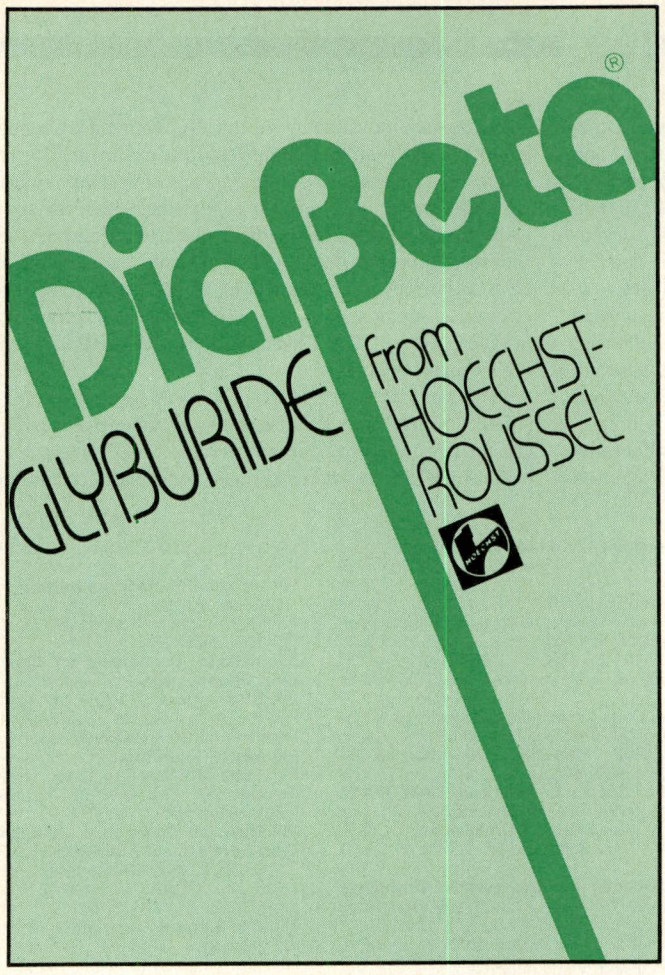
American Association of Electromyography and Electrodiagnosis, Shoreham, *Washington*, DC, September 13-17. Info: Exec Dir, E. M. VanLaningham, AAEE, 732 Marquette Bank Bldg, Rochester, MN 55904; (507)288-0100.

***American Association of Tissue Banks,** Hyatt Regency, *Denver*, Colo, September 30-October 3. Info: Exec Dir, J. C. Mowe, 1350 Beverly Rd, #220A, McLean, VA 22101; (703)827-9582.

***American College of Emergency Physicians,** Grand Hyatt, *Washington*, DC, September 11-14. Info: Exec Dir, C. C. Rorrie, Jr, PhD, PO Box 619911, Dallas, TX 75261-9911; (214)550-0911.

***American College of Nuclear Medicine,** Swiss Grand Hotel, *Chicago*, Ill, September 21-23. Info: Exec Dir, J. D. Watson, Jr, MD, 717 20th St, PO Box 5887, Columbus, GA 31906; (404)322-8049.

American College of Nutrition (30th), Omni International, *Norfolk*, Va, Sept 23-25. Info: Exec Dir, M. S. Seelig, MD, MPH, FACN, 345 Central Ave, #207, Scars-



dale, NY 10583; (914)723-4247.

American Group Practice Association, Hyatt Regency Capitol Hill, *Washington,* DC, September 12-15. Info: Exec Vice-Pres, D. W. Fisher, PhD, AGPA, 1422 Duke St, Alexandria, VA 22314; (703)838-0033.

American Institute of Homeopathy, Dayton Marriott, *Dayton,* Ohio, September 29-October 1. Info: Exec Dir, S. B. Roethel, 1500 Massachusetts Ave, NW, Suite 42, Washington, DC 20005; (202)223-6182.

***American Lung Association (2nd),** The Historic Inns, *Annapolis,* Md, September 20-22. Info: Dir, M. Kling, 1740 Broadway, New York, NY 10019-4374; (212)315-8700.

***American Medical Director Association,** *Minneapolis,* Minn, September 14-17. Info: Exec Dir, L. Tarnove, 325 S Patrick St, Alexandria, VA 22314; (703)549-5822.

American Neurological Association, Sheraton, *New Orleans,* La, September 24-27. Info: Exec Dir, J. W. Kolehmainen, 2221 University Ave, SE, Suite 350, Minneapolis, MN 55414; (612)378-3290.

American Rhinologic Society, *New Orleans,* La, September 23. Info: Exec Sec, A. Marron, 200 First St, SW, Rochester, MN 55905; (507)284-3410.

***American Society for Surgery of the Hand,** Seattle Sheraton Hotel & Towers, *Seattle,* Wash, September 13-16. Info: Exec Dir, G. M. Gorman, 3025 S Parker Rd, Suite 65, Aurora, CO 80014; (303)755-4588.

American Thyroid Association, Inc, Hyatt, *San Francisco,* Calif, September 6-9. Info: Sec, L. Wartofsky, Endocrine-Metabolic Service, Walter Reed Army Medical Service, Washington, DC 20307-5001.

Association of American Physicians and Surgeons, Grosvenor Resort, *Orlando,* Fla, September 21-23. Info: Exec Sec, E. S. Ackley, 9203 Lake Braddock Dr, Burke, VA 22015; (703)425-6300.

Association of Life Insurance Medical Directors of America, Sheraton Hotel, *Seattle,* Wash, September 25-27. Info: Sec, W. J. Baker, Monarch Life Insurance Co, One Monarch Place, Springfield, MA 01133; (413) 784-6962.

***Association of Mental Health Administrators,** Hyatt, *Denver,* Colo, September 24-27. Info: Exec Dir, N. Gordon, AMHA, 840 N Lake Shore Dr, Ste 11W, Chicago, IL 60611; (312)943-2751.

International Conference on Pharmacoepidemiology (5th), Radisson University Hotel, *Minneapolis,* Minn, September 5-8. Info: S. A. Edlavitch, University of Minnesota, Division of Epidemiology, School of Public Health, Stadium Gate 27, 611 Beacon St, SE, Minneapolis, MN 55455; (612)624-5400.

International Workshop on Bone Densitometry, *Rancho Mirage,* Calif, Sept 17-21. Info: B. Ettinger, MD, Permanente Medical Group, 2200 O'Farrell St, San Francisco, CA 94115; (415)929-4789.

Multidisciplinary Perspectives on Menopause, sponsored by The New York Academy of Sciences, Sheraton Centre, *New York,* Sept 21-23. Info: Conf Dept, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212)838-0230.

National Federation of Catholic Physician' Guilds, Adams Mark Hotel, *Houston,* Tex, September 20-23. Info: J. A. Lucci, Jr, 2000 Crawford, #1200, Houston, TX 77002; (414)784-3435.

***Society of Uroradiology,** Westin Resort Hotel, *Hilton Head,* SC, Sept 23-28. Info: J. H. Newhouse, MD, Sec/Treas, Dept of Radiology, Columbia-Presbyterian Hospital, 622 W 168th St, New York, NY 10032; (212)305-7898.

***United States Pharmacopeial Convention,** Wyndham Corpus Christi, *Corpus Christi,* Tex, September 25-27. Info: W. M. Heller, PhD, 12601 Twinbrook Pkwy, Rockville, MD 20852; (301)881-0666.

October

Academy of Psychosomatic Medicine, Riviera, *Las Vegas,* Nev, October 26-29. Info: E. A. Hallberg, 5824 N Magnolia, Chicago, IL 60660; (312)784-2025.

American Academy of Cerebral Palsy and Developmental Medicine, Hyatt Embarcadero, *San Francisco,* Calif, October 25-29. Info: Exec Sec, J. A. Hinckley, PO Box 11086, Richmond, VA 23230-1086; (804)282-0036.

American Academy of Child and Adolescent Psychiatry, New York Hilton, *New York,* NY, October 11-15. Info: Exec Dir, V. Anthony, 3615 Wisconsin Ave NW, Washington, DC 20016; (202)966-7300.

American Academy of Clinical Psychiatrists, Omni Hotel, *St Louis,* Oct 18-21. Info: A. A. Muñoz, Exec Sec, PO Box 3212, San Diego, CA 92103;(619)298-4782.

American Academy of Cosmetic Surgery and the America Society of Liposuction Surgery, *Washington,* DC, October 20-22. Info: C. J. McMann, AACS, 159 E Live Oak Ave, Suite 204, Arcadia, CA 91006; (818)447-1579.

***American Academy of Environmental Medicine Annual Meeting (24th) and Scientific Session (23rd),** Hyatt Regency Ravinia at Atlanta Perimeter, *Atlanta,* Ga, October 28-31. Info: Exec Adm, J. A. Howard, PO Box 16106, Denver, CO; (303)622-9755.

American Academy of Pediatrics, Hyatt Regency Ravinia Hotel, *Atlanta,* Ga, October 5-6. Info: Exec Sec, W. C. Mankin, 4059 Land O'Lakes Dr NE, Atlanta, GA 30342; (404)237-3922.

American Academy of Psychiatry and the Law, Omni Shoreham, *Washington,* DC, October 19-22. Info: J. R. Rappeport, 1211 Cathedral St, Baltimore, MD 21201; (301)539-0379.

American Association of Blood Banks, New Orleans Hilton, *New Orleans,* La, Oct 21-26. Info: G. Clark, JD, Exec Dir, 1117 N 19th St, Arlington, VA 22209.

***American Association for Cancer Education,** Brown Palace, *Denver,* Colo, October 5-8. Info: Sec, S. Brown, Jr, EdD, Univ of Ala at Birmingham, 401 Community Health Services Bldg, Birmingham, AL 35294; (205)934-7442.

American Association for Hand Surgery, Fairmont, *San Francisco,* Calif, October 26-29; Info: Exec Sec, M. H. McGrath, 2150 Pennsylvania Ave, NW, The H. B. Burns Memorial Bldg, Washington, DC 20037; (608)273-8940.

American Association for the Study of Liver Disease, Marriott, *Chicago,* Ill, October 28-31. Info: Off Mgr, S. Crowley, 6900 Grove Rd, Thorofare, NJ 08086; (609)848-1000.

American Association of Tissue Banks (13th), Hyatt Regency, *Baltimore,* Md, October 1-4. Info: Exec Dir, J. C. Mowe, AATB, 1350 Beverly Rd, Suite 220A, McLean, VA 22101; (703)827-9582.

American College of Angiology, *San Francisco,* Calif, October. Info: Exec Dir, D. M. Rossignol-Kapelock, 1044 Northern Blvd, Suite 103, Roslyn, NY 11576; (516)484-6880.

American College of Chest Physicians, Sheraton, *Boston,* Mass, October 30-November 3. Info: Exec Dir, A. Soffer, MD, FCCP, 911 Busse Hwy, Park Ridge, IL 60068; (312)698-2200.

***American College of Clinical Pharmacology,** Hyatt Regency, *Baltimore,* Md, October 11-14. Info: Exec Dir, W. F. Chaveas, 175 Strafford Ave, Wayne, PA 19087; (215)687-7711.

***American College of Gastroenterology,** New Orleans Marriott, *New Orleans,* La, October 20-25. Info: Exec Dir, T. F. Fise, 4222 King St, Alexandria, VA 22302; (703)549-4440.

American College of Surgeons, Hilton, *Atlanta,* Ga, October 15-20. Info: Dir, P. A. Ebert, MD, FACS, 55 E Erie St, Chicago, IL 60611; (312)664-4050.

***American College of Utilization Review Physicians,** Marriott Marquis, *New York,* NY, October 13-15. Info: Exec Dir, B. J. Hamman, 1521 S Tamiami Trail, Venice, FL 34292; (813)497-3340.

American Medical Women's Association, Beverly Hilton, *Los Angeles,* Calif, October 25-28. Info: Exec Dir, Eileen McGrath, 801 N Fairfax St, Suite 400, Alexandria, VA 22314; (703)838-0500.

***American Physiological Society,** Kahler Hotel, *Rochester,* Minn, October 15-18. Info: Exec Dir, M. Frank, PhD, 9650 Rockville Pike, Bethesda, MD 20814; (301)530-7164.

American Public Health Association (117th), *Chicago,* Ill, October 22-26. Info: Exec Dir, W. McBeath, 1015 Fifteenth St NW, Washington, DC 20005; (202)789-5600.

American Society of Anesthesiologist, Hilton/Sheraton, *New Orleans,* La, October 14-18. Info: Exec Dir, G. W. Johnson, 515 Busse Hwy, Park Ridge, IL 60068; (312)825-5586.

American Society of Bariatric Physicians, Sheraton Harbor Island Hotel, *San Diego,* Calif, October 16-18. Info: Exec Dir, J. F. Merker, CAE, 5600 S Quebec St, Suite 160-D, Englewood, CO 80111; (303)779-4833.

***American Society of Clinical Pathologists (annual fall meeting),** Ramada Renaissance Tech World Hotel, *Washington,* DC, Oct 28-Nov 3. Info: P. Raleigh, Dir of Conventions & Exhibits, ASCP, 2100 W Harrison, Chicago, IL 60612; (312)738-1336.

American Society of Internal Medicine, J. W. Marriott Hotel, *Washington,* DC, October 19-22. Info: Exec VP, J. F. Boyle, 1101 Vermont Ave, NW, Suite 500, Washington, DC 20005; (202)289-1700.

American Society of Law and Medicine, *Boston,* Mass, October. Info: Exec Dir, L. O. Gostin, ASLM, 765 Commonwealth Ave, 16th Fl, Boston, MA 02215; (617)262-4990.

American Society of Maxillofacial Surgeons, *San Francisco,* Calif, October 29-November 3. Info: Acct Exec, L. Lofqren, 444 E Algonquin RD, Arlington Heights, IL 60005; (312) 228-9900.

American Society of Plastic and Reconstructive Surgeons, Moscone Convention Center, *San Francisco,* Calif, October 29-November 4. Info: Exec Dir, T. R. Schedler, CAE, 444 E Algonquin Rd, Arlington Heights, IL 60005; (312)288-9900.

American Society for Therapeutic Radiology and Oncology, San Francisco Hilton, *San Francisco,* Calif, October 1-6. Info: Exec Dir, N. Croce, ASTRO, 1891 Preston White Dr, Reston, VA 22091; (215)574-3180.

Association for the Advancement of Automotive Medicine, *Boston,* Mass, October 2-4. Info: Exec Dir, E. Petrucelli, AAAM, 2350 E Devon Ave, Suite 205, Des Plaines, IL 60018; (312)390-8927.

***Association of American Medical Colleges,** Washington Hilton, *Washington,* DC, October 27-November 2. Info: Pres, R. Petersdorf, MD, 1 DuPont Circle, NW,

#200, Washington, DC 20036; (202)828-0460.

Central Neuropsychiatric Association, Williamsburg Lodge, *Colonial Williamsburg,* Va, October 19-21. Info: Sec-Treas, L. E. Tripp, 3707 Gaston Ave, #418, Dallas, TX 75246; (214)820-3534.

Child Neurology Society (18th), Hyatt, *San Antonio,* Tex, October 12-14. Info: Exec Sec, M. B. Currey, National Office, Box 486, UMHC, 420 Delaware St, SE, Minneapolis, MN 55455; (612)625-7466.

Christian Medical Foundation International, Tampa Airport Marriott, *Tampa,* Fla, October 18-22. Info: L. Thorton, 7522 N Himes Ave, Tampa, FL 33614; (813)832-3688.

***College of American Pathologists,** Ramada Renaissance Tech World Hotel *Washington,* DC, October 28-November 3. Info: Chief Exec Officer, H. E. Cartwright, 5202 Old Orchard Rd, Skokie, IL 60077-1034; (312)966-5700.

Congress on Neurological Surgeons, *Atlanta,* Ga, Oct 29-Nov 4. Info: S.L. Giannotta, MD, Sec, LAC/USC Medical Center, 1200 N State St, Box 239, Los Angeles, CA 90033; (213)224-5435.

Congress on Neurological Surgeons, Hilton, *Atlanta,* Ga, October 29-November 11. Info: Sec, S. L. Giannotta, MD, LAC/USC Medical Center, 1200 N State St, Rm 5046, Los Angeles, CA 90033; (213)226-7421.

Hungarian Medical Association of America, Inc, Harley Sand Castle, *Sarasota,* Fla, October 29-November 3. Info: Sec, A. Matolesky, 40 Calhoun Ave, Trumbull, CT 06611; (203)268-7369.

Medical Group Management Association, Las Vegas Hilton, *Las Vegas,* Nev, October 29-November 2. Info: Exec Dir, R. V. Grant, Med Group Management Assoc, 1355 S Colorado Blvd, #900, Denver, CO 80222; (303)753-1111.

National Federation Catholic Physician's Guilds, Adam's Mark, *Houston,* Tex, October 18-21. Info: Exec Dir, R. H. Herzog, 850 Elm Grove Rd, Elm Grove, WI 53122; (414)784-3435.

National Society to Prevent Blindness, *Chicago,* Ill, October 25-29. Info: Exec Dir, M. L. Weamer, 500 E Remington Rd, Schaumburg, IL 60173; (312)843-2020.

Neuropeptides and Immunopeptides: Messengers in a Neuroimmune Axis, sponsored by The New York Academy of Sciences, Sheraton Centre, *New York,* Oct 2-4. Info: Conf Dept, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212)838-0230.

Pacific Dermatological Association, Sheraton Waikiki, *Honolulu,* Hawaii, October 26-31. Info: Deputy Exec Dir, L. E. Rosenthal, 1567 Maple Ave, PO Box 3116, Evanston, IL 60204-3116; (312)869-3954.

Society for Clinical and Experimental Hypnosis, The Clarion, *St Louis,* Mo, October 31-November 5. Info: Admin Dir, M. Kenn, 128-A Kings Park Dr, Liverpool, NY 13090; (315)652-7299.

Western Occupational Medical Association, Hyatt Regency, *Burlingame,* Calif, October 11-15. Info: Exec Dir, R. Massaro, 2600 Garden Rd, Suite 208, Monterey, CA 93940; (408)649-6544.

Western Orthopaedic Association, Disneyland Hotel, *Anaheim,* Calif, October 22-26. Info: Exec Dir, H. J. Martin, 2975 Treat Blvd, D-4, Concord, CA 94518; (415)671-2164.

November

Academy of Psychosomatic Medicine, The Pointe at Squaw Peak, *Phoenix,* Ariz, November 15-18. Info: Exec Dir, E. A. Hallberg, 5824 N Magnolia, Chicago, IL 60660; (312)784-2025.

American Academy of Pain Medicine, Grand Kempinski Hotel, *Dallas,* Tex, November 3-4. Info: Exec Dir, E. Murphy, AAPM, 43 E Ohio, Suite 914, Chicago, IL 60611; (312)645-0083.

American Academy of Physical Medicine and Rehabiliation, Convention Center, *San Antonio,* Tex, November 5-10. Info: Exec Dir I. A. Mayeda, 122 S Michigan Ave, Suite 1300, Chicago, IL 60603; (312)922-9366.

American Association of Certified Allergists, Marriott World Center, *Orland,* Fla, November 10. Info: Admin Dir, J. J. Lotharius, 800 E NE Highway, #1080, Palatine, IL 60067; (312)359-3919.

American Cancer Society, Waldorf-Astoria, *New York,* NY, November 11. Info: Exec Vice Pres & Chief Exec Officer, W. M. Tipping, American Cancer Society, 3340 Peachtree Rd, NE, Atlanta, GA 30026; (404)320-3333.

American College of Allegy and Immunology, Marriott Worldwide, *Orlando,* Fla, November 11-15. Info: Exec Dir, J. R. Slawny, 800 E Northwest Hwy, Suite 1080, Palatine, IL 60067; (312)359-2800.

American Congress of Rehabilitation Medicine, Convention Center, *San Antonio,* Tex, November 5-10. Info: Exec Dir, I. A. Mayeda, 130 S Michigan, Suite 1310, Chicago, IL 60603-6110; (312)922-9368.

American Medical Writers Association, Lafayette, *Boston,* Mass, November 15-18, Info: Exec Dir, L. Sablack, A. H. Robins Co, PO Box 26609, Richmond, VA 23261; (301)493-0003.

American Physicians Art Association, *Washington,* DC, November 5-8. Info: Treasurer, J. A. Canning, 13 Lacy Court, Blue Point, NY 11715; (516)363-7676.

American Society of Cytology, Galt House, *Louisville,* Ky, November 7-12. Info: Sec-Treas, B. Naylor, Box 0054, Pathology, Univ of Michigan Hospital, Ann Arbor, MI 48109-0054; (215)922-3880.

Association for Academic Surgery, *Louisville,* Ky, November 15-18. Info: Sec-Treas, J. M. Becker, Dept of Surgery, Suite 6108, One Barnes Hospital Plaza, St Louis, MO 63110; (314)362-7409.

***Association for the Advancement of Psychoanalysis, Inc.,** *New York,* NY, November 3. Info: Sec, M. Kirley, 329 E 62nd St, New York, NY 10021; (212)838-8044.

***Association of Clinical Scientists,** Hershey, *Philadelphia,* Pa, November 15-19. Info: Sec-Treas, F. W. Sunderman, Jr, MD, Dept of Laboratory Med, Univ of CT School of Med, Farmington, CT 06032-9984; (203)679-2328.

Association of Military Surgeons of the US, Town & Country, *San Diego,* Calif, November 12-17. Info: Exec Dir, Lt Gen, M. B. Barlliar, USAF MC Ret, 9320 Old Georgetown Rd, Bethesda, MD 20814; (301)897-8800.

The Biological Actions of Extracellular ATP, sponsored by The New York American Academy of Sciences, Adam's Mark Hotel, *Philadelphia,* Pa, November 27-29. Info: Conference Department, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212)838-0230.

Central Society for Clinical Research, Drake, *Chicago,* Ill, November 8-10. Info: J. P. Phair, Northwestern Univ, 303 E Chicago Ave, Chicago, IL 60611; (312)951-5610.

***Chinese American Medical Society,** Columbia-Presbyterian Medical Center, *New York,* NY, November 18. Info: H. H. Wang, MD, 630 E 168th St, New York, NY 10032; (212)305-3569.

Gerontological Society of America, Hyatt Regency, *Minneapolis,* Minn, November 17-21. Info: Exec Dir, J. M. Corman, GSA, 1275 K St, NW, Suite 350, Washington, DC 20005-4006; (202)842-1275.

International Conference on Drug Research in Immunologic and Infectious Diseases: Acquired Immune Deficiency Syndrome (AIDS) (3rd), sponsored by The New York Academy of Sciences and the National Institutes of Health, Crystal City Gateway Marriott, *Arlington,* Va, November 6-9. Info: Conference Department, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212)838-0230.

Interstate Postgraduate Medical Association, Town & Country Hotel, *San Diego,* Calif, November 6-9. Info: Exec Dir, H. B. Maroney, PO Box 1109, Madison, WI 53701; (608)257-1401.

Myelination and Dysmyelination, sponsored by The New York Academy of Sciences, Key Bridge Marriott, *Alexandria,* Va, Nov 16-18. Info: Conf Dept, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212)838-0230.

National Kidney Foundation, Sheraton Washington, *Washington,* DC, November 29-December 3. Info: Exec Dir, J. Davis, NKA, 30 E 33rd St, NY 10016; (212)889-2210.

Radiological Society of North America, McCormick Place, *Chicago,* Ill, November 27-December 2. Info: M. Godiksen, 1415 W 22nd St, Oak Brook, IL 60521; (312)571-2670.

Southern Medical Association (83rd), Washington Convention Center, *Washington,* DC, November 5-8. Info: Admin Asst, K. McLendon, 35 Lakeshore Dr, PO Box 190088, Birmingham, AL 35219-0088; (800)423-4992 or (205)945-1840.

Western Surgical Association, Omni International Hotel, *St Louis,* Mo, November 12-15. Info: Sec, J. L. Glover, William Beaumont Hospital, 3601 W 13 Mile Rd, Royal Oak, MI 48072; (313)288-2665.

December

American Academy of Cosmetic Surgery along with the American Society of Liposuction Surgery, *Atlanta,* Ga, December 8-10. Info: Exec Dir, C. J. McMann, AACS, 159 E Live Oak Ave, Suite 204, Arcadia, CA 91006; (818)447-1579.

American Academy of Dermatology, December 2-7. Info: Exec Dir, B. W. Claxton, CAE, 1567 Maple Ave, Evanston, IL 60204-3116; (312)869-3954.

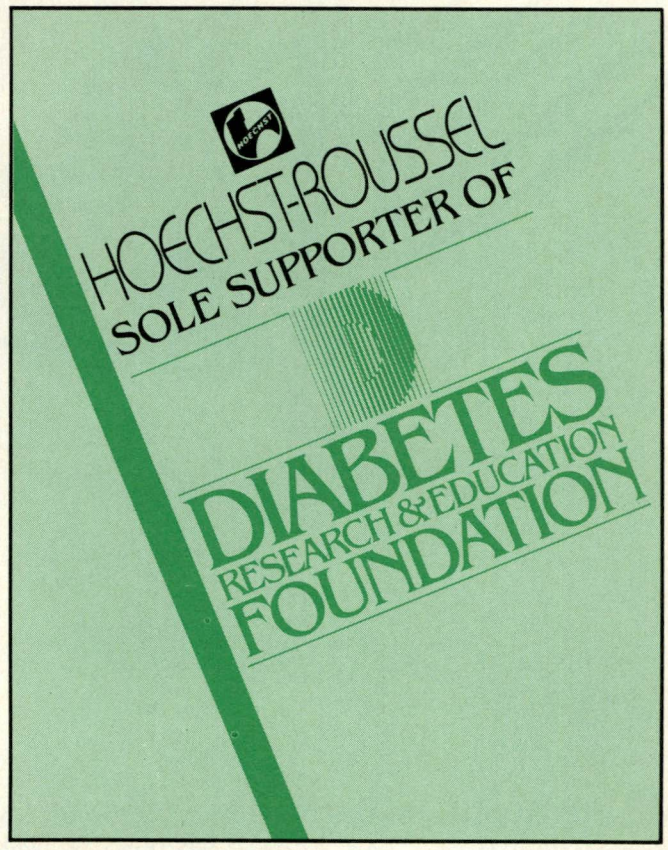
American Academy of Neurological and Orthopaedic Surgeons, Ballys Hotel, *Las Vegas,* Nev, December 12-17. Info: M. R. Rask, Prof & Chairman, 2320 Rancho, Suite 108, Las Vegas, NV 89102-4592; (702)385-6886.

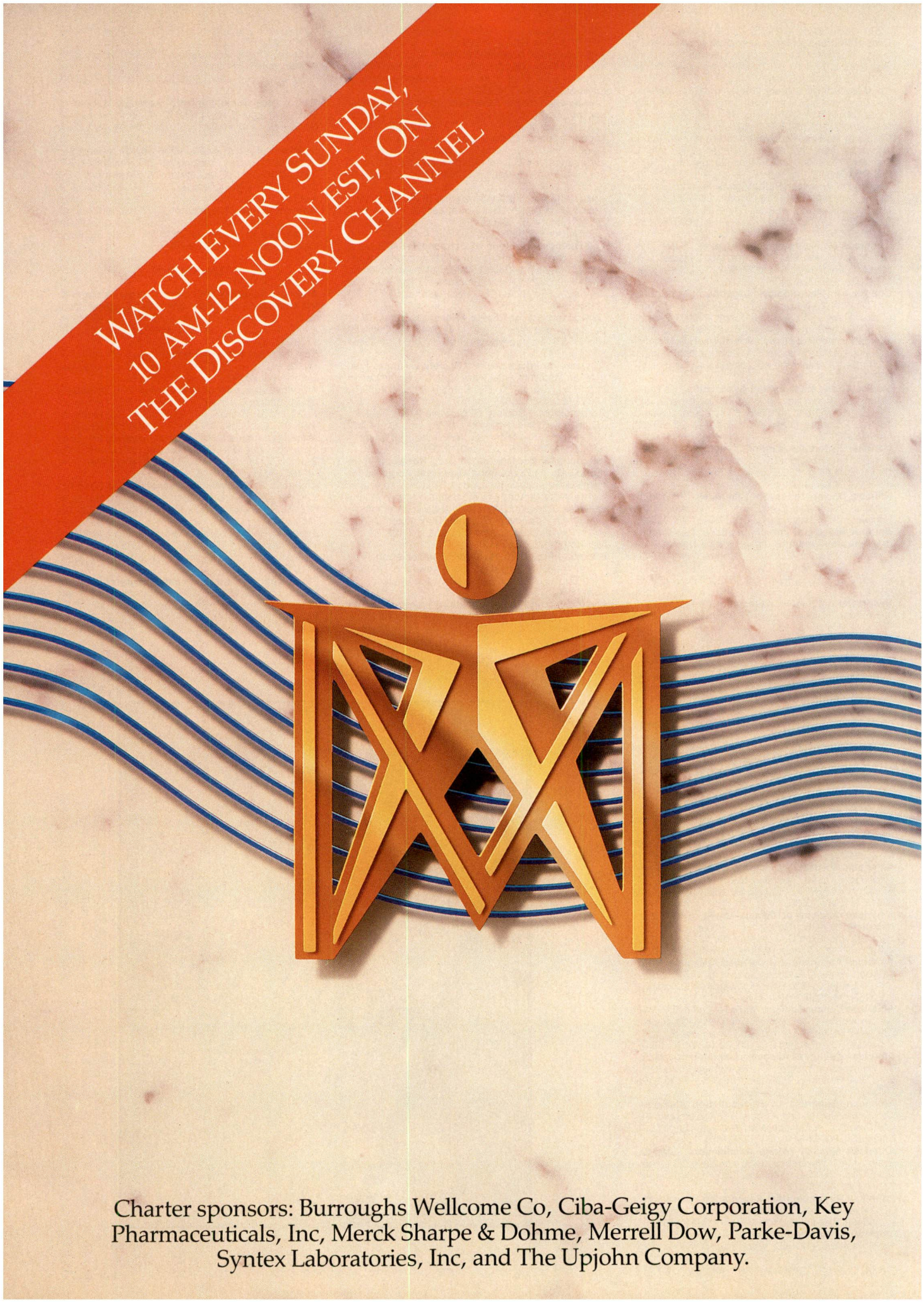
***American Academy of Psychoanalysis,** South Seas Plantation, *Captiva Island,* Fla, December 7-10. Info: Exec Dir, V. Mendelsohn, 30 E 40th St, #206, New York, NY 10016; (212)679-4105.

American Psychoanalytic Association, Waldorf-Astoria, *New York,* NY, December 9-12. Info: Admin Dir, H. Fischer, 309 E 49th St, New York, NY 10017; (212)752-0450.

American Society of Hematology, Atlanta Marriott/Inforum, *Atlanta,* Ga, December 2-5. Info: Exec Dir, J. D. McGreevey, Jr, 6900 Grove Rd, Thorofare, NJ 08086; (609)845-0003.

Presynaptic Receptors: An Examination of Different Views, sponsored by The New York Academy of Sciences, Sheraton Centre, *New York,* Dec 6-8. Info: Conf Dept, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212)838-0230.





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Obituaries

Curt Paul Richter, PhD, professor emeritus of psychobiology at The Johns Hopkins University School of Medicine, Baltimore, Md, died on December 21, 1988, at the age of 94 years.

Dr Richter was a graduate of Harvard University, Cambridge, Mass, and received his PhD degree from The Johns Hopkins University in 1921. He began his work at Johns Hopkins in John B. Watson's laboratory in 1921. In 1922 he became director of the Psychobiology Laboratory in the Henry Phipps Psychiatric Clinic of The Johns Hopkins Hospital. He held this post until 1957, when he was appointed professor of psychobiology at The Johns Hopkins Medical Institutions.

Dr Richter was the complete biologist and experimentalist, who found at Johns Hopkins an atmosphere perfectly suited to his needs to do research. He frequently told the story of his arrival in the laboratory of J. B. Watson, with Watson saying, "I am only interested in getting a good piece of research from you. You are strictly on your own." And this, said Dr Richter, encouraged him to start quickly on experiments of many kinds that resulted eventually in the publication of 375 articles, many lectures, and books.

From the beginning, Dr Richter's work was aimed at showing the importance of behavior as an instrument for the maintenance of the organism. Since Claude Bernard's work in the 1800s, we have appreciated that the internal environment of the body can vary only within fixed limits. His work displayed the dynamic nature of animal life, where behavior is appropriately modified to supply the body. His classic studies, which demonstrate (1) the salt appetite developing in rats needing salt, (2) the capacity of animals to make selections conducive to their normal growth and reproduction in the so-called cafeteria experiments, and (3) his application of these results to such issues as taste preferences, food aversions, and feeding capacities of animals and men, form the foundations for physiological psychology.

His study of spontaneous activity in animal behavior led to more focused experiments on the capacities crucial to biologic homeostasis. He showed that behavior could be measured reliably, is regular in its appearance, and is dependent on endogenous controls integrated from the nervous and endocrine systems. This represented a major challenge to radical behaviorism and was the foundation work for chronobiology.

One could continue discussing the details of Dr Richter's contributions, but all would add further to the view that this man was one of the 20th century's great biologists and psychologists. Through him, physiology is animated with an appreciation of its psychological and behavioral supports, and medicine and psychiatry have been given tools and directions that illuminate a variety of disorders. Few other scientists can claim as much.

Dr Richter was a member of the National Academy of Sciences, the American Philosophical Society, and the American Academy of Arts and Sciences. He received honorary degrees from the University of Chicago (Ill), The Johns Hopkins University, and the University of Pennsylvania, Philadelphia. In 1980, he was awarded the Lashley Award in Neurobiology from the American Philosophical Society.

Dr Richter was a lively and energetic individual who played a ferocious game of tennis into his late 80s and remained to the end of his life curious and interested in young people and their progress in science.

He is survived by his wife, Leslie Bidwell Richter, and by his children, Dr Peter Richter of New York, NY, Ann Roy of New Orleans, La, and Martha Richter Bailey of Boston, Mass. He had nine grandchildren and five great-grandchildren.

—by Paul R. McHugh, MD

Joseph C. Eggleston, MD, professor of pathology at The Johns Hopkins University School of Medicine and director of surgical pathology at The Johns Hopkins Hospital, Baltimore, Md, died on January 6, 1989. He was 52 years old.

Dr Eggleston was born in Memphis, Tenn, on August 4, 1936. He graduated from Duke University, Durham, NC, with an AB degree (Phi Beta Kappa) in 1958 and from The Johns Hopkins University School of Medicine with an MD degree (Alpha Omega Alpha) in 1962. After training in pathology and serving in the Air Force, he joined the faculty of the Department of Pathology at Johns Hopkins in 1969, and there spent the rest of his professional career.

Appointed director of surgical pathology in 1975, Dr Eggleston chose his staff carefully, and he rapidly built up a division that was unrivaled. At an early stage he appreciated the need to apply the newly emerging techniques of immunohistology to service work, and on a limited budget he succeeded in creating a laboratory that is now an institutional resource. Dr Eggleston was a superb teacher of medical students and house staff and was responsible for training many of the country's younger generation of surgical pathologists. His diagnostic acumen in surgical pathology was legendary and his opinion was sought widely.

His quick mind, common sense, and ability to express himself clearly made Dr Eggleston an ideal committee member, and he served on many at the university, medical school, and departmental levels. He was involved in various national cancer organizations, was a member of the editorial board of the *American Journal of Surgical Pathology,* and at the time of his death was president-elect of the Arthur Purdy Stout Society of Surgical Pathologists. Dr Eggleston also was the author of some 150 scientific articles and the coauthor of two books.

His appointment to the faculty was one of the first and certainly one of the best made during my time as director of the Department of Pathology. He was a loyal colleague, a source of wise counsel, and a delightful companion who could converse on any topic imaginable. My lasting impression will be of the tremendous courage he showed in the face of a relentless illness. Learning of his illness some years ago, Dr Eggleston never wavered in his determination to carry on as usual. He worked right up to the end and taught us all a lesson on how to deal with adversity.

Dr Eggleston is survived by his wife of 26 years, Sylvia, and their three daughters, Elizabeth, Anne, and Elaine.

—by Robert H. Heptinstall, MD

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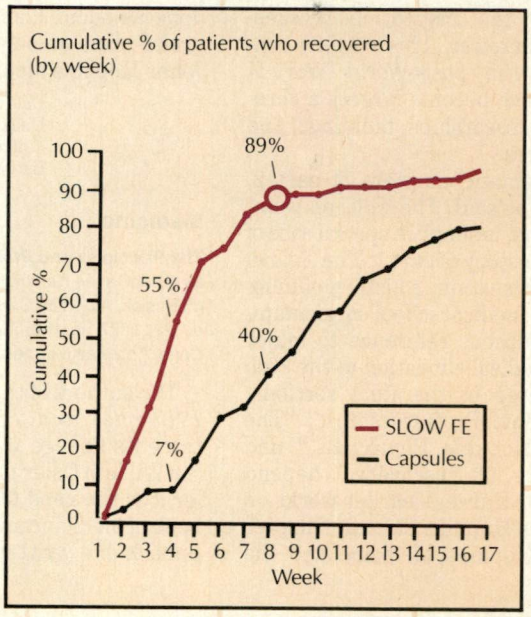

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1. Data on file, available upon request; CIBA Consumer Pharmaceuticals.
2. Brock C, Curry H: Comparative incidence of side effects of a wax-matrix and a sustained-release iron preparation. *Clin Ther* 1985;7(4):492-496.
3. Brock C, et al: Adverse effects of iron supplementation: A comparative trial of a wax-matrix iron preparation and conventional ferrous sulfate tablets. *Clin Ther* 1985; 7(5):I-VI.

CIBA Actual tablet size

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Books

Hopkins History

A Model of Its Kind, vol 1: **A Centennial History of Medicine at Johns Hopkins,** by A. McGehee Harvey, Gert H. Brieger, Susan L. Abrams, and Victor A. McKusick, 368 pp, with illus, $30; vol 2: **A Pictorial History of Medicine at Johns Hopkins,** 136 pp with illus, $20, Baltimore, Md, The Johns Hopkins University Press, 1989.

The authors of *A Model of Its Kind* have prepared a unique centennial history of a medical center. These volumes were clearly a labor of love, prepared to celebrate important institutions the histories of which are bound up with the last century of American medicine. The work is in three parts in two volumes. Part 1 is a chronological history of The Johns Hopkins Medical Institutions, part 2 is a series of thematic essays on what the authors view as the most significant or distinctive contributions of those institutions, and part 3 in the second volume is a collection of photographs drawn from institutional archives.

The story of the founding and disproportionate influence of The Johns Hopkins University is well known to all interested in the history of American medicine or American education. A Baltimore merchant—Johns Hopkins—left his fortune to endow a hospital and a university. In a letter of instructions to the trustees of the hospital, he called on them to "form a part of the Medical School of" The Johns Hopkins University. No one has ever explained the origins of this instruction. The phrase provided at minimum a license for cooperation in founding a new type of medical school; it may have been even more important in shaping the development of the institutions created by the bequest. The trustees of the hospital invited contributions on planning the new institution; the plan selected was that of John Shaw Billings, who became a consultant to the trustees. The university trustees selected Daniel Coit Gilman as the president of the new university. For both men, research in the laboratory and on the ward by teacher and student was critical, and the institutions they built truly were models of their kind.

When the hospital opened in the spring of 1889, its senior staff were professors in the university, which expected to open a medical school in the near future. Financial reverses stalled the medical school until a group of women led by M. Carey Thomas and Mary E. Garrett provided enhanced endowment to open the medical school in 1893. Their conditions, which required baccalaureate degrees for admission and the admission of women on the same basis as men, helped shape the school. As a medical faculty, the initial hospital staff—William Welch, William Osler, William Halsted, and Howard Kelly—and their associates—Franklin Mall, John Abel, and William Howell—are probably more famous than any comparable group in modern history. By example and influence, they helped shape the transformation of American medical education in the early 20th century.

This initial composite medical institution was a model, but that model was a pattern for others, and medical America changed as the 20th century progressed. On the initial Johns Hopkins foundation a new generation of research ers/teachers continued to build in the era between the two world wars. The building of a pediatrics program under John Howland and Edward Parks, the elaboration of the Department of Medicine under Theodore Janeway and Warfield Longcope, and the development of Philips Psychiatric Clinic under Adolph Meyer are well-known stories. But the difficult relationships of medicine and pathology over clinical pathology/laboratory medicine are mentioned only in passing, and the Johns Hopkins relationship to the national debate over the interrelations of surgery, gynecology, and obstetrics is not alluded to by this history. As the institutions have matured, the impact of national forces on Johns Hopkins has become ever stronger and history written exclusively from inside the institutions correspondingly narrower. This pattern continues into the post–World War II sections, which become largely a chronology of professorships, buildings, and administrators.

Of the thematic chapters of part 2, little should be said. The first, on women in medicine, is simply a special case of the general history of part 1. The "learning by doing" section, a history of innovation in the medical school curriculum, is written without reference to major studies of medical education in the 20th century. Three of the final sections, "The Full-Time Professorships," "The Export of Hopkins Physicians," and "The Nature of Discovery," depend heavily on Dr Harvey's earlier works on famous Johns Hopkins alumni. Chapter 10, "Johns Hopkins Medicine and the Community," is an honest appraisal of extension of the medical center idea into community medicine and health maintenance activities.

Much of volume 1 is impressionistic—Johns Hopkins began as a good place, it has had many good people since, and it remains a good place. We are perhaps too close to the events of massive federal funding and the rapid expansion of medical centers to understand them fully, but a simple tone of sadness or perhaps bitterness frequently comes through the current text. When monographic studies have been done, a balanced synthetic history of mid–20th-century medicine will be easier to prepare. In the current volume, the use of secondary sources is, as one would expect, extensive. Many of them are by Dr Harvey and other members of the Johns Hopkins faculty; when the source used changes, the style of the text changes as though to imitate the style of the new source. The story might have been a better read if the authors had gotten further from their research before they began to write. Even so, this work will expose some alumni or other centennial celebrants to portions of the history of The Johns Hopkins Medical Institutions and so serve its purpose.

Volume 2, *A Pictorial History of Medicine at Johns Hopkins*, prepared with the addition of Jonathan M. Fishbein to the author credits, is just that. The pictures chosen are representative, and many have appeared in other works; most of the famous faculty are depicted, and student life, at least of the mid–20th century, is chronicled. This is pure centennial celebration and is well done as such. I am sure it will find a proud place among the books of many Johns Hopkins medical alumni.

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Medicine

The Principles and Practice of Medicine, edited by A. McGehee Harvey, Richard J. Johns, Victor A. McKusick, Albert H. Owens, and Richard S. Ross, ed 22; 1277 pp, with illus, $49.95, East Norwalk, Conn, Appleton & Lange, 1988.

The authors of the 22nd edition of *The Principles and Practice of Medicine* trace its lineage to the first edition by Sir William Osler published in 1892. Osler saw the need for an American textbook of medicine and conceived a plan to publish one written by members of his

Edited by Harriet S. Meyer, MD, Contributing Editor; adviser for software, Robert Hogan, MD, San Diego.

department at The Johns Hopkins Hospital to be revised at regular intervals.

Unable to find anyone to take over this "one-department book" at Hopkins when he left there, Osler first recruited Thomas McCrae at Jefferson Medical College and later Henry Christian at Harvard Medical School, who assumed responsibility for the 10th through the 16th editions (1926 through 1947). A 21-year hiatus followed until, in 1968, Hopkins again took up the task beginning with the 17th edition, and with two decades of sponsorship by Hopkins the textbook appears to have a durable home there.

"Osler saw the need for an American textbook . . ."

At the time of Osler's early editions the implication of a one-department book was different from what it is today. Then the full scope of medical knowledge could be encompassed by one person with a few willing assistants, but now a bewildering technical maze requires scores of willing writers. Fortunately, the editors have the human resources to meet the challenge, and with all working in the same institution the coherence of the book should be enhanced. Nevertheless, a wide geographic dispersal of contributors might be a valuable safeguard against parochialism.

In the preface to the 17th (1968) edition the editors proposed an emphasis on "clinical problems rather than disease entities," and this remains the keynote of the text. Section One, "The Approach to the Patient," is a wide-ranging discussion of how the scientific method may be applied to gathering and processing clinical facts to help the physician arrive at an appropriate diagnosis and plan of treatment. I have not seen a better exposition of how to scientifically select the most suitable from among myriads of tests and treatments. The same section also deals with the humanistic, social, economic, and preventive aspects of medical care.

Following this logical framework within which the physician sorts out accumulated facts about a patient, the next 16 sections convey the specific knowledge needed to solve clinical problems. They deal with the facts about disease entities that constitute the core of most textbooks of medicine, but here the material tends to be parsimonious. As an example, one of Osler's favorite diseases, one that eventually brought about his demise, was pneumonia. The chapter on pneumonia contains all the clinical facts necessary for applying sophisticated clinical analysis, but the bedside findings in a patient with lobar pneumonia are described in three short paragraphs, about half as much as most other current textbooks and a small fraction of the amount written on pneumonia by Osler in his editions. This brevity, however, may be consistent with the author's avowed objective, to teach the methods of problem solving, but it may also shortchange the art of medicine.

Osler's original textbook was replete with observations from his previous experiences at the bedside. Diagnosis was a matter of recognition, just as one recognizes the painting of an artist by characteristic mood, color, and technique. Today's diagnostic clues are technical and have mathematical expressions; we have changed the medium in which our problem-solving techniques are formed, but not their quality.

This textbook is well written. The material is up-to-date and has been revised where appropriate. During the last six editions chapters have been added or reorganized as necessary, including, for example, chapters on aging, adolescence, congenital heart disease, and pulmonary thromboembolism. The fact that the book weighs less than most contemporary texts will be appreciated by those who like to read while riding on planes, trains, or buses.

The 22nd edition of *The Principles and Practice of Medicine* differs from the first edition in its approach to clinical diagnosis and treatment, but like its 19th-century progenitor, it is intellectually stimulating for medical students. The mature physician might not find the same reward.

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Genetics

Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-Linked Phenotypes, by Victor A. McKusick, ed 8; 1626 pp, $85, Baltimore, Md, The Johns Hopkins University Press, 1988.

In 1966 Victor McKusick published the first edition of this catalog. The book attempted to document in a single reference volume all known human genes, traits, and diseases that segregated by monogenic or Mendelian inheritance. Conditions that incontestably followed a given Mendelian mode of inheritance were starred (*), but many conditions whose mode of transmission was less certain were also listed. Each entry was given a unique identification number, and a short description of each entity was followed by a list of key references.

The eighth edition of this reference work has now appeared. From a total of 1487 entries in 1966, the number has grown to 4344 in 1988. There are 2208 definite Mendelian entities (1443 autosomal dominant, 626 autosomal recessive, and 139 X-linked) and 2136 entries where the mode of inheritance is less certain. Many new data are provided regarding linkage and chromosomal localization.

There are thought to be 50 000 to 100 000 genes in the human genome. Thus, the listing of over 4000 genetic loci is a solid achievement but is dwarfed by the many thousands of genes that wait to be cataloged. Yet, it is exciting to realize that the task of describing *all* human genes is likely to be accomplished within a foreseeable future.

The origin of citations in the catalog is of some interest. *Proceedings of the National Academy of Sciences USA* (1384), the *American Journal of Human Genetics* (1391), *Human Genetics* (1292), and the *New England Journal of Medicine* (1095) all have more than 1000 citations. *JAMA* is cited 218 times. Most citations come from journals in the fields of human and medical genetics (7386) and pediatrics (2586).

". . . the task of listing all human genes is likely to be accomplished within a foreseeable future."

McKusick's compendium has tremendous usefulness. As a medical geneticist, I use this book practically every day. Its utility has been further enhanced recently by now being available "on line" (OMIM™—Welch Medical Library, The Johns Hopkins University, Baltimore, Md, via TelNet). The advantage lies in having access to the most recent information, since updating is carried out as new information becomes available. However, the physical book has advantages. Thus, I usually find it profitable as well as enjoyable to glance over one or two additional entries beyond the specific disease or gene under inquiry. Besides factual information, there are many interesting bits of historical information. An excellent subject and author index makes it relatively easy to locate a given topic.

While McKusick's reference is well known and heavily used by medical geneticists and related specialists, it deserves to be known and utilized by physicians in all fields as well as by biomedical scientists in general. However, its encyclopedic nature makes its use more cumbersome as the volume has grown. With each new edition many entries have become longer, particular-

ly in conditions where much research has been done. Thus, for X-linked muscular dystrophy there is a description of about 5000 words (three double-columned pages of small print without any paragraphs) with 142 references. Much of the information in this entry deals with detailed linkage data. Just as the Oxford dictionary and others exist in encyclopedic and smaller editions, there is a real opportunity for Dr McKusick and a group of colleagues to reduce the text to a smaller companion volume so that users not interested in all the details could obtain essential information.

In addition to specific entries, the front matter of the book has much interesting and useful material. The foreword is a masterful overview and analysis of medical genetics principles. There is an up-to-date account with diagrams of the status of the human gene map as well as a listing of the known molecular defects in Mendelian disorders.

Clinicians and biomedical scientists alike owe tremendous gratitude to Dr McKusick for spending the necessary energy and effort in keeping this reference book up-to-date. It can be considered an international treasure, and the international medical genetics community should ensure its continuance if Victor McKusick ever retires. It is difficult to imagine professional work in medical genetics without McKusick's book at one's side. Because of its nature the book is an absolute necessity for any medical or biologic library. As the mapping of the human genome unfolds in the next decade, the usefulness of McKusick's reference will continue to gain in importance.

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Radiation

Living With Radiation: The Risk, the Promise, by Henry N. Wagner, Jr, and Linda E. Ketchum, 202 pp, with illus, $17.95, Baltimore, Md, The Johns Hopkins University Press, 1989.

Most of us think that we understand the heat that we feel, the light that we see, and even chemicals, if we can smell them. But, for most people, imperceptible ionizing electromagnetic radiation, x-rays and gamma rays, and fast charged particles are a mystery. Most people know that these entities, loosely described as "radiation," can cause great havoc to tissue, but do not seem to know that they have always been with us in some measure, and that a careful, selective use of them is highly beneficial. Only a limited number of people have the experience and capability to understand how much is good and how much excessive. Nevertheless, many more want to participate in decisions involving radiation.

The fact that an atom is radioactive and emits ionizing radiation is not necessarily bad. These atoms can be dangerous in large quanitity, yet safe and useful in small quantity.

When we burn, chemically, natural gas, oil, or coal, we get almost the same amount of energy (to within a factor of two) for every unit of weight. When we burn uranium 235 or plutonium 239 in a nuclear reactor, we get 3 million times more! The ramifications are enormous: We need less mining. We can afford to purify the smaller amount of material after burning and reduce the waste problems. We can contemplate keeping the waste out of the environment, until it has decayed, which we can do with no other waste product of man. On the other hand, we can make a bomb 3 million times as powerful for the same weight.

Many of the undesirable effects of radiation have always been with us. Radon gas has been coming out of the ground since the beginning of the earth, although the construction of airtight houses has made some of its attributes worse. If humankind is to progress, there is no other option than to reject the adverse, whether natural or synthetic.

One of the big problems of society is how those who wish to participate in decisions about radiation can be properly helped to understand enough about it that their decisions will be in the public interest. One method is for those who understand radiation to explain their personal experiences, the method adopted by the authors of this book.

Henry Wagner is a physician who has spent most of his life on the uses of radiation for medical diagnosis and research, for the last 10 years on positron emission tomography. He has been director of the Department of Radiation Medicine at The Johns Hopkins University Hospital for 20 years. For the last 10 he has also been associated with the School of Public Health. He has served on numerous committees, and has thereby developed an understanding of radiation, its risks and its uses, that extends far beyond his own field; in this book he gives us a taste of that understanding. Linda Ketchum is a medical writer and editor.

The book begins with a prologue describing the "tin trial" in Malaysia, where the Asian Rare Earth Company has been extracting rare earths from the monazite sand, a residue of tin mining, and disturbing the natural radioactivity in the ground, concentrating the thorium in the sand to about twice its original level. Objections have been made to the plant on the ground of the hazard of the radioactivity, although there has been no good evidence that the hazard is unusually large. This is an interesting case, because it shows the fear of radiation extends far beyond the atomic bomb.

The first chapter is an interesting account of the discovery of radioactivity, the realization that much in the world is radioactive, and the early applications of radiation in medicine. The use of deuterium as a tracer by Hevesy is described, as is the discovery of artificial radioactivity, which led to the rapid expansion of radioactive tracers.

The adverse effects of radiation were discovered before 1901. Nonetheless, a thorium-containing solution called Thorotrast was introduced into medical practice as late as 1930, and not discontinued until 1976. The authors quote Paul Hoffer to the effect that under certain assumptions "10,000 persons have died from Thorotrast-induced liver tumors alone. Yet when one speaks of radiation disasters, Thorotrast is rarely considered." Its effect on health is numerically comparable to the effect of the Chernobyl disaster! Are we worrying about the right things?

Much, but certainly not all, of the present fear of radiation may be due to the atomic bomb explosions of 1945, which made the world aware of the enormous energy in nuclear fission. To this development Wagner and Ketchum devote chapter 2, explaining in simple language how the bombs were developed and describing the attempts since then to ensure that there is international control to prevent any further use of nuclear weapons in war. It is important that the reader understand clearly the relationship between the use of nuclear fission to make bombs and the use for nuclear electric power; between radiation use in medicine and radiation exposures in war and accidents. These connections, which are far from direct, have been widely misunderstood, and nuclear power and nuclear medicine have both suffered. It is important that this misunderstanding be faced directly, as it is in this book, rather than indirectly. I deplore, for example, the cowardly way physicians have dropped the word "nuclear" in nuclear magnetic resonance, to make "magnetic resonance imaging," thereby missing an opportunity for public education.

The extraordinary revolution in medicine brought about by the use of radiation, radioactive tracers, and nuclear imaging devices is described in chapter 3. The three main radioactive tracers, carbon 14, tritium, and phosphorus 32,

are now the mainstays of biomedical science. Few patients receive major surgery or other treatment without either a computed tomographic scan with x-rays, (nuclear) magnetic resonance imaging, or positron emission tomography. It is hard to imagine the course of modern medicine without these uses of radiation. I am a greater believer in the inevitability of some discoveries and technologies than Wagner and Ketchum, and do believe that the nuclear reactor at Oak Ridge would have been built with a delay of no more than 10 years even if the plutonium (not uranium) had not been wanted for nuclear bombs.

Perhaps the most difficult chapter, and the most important, is chapter 4, "Living With Uncertainty." Here Wagner and Ketchum lay out the way that they believe mankind should look at the difficult problems of deciding whether the benefits of radiation should force an action, or the risks of radiation prevent it. The procedures for comparison must not be a mystery, but must be based upon common sense. Excellent guidelines are given for keeping medical x-ray exposures to a minimum, eg, "Ask the doctor why an X-ray is needed. Will it influence future treatment or the medical outcome? . . . Don't insist on an X-ray procedure, either directly or subtly. . . . Don't refuse an X-ray procedure because of fear of harmful effects of ionizing radiation. Often [I would say usually] not having an X-ray is much more harmful than the risk of the radiation. . . . Keep a record of your X-ray examinations. . . . Retrieving previous X-rays can sometimes eliminate the need to repeat them. . . ." If similar rules were applied to nuclear electric power, for example, a lot of the present misunderstanding about its use would disappear.

The errors of this book are fortunately of detail rather than of principle. The authors describe how Hans Bethe had "concluded that the sun's energy must come from thermonuclear reactions during which hydrogen atoms are fused into helium." It is indeed now generally believed that the direct fusion of hydrogen atoms is the source of energy from the sun; but Bethe was not the first to suggest this. Bethe *was* the first to suggest that an indirect set of reactions using a cycle involving carbon and other atoms, which had a *net* effect of transforming protons (not hydrogen atoms) into helium could be a source of energy in some stars.

The description of the nuclear reactor accident at Chernobyl, on pages 108 to 113, while correct in general, differs in several important details from the version of the Soviet authorities, which is generally accepted. The authors describe how the reactor power was ultimately reduced to 7% to simulate shutdown, whereas the plan was to perform the experiment at 30% power. The actual reduction to 7% came about because of a mistake in setting the computer. The authors state that "the operators disengaged the system that would have automatically shut down the reactor in case of overheating." The actual shutdown systems that were disconnected were on trip of both turbines, and on level of the drum (steam) separator.

Contrary to the statement of the authors, the two operators were not killed instantly. According to Dr Valeri Legasov, head of the government investigation team, the operator in charge lived long enough to describe what he had done; but he could not be questioned again, because, as Dr Legasov explained to a suddenly hushed audience at Vienna in August 1986, he died in hospital 2 days later.

The emergency core cooling systems had indeed been manually disengaged, and contrary to regulations, the reactor had run at half power for 10 hours. But the emergency core cooling system would not have changed the course of this particular accident or mitigated its consequences. But the general statement of the authors is right, that "The operators were unbelievably reckless, had a poor understanding of the operation of a reactor, and did not appreciate the extreme danger of what they were doing."

"Radiation need not, and indeed must not, be a mystery. . ."

Although the authors are right in their general comparison of the accident at Three Mile Island and that at Chernobyl, the details are not completely correct. Correctly stating that only 17 curies of radioactive iodine was released to the environment at Three Mile Island compared with 30 million curies at Chernobyl, they incorrectly state that the radioactivity was kept within the containment building of Three Mile Island 2. The true story is more complex. We do not know what happened to all the iodine. The containment did, indeed, prevent any escape of gases, except in controlled releases through filters, but a large amount may have left the containment, dissolved in the water. The water, which went to the auxiliary building, would have retained most of its radioactivity.

Because of errors such as these, and also because this is not a book with detailed references, the book is not a reference to which readers will return time after time for details of nuclear issues. It remains an important book in giving perspective to anyone's understanding of radiation and the technologies that produce and control it. Radiation need not, and indeed must not, be a mystery. This book will do a great deal to help in the task of "demystification."

I enjoyed reading this book. I recommend it highly as a book describing people's finding an approach to living with radiation—as we must all do, have done, and always must do.

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Reasoning and Decision Making

Reasoning in Medicine: An Introduction to Clinical Inference, by Daniel A. Albert, Ronald Munson, and Michael D. Resnik (*The Johns Hopkins Series in Contemporary Medicine and Public Health*), 263 pp, $30, Baltimore, Md, The Johns Hopkins University Press, 1988.

Medical Decision Making, by Harold C. Sox, Jr, Marshal A. Blatt, Michael C. Higgins, et al, 406 pp, with illus, $24.95, Boston, Mass, Butterworths, 1988.

There are two modes of acquiring knowledge, namely by reasoning and experience. Reasoning draws a conclusion . . . but does not make the conclusion certain, nor does it remove doubt so that the mind may rest on the intuition of truth, unless the mind discovers it by the path of experience.

Roger Bacon
English philosopher and scientist

As with many physicians, the seeds of my ability to reason clinically, though sewn during medical school, really only began to sprout in my internship. Through regular exposure to an Oslerian internist legendary in the community for his ability to assimilate clinical information and make appropriate judgments about diagnosis and treatment, I had the opportunity to comprehend in almost unspoken ways what the "art" of medicine was. My guess is that each one of our group of 12 interns took away from that year a somewhat different set of impressions of just exactly how this particular physician arrived at his almost magically insightful conclusions. And in all likelihood we have continued to whatever level of skill we now have with these biased perspectives acting as enablers, modifiers, and filters of our experience.

Herein lies a key problem with contemporary medical education: the understanding and development of clinical reasoning is essentially left to chance. That is, who our teachers are and how

they (seem to) think is more important than what they teach.

Both of these books address this problem in important and useful ways. Both are primarily aimed at medical students and house officers. There is some overlap between the two. In my ideal world, a medical school semester would be devoted to each book and remedial education would be required of those in practice.

Reasoning in Medicine, the broader, more introductory text, is the collaborative effort of a clinician, a philosopher of science, and a logician. After noting that "Clinical reasoning and decision making take place within a dense and complicated conceptual matrix," the authors, successfully I think, go on to explore the implications of this matrix for the character of clinical medicine. An introductory case presentation of a diseased patient is dissected into its components through chapters on data; inductive inference; deductive inference; hypotheses, laws, and theories; disease; diagnosis; and decision making and patient management.

The authors' discussion not only of what these concepts are but of where our comprehension of them comes from is particularly rewarding. For example, in the chapter on inductive inference the meaning of probability is teased out of four separate concepts: the logical (Mendelian), the statistical, the propensity, and the subjective. The resulting proposed "compromise" view both informs the reader about and respects the still-evolving understanding of this field of mathematics and philosophy.

The chapter on hypotheses, laws, and theories includes a particularly good discussion of the ways in which we conceptualize what we do in medicine. It includes a brief presentation of Thomas Kuhn's views of the structure of scientific thought and its basis in paradigms that periodically transform over time. For those of us who may become smug about our "knowledge," such thoughts are beneficial. The chapter on disease provides a similarly insightful frame of reference for a concept too often taken for granted.

Each chapter of *Reasoning in Medicine* is well referenced from both the medical and philosophical literature. In fact, this is one of the true delights of this book: that it is unabashedly interdisciplinary.

Medical Decision Making, by Sox et al, is a comprehensive user's guide to the increasingly popular science of clinical decision analysis. This book contains chapters on differential diagnosis, probability (and quantifying uncertainty), Bayes' theorem, clinical data measurement, expected value decision making, outcome of care measurement and utility theory, diagnostic test selection, and cost-benefit and cost-effectiveness analysis. Each chapter is clearly organized in outline style and concludes with a summary, a glossary of new words introduced in the chapter, and references. Most chapters also conclude with sample problems, the answers to which are provided at the end of the book. For the benefit of practitioners of decision analysis (and arguably worth the price of the book by itself!), appended is an extensively referenced and annotated list of the characteristics (sensitivity, specificity, and likelihood ratios) of dozens of commonly used diagnostic tests.

> "a key problem with contemporary medical education: the understanding and development of clinical reasoning is essentially left to chance"

Medical Decision Making is very well written, contains numerous clinical decision making "pearls," and includes a particularly strong presentation of utility theory with a step-by-step explanation of how to involve patients in the process of informed choice regarding their diagnostic or therapeutic options. (My impression has always been that this is the most difficult aspect of bedside decision analysis.) Overall, *Medical Decision Making* is the most accessible book to date on the subject and should be ideal for both undergraduate and graduate medical educational environments.

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Books Received

Allergy-Immunology

Allergic Diseases From Infancy to Adulthood, by C. Warren Bierman and David S. Pearlman, 2nd ed, 824 pp, with illus, $95, Philadelphia, Pa, WB Saunders Co, 1988.

Detecting Your Hidden Allergies, by William G. Crook, 209 pp, with illus, paper $11.95, Jackson, Tenn, Professional Books, 1988.

Environmental Health

Agent Orange and Vietnam: An Annotated Bibliography, by Caroline D. Harnly, 401 pp, $37.50, Metuchen, NJ, Scarecrow Press Inc, 1988.

Environmental Hygiene, edited by N. H. Seemayer and W. Hadnagy (workshop, Düsseldorf, West Germany, May 1987), 214 pp, with 69 figures, $55.90, New York, NY, Springer-Verlag, 1988.

Immunology

H-2 Antigens: Genes, Molecules, Function, edited by Chella S. David (*NATO ASI Series*, vol 144, workshop, Bar Harbor, Me, 1987), 849 pp, with illus, $129.50, New York, NY, Plenum Press, 1987.

Interferon and Nonviral Pathogens, edited by Gerald I. Byrne and Jenifer Turco (*Immunology Series*, vol 42, N. R. Rose and Z. Trnka, eds), 317 pp, with illus, $99.75, New York, NY, Marcel Dekker Inc, 1988.

Nephrology

The Nephrotic Syndrome, edited by J. Stewart Cameron and Richard J. Glassock (*Kidney Disease*, vol 8), 1078 pp, with illus, $195, New York, NY, Marcel Dekker Inc, 1988.

Otolaryngology

Endoscopic Paranasal Sinus Surgery, by Dale H. Rice and Steven D. Schaefer, 129 pp, with illus, $79, New York, NY, Raven Press, 1988.

Otolaryngology: Problems in Primary Care, edited by D. Thomas Upchurch (*Problems in Primary Care Series*), 344 pp, with illus, paper $42.95, Oradell, NJ, Medical Economics Books, 1989.

Pediatrics

Developmental-Behavioral Disorders: Selected Topics, vol 1, edited by Marvin I. Gottlieb and John E. Williams (*Critical Issues in Developmental and Behavioral Pediatrics*, vol 1), 366 pp, with illus, $59.50, New York, NY, Plenum Medical Book Co, 1988.

I Never Called It Rape: The Ms. Report on Recognizing, Fighting, and Surviving Date and Acquaintance Rape, by Robin Warshaw, 229 pp, paper $7.95, New York, NY, Harper & Row Publishers, 1988.

Treatment of Adult Survivors of Childhood Abuse, by Eliana Gil, 301 pp, paper $16.95, Walnut Creek, Calif, Launch Press, 1988.

Reproduction

Advances in Clinical Andrology, edited by C. L. R. Barratt and I. D. Cooke, 118 pp, with illus, $47, Boston, Mass, MTP Press Limited, 1988.

Condom Info Guide, by James M. Brackett, 99 pp, Durant, Okla, Essential Medical Information Systems Inc, 1988.

Contraceptive Sterilization, by William M. Moss and Association for Voluntary Surgical Contraception, 182 pp, Amityville, NY, Essential Medical Information Systems Inc, 1988.

Frontiers in Reproductive Endocrinology and Infertility, edited by Charles S. A. Ng, Seang-Lin Tan, F. M. Maurine Tsakok, et al, 112 pp, $44, Boston, Mass, Kluwer Academic Publishers, 1988.

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Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be non-systemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

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Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

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The Johns Hopkins Hospital

. . . The opening of the Johns Hopkins Hospital in 1889 marked a new departure in medical education in the United States. It was not the hospital itself, as there were many larger and just as good; it was not the men appointed, as there were others quite as well qualified; it was the organization. For the first time in an English-speaking country, a hospital was organized in units, each one in charge of a head or chief. The day after my appointment I had a telegram from Dr. Gilman, president of the university, who had been asked to open the hospital, to meet him at the Fifth Avenue Hotel, New York. He said to Dr. Welch and me: "I have asked you to come here as the manager is an old friend of mine, and we will spend a couple of days; there is no difference really between a hospital and a hotel." We saw everything arranged in departments, with responsible heads, and over all a director. "This," he said, "is really the hospital, and we shall model ours upon it. The clinical unit of a hospital is the exact counterpart of one of the subdivisions of any great hotel or department store."

Fortunately the university had not enough money at first to open the medical school, so that we had several years to wait, during which there was only postgraduate teaching, and we were able to complete our organization.

. . . By the time the first class of medical students had reached the final stage the hospital was in very good working order. The medical unit consisted of about seventy beds (the number gradually increased to above one hundred), a large out-patient department, and a clinical laboratory close to the chief wards. In charge was the head, *ex officio* professor of medicine in the university, a resident staff of first, second, and third assistants (nominated by the professor), a fourth assistant in charge of the laboratory; and in addition four house physicians, appointed annually. . . .

I have always felt that the success which followed this experiment—for such it was in hospital work in the United States, at any rate—was due to the type of men we had as senior assistants in the various departments. We chose the best that were to be had; the nomination was in the hands of the chief of the department; they were given responsibility, encouraged to teach, and to write, and their professional development was promoted in every way. An excellent plan, greatly favored by the director of the hospital, Dr. Hurd, was to allow the senior assistants every couple of years a vacation of from four to six months to go abroad for study. The out-patient section of the medical unit was in charge of a separate staff, usually men who had been senior assistants and had gone into practice in the city. There were three; each took two days a week, and had his own staff of three or four assistants, and all were directly engaged in teaching. You may gather from this some idea of the size of a medical unit and of the number of men at work in it, at least twenty-three or twenty-four when I left the hospital. This may be said to be an impossible task for one man to control. Not at all; it is all a question of organization, of subdivision of labour, and of co-operation among workers, and the introduction into a department of modern business methods.

From Sir William Osler's *The Medical Clinic*, an address given at St Bartholomew's Hospital, London, England, December 1913 (*The Collected Writings of Sir William Osler*, Birmingham, Ala, The Classics of Medicine Library, 1985, vol 11).

Edited by Charlene Breedlove, Associate Editor.

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UPDATE: SEXUALLY TRANSMITTED DISEASES

AIDS: PATIENTS TALK WITH PHYSICIANS

Understanding the issues surrounding AIDS is important to facilitate effective interaction with your patients. This Sunday, a special program on American Medical Television will provide insight into a broad spectrum of clinical, social and personal matters affecting the patient with AIDS.

The forum will be moderated by *Marcus Conant, MD,* Chairman of the California State Department of Health Task Force on AIDS and Clinical Professor of Dermatology at UC-San Francisco, with *Ronald Grossman, MD,* Clinical Instructor in Medicine at New York Hospital at Cornell University.

Tune in to learn:

How Patients cope emotionally.

- Useful techniques.
- "Quality of Life": the patient's definition.

The physician's role.

- How to initiate and manage therapy.
- Effective answers to difficult questions.

Physicians Discuss Emerging Associations between STDs

Ominous statistics are beginning to show associations between sexually transmitted diseases (STDs).

Immediately following the program on AIDS, stay tuned for a symposium on the controversial questions surrounding this grave public health issue.

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Tune in to learn:

The mechanisms that link STDs.

- Female-to-male versus male-to-male transmission rates of HIV.
- How the AIDS epidemic can be controlled.
- The role of the primary care physician in STD management.

Tune in this Sunday, June 4, 11:00 a.m. (Eastern) to American Medical Television on the Discovery Channel for useful new information on STDs.

Check your local television listing for American Medical Television on The Discovery Channel. For a study guide and CME credit information, call **1-800-289-6000.**

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Allergy & Immunology

IMMUNOLOGIST/INFECTIOUS DISEASE SPECIALIST with experience in transplant patient management sought to open clinical practice in Florida's capital city. Must be board eligible/certified. Will interact with active, 300-member medical staff and family practice residents serving 771-bed medical center with active transplant program. Regional pop. base of 500,000. Two major universities and Gulf beaches available. Medical Center willing to offer attractive benefit package and hospital-based practice to qualified individual. Send curriculum vitae and names of three references to I. B. Harrison, M.D., Director of Medical Affairs, Tallahassee Memorial Regional Medical Center, Magnolia & Miccosukee, Tallahassee, FL 32308. Telephone: (904) 681-5121.

ALLERGY/IMMUNOLOGY: MARSHFIELD CLINIC SECTION of Allergy is seeking a BE/BC allergist, preferably with a pediatric background, to replace a retired colleague. This specialist would join two allergists in a large regional referral practice covering the entire spectrum of present day allergy. Marshfield Clinic is a 290 physician multispecialty private group practice located in Central Wisconsin. Pediatric Residency Program, Medical Research Foundation, and University of Wisconsin Medical School affiliation contribute to a very stimulating environment. Send inquiries and curriculum vitae to John T. Twiggs, M.D., Marshfield Clinic, 1000 North Oak Avenue, Marshfield, WI 54449 or call collect at (715) 387-5186.

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CARDIOTHORACIC SURGEON: BOARD CERTIFIED OR ELIGible is sought to join academic practice in the midwest. Please direct curriculum vitae or inquiries to J. Terrance Davis, M.S., Medical College of Ohio, C.S. #10008, Toledo, OH 43699. An Equal Opportunity Employer.

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EMERGENCY MEDICINE, BE/BC, EM, FP, IM, FULL/PART time. Salary and benefits over $100,000 a year. Community Hospital, 27,000 visits. ACLS/ATLS required. Replies: Dr. Elman 716-862-2841.

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FAMILY PRACTICE — CA BOARD CERTIFIED/ELIGIBLE Family Practice physician sought by large medical group for a rural satellite location 15 miles from Sacramento. Competitive salary and benefits first year. For more information, please send current C.V. to: Warren J. Boyer, Jr., M.D., Marysville Medical Group, 800 Third St., Marysville, CA 95901.

MAUI, HAWAII. CLINIC NEEDS FAMILY PRACTITIONER to start November 1, 1989. Send CV to John N. Withers, M.D., 53 Puunene Ave., Kahului, Maui, HI 96732.

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Family practitioners, BC/BE to join a 4-physician family practice group which staffs two satellite health centers. No obstetrics. Flexible working hours. Incredible ski/recreational opportunities nearby. Good family area. Guaranteed salary, plus productivity incentives; partnership buy-in available after one year. Pension and profit sharing plan. Send letters of application and resume to: Sharon Strong, MD, Magna Health Center 8370 West 3500 South, Magna Utah 84044.

LEXINGTON, KENTUCKY — HUMANA'S GROUP HEALTH Division is seeking Primary Care physicians for its staff model HMO clinics. Salary commensurate with experience plus excellent benefits including paid malpractice, health, life and disability insurance, participation in pension plan, paid vacation and CME. Work schedule is four and one half days per week, plus hospital rounds and some on-call. Call Collect 606/263-1440, or send your CV to: Susan Miller, 101 Prosperous Place, Suite 300, Lexington, KY 40509.

FREE BEACH PRACTICE — ASSUME YOUNG PRIMARY care practice San Diego, while I pursue other oppty; no buy-in, xchg for option to return/share. "UC", 7486 La Jolla Blvd, Ste 491, La Jolla, CA 92037.

FAMILY PRACTICE: MARSHFIELD CLINIC, A MULTISPEcialty group practice with over 300 physicians, is seeking BE/BC family practitioners to join expanding regional centers. Practice opportunities range in size from single specialty groups of three to multispecialty groups of five. Positions available in six locations: two in northwestern Wisconsin within 70 and 90 miles of Minneapolis; two in northcentral Wisconsin within 80 and 90 miles of Lake Superior; and two in central Wisconsin within 25 and 35 miles of Marshfield. Full specialty consultation readily available. Positions offer strong economic stability combined with exceptional recreational, cultural, and educational opportunities. Starting salary up to $89,400 with salary in two years up to $113,100. Fringe benefit package outstanding. Send C.V. and references to: David L. Draves, Director Regional Development, 1000 North Oak Avenue, Marshfield, WI 54449 or call collect at (715) 387-5376.

FAMILY PRACTICE — BOARD CERTIFIED/ELIGIBLE — opportunity available in Northeastern PA located in the beautiful Endless Mountains. 39-bed hospital with very active outpatient department is looking for a replacement for physician with very successful family medicine and OB practice. Interested physicians may contact Rex Catlin or Eudora Bennett, 3 Grow Avenue, Montrose, PA 18801 or call 717-278-3801. Equal opportunity employer.

MAUI, HAWAII — PROGRESSIVE RESORT PRACTICE seeks enterprising, energetic physician for management and general practice responsibilities. Opportunity for early equity. Salary negotiable. Available immediately. Call Max Frankum, M.D. person-to-person (808) 667-7676.

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COLORADO SPRINGS AND PUEBLO POSITIONS AVAILable in newly built hospital-affiliated urgent care facilities for primary care or family practice physicians with general medical experience. Send your C.V. including salary requirements in confidence to: James Simerville, M.D., Interstate Health Services, Inc., 7606 N. Union, Suite D, Colorado Springs, CO 80920. No Agencies Please.

OBERLIN, OH MULTISPECIALTY GROUP SEEKS ADDITIONAL BC/BE family physicians. Small northern Ohio college town serving drawing area 275,000. Salaried position first year; full shareholder status available second year. Send CV to Dr. VanDyke, 224 W. Lorain, Oberlin, OH 44074.

FP PHYSICIAN NEEDED IN CENTRAL KY OB INTEREST required. Bluegrass regional hospital offers guaranteed income with office space beside the hospital. Send CV to Ms. Stalker, Clark County Hospital, PO Box 630, Winchester, KY 40391.

FAMILY PRACTICE FACULTY — NORTHERN CALIFORNIA. UCSF-affiliated 211-bed acute care hospital in Monterey County seeks full-time BE/BC Family Practice Practitioner. Responsibilities include inpatient/outpatient teaching, clinic practice and some administrative duties. Requires 2 years post-residency experience, Spanish language ability a plus. Salary range $67,900-$84,150 with full benefit package. CVs to: Anthony Sforza, MD, Natividad Medical Center, P.O. Box 81611, Salinas, CA 93912-1611.

WISCONSIN — FAMILY PRACTITIONER NEEDED BY PROgressive and stable HMO in West Central Wisconsin city of 50,000. Highly competitive salary with excellent fringe. Practice high quality care in a good recreational area. Send CV to Stuart Lancer, M.D., 1030 Regis Court, Eau Claire, WI 54701.

FAMILY PHYSICIAN BC/BE FOR ESTABLISHED PRACTICE in Baltimore City: Excellent salary, benefits, paid malpractice, health insurance, early partnership. Marc S. Posner, M.D., 107 E. West Street, Baltimore, MD 21230. (301) 752-5425.

WESTERN PA. & EASTERN OHIO: FULL-TIME PHYSICIAN for Urgent Care Center. Should have experience in Family Practice, Int. Med. or ER Med. Excellent salary & benefits. Send CV to: DOC, 114 N. 4th St., Steubenville, OH 43952.

FAMILY PRACTITIONERS: NEEDED AND APPRECIATED in Texas and California. Locum tenens, practice trials, permanent placements available through doctor-owned PRN, Ltd., "large enough to offer you options, small enough to care." Call toll-free for "no obligation" information: 1-800-531-1122. One Thousand N. Walnut St., Suite B, New Braunfels, TX 78130.

FAMILY PRACTITIONER FOR 35 BED COMMUNITY HOSpital in a relatively small city in Western Oklahoma, Great Plains area. Cattle, farming, oil and gas, great place to raise a family. Contact Marilyn Bryan, 405-225-2511, Ext. 381.

Fifty-five physician multi-specialty practice has excellent opportunities in the new development of a family practice section. First opening 20 min from major college/med school campus. Income potential 400K annual gross revenue. Salary guarantee. Incentives negotiable. Contact Doug Kelly, 404 Keene St., Columbia, Missouri 65201. Phone: 314-875-9335.

FAMILY/GENERAL PRACTICE: PHYSICIAN NEEDED FOR out-patient Medical Center located in Southwestern Pennsylvania, immediate openings. Desirable hours with minimal on call. $91,000 yearly base plus $27,000 incentive package. Competitive benefits including: Health insurance, Malpractice insurance, plus two weeks paid vacation. Interested physicians call (412) 628-6666 and ask for Kristin Monday through Friday 8:00 a.m. till 5:00 p.m.

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FAMILY PRACTICE PHYSICIANS (2) (BC/BE) TO JOIN A multispecialty group in a lovely community of 34,000 with 100,000 referral area in Eastern Iowa on the Mississippi River. Excellent practice opportunity with modern hospital facilities. Solid industrial base. Excellent educational system. Chicago three hours via expressway. Generous first year salary plus bonus incentive and fringe benefits. Full member after one year. Contact Phil Sayles, Adm., Bluff Medical Center, P.C., 240 North Bluff Blvd., Clinton, IA 52732. Phone (319)243-5600.

FAMILY PRACTICE/INTERNAL MEDICINE. EXCELLENT opportunity for BC/BE Family Practitioner to join eight-member primary care group. Competitive salary, paid malpractice, growing patient population, great schools, university, and outdoor family activities in this scenic upstate NY community. Send CV to: D. Precopio, 33 Mithcell Avenue-Suite 204, Binghamton, NY 13903; 607-723-3346.

NEW MEXICO STATE UNIVERSITY, STUDENT HEALTH Center, needs Family Practitioner to join four physicians and two nurse practitioners in providing primary care (including Gyn care but excluding obstetrics) for a growing student population, with a fall '88 census of 14,284. Estimated patient visits per year: 27,000. Activities are primarily outpatient primary care, with a small in-patient unit. Salary: 42,000 (10. month position) with possibility of extension to a 12 month position as need arises. Must have or be eligible for New Mexico State License. Send letter of application, resume, copy of medical school diploma, and names of three references to: W. Terrence Meyer, M.D., Director, New Mexico State University, Student Health Center, P.O. Box 30001, Dept. 3529, Las Cruces, NM, 88003, Telephone: 1-505-646-1512. Application deadline: June 15, 1989, or until position is filled. New Mexico State University is an Equal Opportunity/Affirmative Action Employer.

TYLER AND LONGVIEW, TEXAS. CATCH THE DREAM! Outpatient family practice opportunities. $80,000 plus annually. Contact: D. J. Woods, Taylor Medical Systems, (214)534-1331.

PRIMARY CARE PHYSICIANS — BOARD CERTIFIED OR eligible; Illinois license and ACLS. Positions available July 1, 1989. Call (312) 383-6200 x.6715 or forward CV to: Physician Relations, West Suburban Hospital Medical Center, Erie at Austin, Oak Park, Illinois 60302. EOE.

$135,000 PRACTICE OPPORTUNITY. FAMILY OR GENERAL Practitioner — Rolling Plains, Texas Panhandle — Practice should include Surgery and Obstetrics — Fully equipped clinic adjacent to 42 bed hospital — $135,000 first year guarantee. For more information contact Administrator, Hall County Hospital — 1-806-259-3504.

NORTH HOUSTON AREA NEAR LAKE AND BEAUTIFUL Conference center — established medical-dental group opening solo family practice office in progressive community near three hospitals. Contact Jodie Roberds, Manager, 409-756-4711.

EMERGENCY MEDICINE: MARYLAND/D.C. VICINITY — New urgent care center in a young community. Work with emergency specialists in a modern, pleasant facility. Competitive salary and benefits. Send CV to: Michael Shuster, M.D., Medical Access, 13051 Wisteria Drive, Germantown, MD 20874.

FP/GP NEEDED FOR QUAINT, SMALL TOWN 20 MINUTES from the Gulf Coast in Northern Florida. This community of 20,000 is 45 minutes from Tallahassee, the State Capital, and home to 2 state universities and approximately 200,000 residents. Hospital offers attractive income guarantee, plus a retiring physician's pracitice currently grossing $200,000 a year. Contact Mark Rooney, Jackson & Coker, 400 Perimeter Center Terrace, Suite 760 MYJC9, Atlanta, GA 30346, Tel. 1-800-544-1987.

PHYSICIANS WANTED — FAMILY PRACTICE, BOWLING Green, KY. Primary Care Center/Health Department in South Central KY seeking Board Eligible/Certified physician to join existing MD staff (OB/GYN, FP, PED) team. Practice includes full range of ambulatory primary care and has in-house lab and x-ray facilities. Benefits include: Regular working hours, malpractice insurance, dental & health insurance, retirement, deferred compensation and continuing education reimbursement. Salary commensurate with training and/or experience. Send CV or inquire to Chuck Bunch, District Director, P.O. Box 1157, Bowling Green, KY 42101-1157. EOE.

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FAMILY PRACTICE — BOARD CERTIFIED OR BOARD ELigible. Needed immediately for a satellite clinic of a 23 physician multi-specialty group. Guaranteed salary with incentive and excellent benefit program. Send curriculum vitae to John Reed, Administrator, Weber Medical Clinic, 1200 N. East Street, Olney, IL 62450.

SOUTHERN CALIFORNIA. 3 F/P GROUP SEEKS BC/BE FP to replace retiring associate. Generous salary + production income. Opportunity for partnership in one year. Beautiful climate, excellent schools. Contact: H. Drummond, M.D., 1376 Erringer Road, Simi Valley, CA 93065 (805-526-5240).

General Practice

UNIVERSITY PHYSICIANS: STUDENT HEALTH SERVICE, University of Wyoming, Laramie, is seeking two physicians for full-time employment. Applicants must have a Medical Doctor's degree plus be BC/BE by either A.A.F.P. or American Board of Internal Medicine. Must have a license or qualify for licensure to practice medicine in the State of Wyoming. Prefer candidate to have at least four years of primary care experience. Physicians to join two full-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray and pharmacy. Salary commensurate with qualifications and experience. Closing date: July 5, 1989 and continues until position is filled. Applications may be obtained from: Personnel Office, University of Wyoming, Box 3422, Room 139 Wyo Hall, Laramie, WY 82071. The University of Wyoming is an EO/AA employer.

GENERAL PRACTITIONER TO JOIN A WELL ESTABlished Surgical practice in south-central location. Excellent benefits available. Please submit complete CV. Box 5816, c/o JAMA.

Infectious Diseases

INFECTIOUS DISEASES — MARSHFIELD CLINIC, A 290 physician multi-specialty clinic, located in Central Wisconsin, is seeking to add a fifth BC/BE Infectious Disease Specialist to its current four member section. This opportunity offers the best of clinical medicine and the advantages of academics as well. Our expanding facilities are physically attached to Saint Joseph's Hospital, a 529 bed acute care teaching facility, that is comparably modern. A full range of benefits includes health and dental insurance, liberal educational fund, a fully vested retirement plan, and more. For additional information send a CV to: James Mikula, Assistant Director-Patient Services, 1000 N. Oak, Marshfield, WI 54449, or call collect at (715) 387-5830.

Internal Medicine

A 46-PHYSICIAN MULTI-SPECIALTY GROUP LOCATED 40 miles north of Sacramento seeks an ABIM eligible/certified General Internist to join our 8-physician department. Partnership potential after the first year or two. The salary is negotiable with incentives. PLS. Send C.V. to: Warren J. Boyer, Jr., M.D., Marysville Medical Group, 800 Third St., Marysville, CA 95901.

BC/BE GENERAL INTERNISTS NEEDED FOR GROUP practice HMO-Denver, Colorado. The Colorado Permanente Medical Group, an expanding multispecialty prepaid group practice caring for members of the Kaiser Foundation Health Plan is seeking general internists to join group. Fully equipped outpatient facilities and superior community hospital. Competitive salary and benefits. For additional information, please contact: V.A. LaFleur, M.D., Associate Medical Director, Colorado Permanente Medical Group, P.C., 2045 Franklin St., Denver, CO 80205; (303)861-3262. EOE.

Staff Physician

Northwestern University Student Health Center

Need Staff Physician in General Medicine Clinic weekdays plus assigned on-call night and weekend duties for Outpatient Dept., Evanston Hospital Emergency Room, and Infirmary. Participation in assigned committee work expected.

Qualifications required include: M.D. degree, Board Certified or Board Eligible in Internal Medicine and Illinois State License. Must be well trained and credentialled in Internal Medicine.

Forward resume to:

Staff Physician Search
Northwestern University
720 University Place
Evanston, IL 60208-1142

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Christy Jensen or Maureen Forrester in
Physician Recruitment at
45 So. 17th Street, San Jose, CA 95112
(408) 282-7833
(408) 282-7757

IMMEDIATE OPENING IN GENERAL INTERNAL MEDICINE for a board-eligible/certified physician. Would associate with 13 Internists, located within a 38-physician, fee-for-service, long standing, multi-specialty group practice located in the east San Gabriel Valley, 20 miles from Los Angeles. First year guaranteed salary, plus incentive bonus, leading to full partnership. Please send resume to Barton H. Ghormley, Administrator, 420 W. Rowland, Covina, CA 91723.

BOULDER, COLORADO . . . GENERAL INTERNIST needed for Kaiser Permanente Medical Care Program at the foot of the Rocky Mountains in Boulder. Competitive salary and benefits. For additional information, please contact: V. A. LaFleur, M.D., Associate Medical Director, Colorado Permanente Medical Group, P.C., 2045 Franklin St., Denver, CO 80205; (303) 861-3262. EOE.

BC/BE INTERNAL MEDICINE/NEPHROLOGY

We are a young rapidly growing medical community. Our Medical Center is currently in a rebuilding program. Convenient to teaching hospital and transplant center, and only 30 miles from a major metropolitan area. We offer an opportunity for research as well as an established dialysis clinic with an acute program. Terms negotiable. Send resume to: David Hagewood, Director of Human Resources, 1600 Hayes St., Suite 300, Nashville, TN 37203.

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IMMEDIATE OPENING. INTERNIST PREFERABLY WITH GI background to join a BC group practice. Excellent benefits. Apply Box 5741, c/o JAMA.

SOUTH EAST FLORIDA — GENERAL INTERNAL MEDICINE. Earnings guarantee 75K/year. Attractive hours and location. Some hospital work and call. Malpractice provided. Send CV to: Jerry Hermanson, 100 E. Sample Road, Suite 300, Pompano Beach, FL 33064.

INTERNAL MEDICINE/FAMILY PRACTICE UPSTATE NEW York. FT/PT positions for urgent care medical service. One year contract required with opportunity to lead to FP/ER. Competitive salary, paid malpractice, and benefits. Send CV to: D. Precopio, 33 Mitchell Avenue-Suite 204, Binghamton, NY 13903; 607-723-3346.

INTERNAL MEDICINE — IMMEDIATE OPENING. INTERnist preferable with GI background to join a busy group practice. Good fringe benefits. Located in Ocean County, New Jersey. Apply to Box 5759 c/o JAMA.

INTERNIST — THE ELKO REGIONAL MEDICAL CENTER seeks a Board Certified/Board Eligible Internist to join three other Internists in a very busy practice. All fee for service with excellent collection ratio. Guaranteed salary for six months leading to full partnership. Comprehensive benefit package including malpractice insurance. Elko is a thriving community surrounded by mountains and wilderness areas. Recreation year round. Please send C.V. to Cherie Atwood, Administrator, Elko Regional Medical Center, 762-14th Street, Elko, Nevada 89801. (702) 738-3111.

INTERNIST — OPPORTUNITY WITH 7 PERSON MULTIspecialty staff, including 1 Internist. 40-bed JCAH hospital, S.E. Colorado community of 10,000. Send CV to James Giedd, Administrator, Prowers Medical Center, 2101 S. Memorial Drive, Lamar, CO 81052. 719-336-4343.

BC/BE INTERNIST — INTERNIST IN SW FLORIDA COAST has busy practice after 14 months, seeking BC/BE to join him. Generous salary/benefits with early partnership offered. Send CV to: 1206 SE 40th Street, Suite 303, Cape Coral, FL 33904.

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Immediate need to develop an aggressive full-range practice. 120-bed hospital will support you with a $200,000 income guarantee. Family-oriented community of 20,000 in a county of over 300,000. For more information call Stephen Thomas (800) 288-1210 or (714) 757-7750 or send your CV to Merritt, Hawkins & Associates, 17300 Redhill Avenue, Suite 250, Irvine, CA 92714.

GASTROENTEROLOGY. IMMEDIATE POSITION AVAILable in our 46 doctor group, 40 miles north of Sacramento. Applicants must be CA Board certified/Eligible. Excellent compensation and benefits. Partnership opportunity after first year. For additional information, send C.V. to: Warren J. Boyer, Jr., M.D., Marysville Medical Group, 800 Third St., Marysville, CA 95901.

ARIZONA, ESTABLISHED MULTI-SPECIALTY GROUP IN Tucson seeks BC/BE internist with sub-specialty in Pulmonary Disease. Submit CV to Chairman, Physician Recruiting, 5402 E Grant Rd, Bldg E, Tucson, AZ 85712.

GENERAL INTERNIST NEEDED BY GROWING MULTIspecialty group to join seven-member department. Excellent initial salary and benefits leading to shareholder status. Reply Box 5801, c/o JAMA.

MAUI, HAWAII. CLINIC NEEDS GENERAL INTERNIST TO start November 1, 1989. Send CV to John N. Withers, M.D., 53 Puunene Ave., Kahului, Maui, HI 96732.

UNIVERSITY OF OKLAHOMA, DEPARTMENT OF MEDIcine is accepting applications for positions as Assistant Professor. Direct patient care and clinical teaching of residents and students as well as clinical research. Must be board certified or board eligible in Internal Medicine. C.V.s may be directed to Patrick A. McKee, M.D., University of Oklahoma, Department of Medicine, P.O. Box 26901, Oklahoma City, OK 73190. We are an equal opportunity employer.

GENERAL INTERNIST NEEDED TO JOIN VERY BUSY Endocrine/Internal Medicine physician in a well established practice in Southern California. BC with special interest in Vascular Disease. Excellent salary and benefits, with future partnership potential. Send CV to D. K. Robbins, 44241 15th Street West, Suite 304, Lancaster, CA 93534; or call (805) 945-7806.

INTERNISTS BC/BE NEEDED IN THIS PROGRESSIVE 200bed acute medical/surgical facility in the beautiful upper peninsula of Michigan. The Iron Mountain area has a population of about 25,000 and boasts good schools and churches, a low crime rate, and abundant recreational opportunities, including hunting, fishing, skiing, and aquatic sports. Send letter of interest and CV to: A. J. Papp, M.D., Chief of Staff, VA Medical Center, Iron Mountain, MI 49801. An equal opportunity employer.

GENERAL INTERNIST. ASSISTANT PROFESSOR POSITIons (2) available for board certified or eligible individuals interested in primary care in academic setting. CV to LeeRoy Meyer, M.D., Dept. of Internal Medicine, University of Nebraska Medical Center, 42nd & Dewey Ave., Omaha, NE 68105. An Affirmative Action/Equal Opportunity Employer.

GENERAL INTERNIST: MARSHFIELD CLINIC, A MULTIspecialty group practice with over 300 physicians, is seeking BE/BC general internists to join expanding regional centers. Practice opportunities range in size from multispecialty groups of 11 to 25. Positions available in three locations. One in northwestern Wisconsin, 90 miles from Minneapolis; one in northcentral Wisconsin in close proximity to the U.P. of Michigan and Lake Superior, and one in central Wisconsin within 35 miles of Marshfield. Full specialty consultation readily available. Positions offer strong economic stability combined with exceptional recreational, cultural, and educational opportunities. Starting salary up to $89,400 with salary in two years up to $113,100. Fringe benefit package is outstanding. Send C.V. and references to: David L. Draves, Director Regional Development, 1000 North Oak Avenue, Marshfield, WI 54449 or call collect (715) 387-5376.

VETERANS HOSPITAL, SAGINAW, MICHIGAN, NEEDS BC Internist with or without subspecialty. Call Joyce Shappee, Personnel Service, 517-793-2340, extension 3076. An Equal Opportunity Employer.

GASTROENTEROLOGIST, NORTHERN CALIFORNIA — EXcellent opportunity for BC/BE Gastroenterologist to join solo Gastroenterologist — July 1989. 100% G.I. practice. Advanced endoscopy skills desirable. Excellent salary package with early partnership. University affiliation and teaching opportunities. Respond Physician Relations Manager, Mercy San Juan Hospital, 6501 Coyle Ave., Carmichael, CA 95608 or call collect 916-537-5009.

INTERNIST, BC/BE. ASSOCIATE WANTED TO JOIN WELL established solo practice of BC internist in Sacramento, CA. Growing patient population and strong subspecialty support make this an excellent opportunity. Reply: Physician Relations Manager, Mercy San Juan Hospital, 6501 Coyle Ave., Carmichael, CA 95608. Call Collect 916-537-5009.

GENERAL INTERNIST BC/BE NEEDED TO JOIN WELL established solo practice in Baltimore MD. Immediate opening. Competitive salary & benefit package. Early partnership. Send C.V. to Box 5818, c/o JAMA.

INTERNIST — SARATOGA SPRINGS, NY. ATTRACTIVE opportunity for BC/BE internist to establish primary care practice just outside of Saratoga, in the growing community of Ballston Spa. Competitive guarantee offered. Excellent living and practice environment. Please send CV to: Denise Romand, Saratoga Hospital, 211 Church Street, Saratoga Springs, NY 12866. (518) 584-6000, ext. 465.

INTERNIST — FACULTY POSITION, UNIVERSITY OF ALabama School of Medicine, Huntsville Component. Staffing VA Internal Medicine Outpatient Clinic, teaching medical students and family practice housestaff, attending on inpatient service. Respond by July 1, 1989 to Internal Medicine Programs, UMC-201 Governors Drive, Huntsville, Alabama, 35801. Equal Employment/Affirmative Action Employer.

SUCCESSFUL CONSULTATIVE-PRIMARY CARE INTERnal Medicine Group in Maryland seeking BC-BE Internist. Active inpatient and outpatient practice with complete diagnostic capabilities in office including certified lab and x-ray. Guaranteed salary with incentive bonus and plans for partnership offer. Liberal benefit package including CME, personal vacation, and insurance coverage. Practice close to Baltimore, Washington, and Annapolis. Send CV to Box 5828, c/o JAMA.

INTERNIST — BOARD CERTIFIED OR BOARD ELIGIBLE with or without sub-specialty to join 20+ physician multispecialty group in lower midwest. Guaranteed minimum with excellent benefit program. Family oriented community. Send curriculum vitae to Box 5770, c/o JAMA.

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INTERNIST TO JOIN SOLO PRACTITIONER ON BOSTON'S North Shore. Send CV to Box 5829, c/o JAMA.

INTERNIST BC/BE TO JOIN MULTISPECIALTY GROUP practice in Midwest. Subspecialty desirable but not necessary. Excellent opportunity with competitive salary and fringe benefits leading to early shareholder status. Fine living and work environment. Reply Box 5698, c/o JAMA.

GROUP HEALTH ASSOCIATES, A 50+ PHYSICIAN MULTIspecialty group practice is searching for a board eligible/board certified internist to start in mid-1989 or the Summer of 1990. Guaranteed salary first year with salary plus bonus the second year and ownership participation after two years. Extensive fringe benefit plan. Practice offers comfortable lifestyle with reasonable call schedules and an attractive practice location. Inquiries and C.V.'s to: Search Committee-GHA, 2915 Clifton Avenue, Cincinnati, Ohio 45220.

Practice in the Puget Sound area

CompHealth has unique 2-yr opportunity for internist to work as an independent contractor at a military STD clinic. Enjoy a clearly defined schedule with no weekend work or call responsibilities. Ample holiday time will allow you to explore the Pacific Northwest. Perfect opportunity to escape the hassles of third party payers while earning a competitive income with paid malpractice premiums. For additional information call Christy Phifer at 1-800-453-3030 toll-free (in Utah, 801-532-1200).

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NEUROLOGIST BC/BE — IMMEDIATE OPPORTUNITY TO associate with multispecialty group. Neurosurgery coverage is also available. Excellent professional environment and pleasant living in Midwestern community with fine educational and recreational opportunities available. Reply Box 5696, c/o JAMA.

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OB/GYN — WE ARE SEEKING A HIGHLY QUALIFIED physician to join us in our busy OB/GYN practice. We are a 54 physician multi-specialty clinic in the suburban Minneapolis area. Practice offers: utilization of one hospital, full day off during week, and opportunity to grow with a strong community. Must be Board Certified or Board Eligible. Feel free to call or send CV to: Tom Behrend, Columbia Park Medical Group, 6200 Shingle Creek Parkway, Suite 480, Brooklyn Center, MN 55430. (612) 560-3450.

WANTED: OB/GYN, B.E., B.C. TO JOIN BUSY SOLO PRACTItioner in beautiful area of East Coast of Central Florida. Association leading to partnership/or sharing office space and laboratory near large medical center. Send CV to Box 5833, c/o JAMA.

OBSTETRICIAN/GYNECOLOGIST, VIRGINIA — MODERN 153 bed acute care hospital has an excellent opportunity for a Board Certified/Eligible Obstetrician/Gynecologist. Medical service area population of 55,000. Partnership/association available with coverage. New office building available. Very competitive financial package and relocation. Beautiful mountainous plateau area 50 miles from Roanoke, with exceptional cultural, educational and recreational opportunities. Contact: Assistant Administrator, P.O. Box 759, Pulaski, Virginia 24301, 703-980-6822.

WESTERN PACIFIC, COMMONWEALTH OF THE NORTHern Mariana Islands. Seeking BC/BE OB/GYN Physician to join multi-specialty medical staff; modern 74-bed government hospital, on beautiful island of Saipan, U.S. Commonwealth, 120 miles north of Guam. Superb climate, island lifestyle, recreational and travel opportunities and tax advantages. Dr. Jose T. Villagomez, Director of Public Health & Environmental Services, Commonwealth Health Center, Saipan, MP 96950, Fax number 011 (670) 234-8930.

GYN — NO O.B. — OPPORTUNITY WITH 7 PERSON MULTIspecialty staff. 40-bed JCAH hospital, S.E. Colorado community of 10,000. Send CV to James Giedd, Administrator, Prowers Medical Center, 2102 S. Memorial Drive, Lamar, CO 81052. 719-336-4343.

THERE IS MORE TO LIFE THAN MEDICINE. WE'LL GIVE YOU all the time you need to discover this simple truth and still enjoy practicing quality medicine. As a member of our locum tenens group, you set your schedule; take large blocks of free time; catch up on postponed pleasures . . . or discover new ones. We expand your future practice opportunities, guarantee excellent income, provide malpractice insurance, make all the arrangements, and pay all the expenses. For details, contact your colleagues at KRON Medical, America's locum tenens group. Call toll free 1-800-MEDICAL or write KRON Medical Corporation, 725 Airport Road, 3rd Floor, Chapel Hill, NC 27514.

SEATTLE AREA OB/GYN: A BUSY, WELL-ESTABLISHED 3 physician Ob/Gyn group seeks BC/BE associate. Unusual opportunity for the right person. Please address inquiries to: Manfred Laband, MD, 707 Cobb Medical Center, Seattle, Washington 98101. 206-277-1212.

WISCONSIN — OB/GYN (BC/BE) NEEDED TO JOIN DYNAMIC HMO-based multispecialty group practice. University town of 55,000 near Minneapolis. Community and recreation outstanding. Competitive salary and fringes. We take pride in our patient care. Contact: Robert A. Brasstad, M.D., Group Health Cooperative, 1030 Regis Court, Eau Claire, WI 54701; (715) 836-8552.

BOULDER, COLORADO . . . GENERAL INTERNIST needed for Kaiser Permanente Medical Care Program at the foot of the Rocky Mountains in Boulder. Competitive salary and benefits. For additional information, please contact: V. A. LaFleur, M.D., Associate Medical Director, Colorado Permanente Medical Group, P.C., 2045 Franklin St., Denver, CO 80205; (303) 861-3262. EOE.

OBERLIN, OH MULTISPECIALTY GROUP SEEKS ADDITIONAL BC/BE OB/Gyn. Small northern Ohio college town serving drawing area 275,000. Salaried position first year; full shareholder status available second year. Send CV to Dr. VanDyke, 224 W. Lorain, Oberlin, OH 44074.

OB/GYN BE/BC FOR UCSF-AFFILIATED TEACHING HOSpital with F.P. residency program located on beautiful Monterey Peninsula of Northern California. Busy OB practice considers both inpatient/outpatient practice in 211-bed JCAHO accredited hospital. Salary range $95,350-$118,130 with full benefit package and generous paid time off. CV to: Anthony Sforza, MD, Natividad Medical Center, P.O. Box 81611, Salinas, CA 93912-1611.

BC/BE OB/GYN TO JOIN THREE-PERSON DEPARTMENT with multi-physician, multi-specialty group practice. Pratt Medical Center is located near beaches, mountains, and rivers one hour south of Washington, D.C. in historic Fredericksburg, VA. Busy practice, exceptionally pleasant working conditions, partnership possible after one year, 1701 Fall Hill Avenue, Fredericksburg, VA 22401.

TWO OB/GYNS NEEDED FOR COMMUNITY OF 130,000 ON coast of Virginia. 370-bed hospital will help set-up practice, provide guaranteed income and patients. Coverage available. Beautiful area. Excellent recreational amenities and good schools. Excellent opportunity for doctor desiring successful practice in beautiful coastal community with hospital support. Contact Gary Long, Jackson & Coker, 400 Perimeter Center Terrace, Suite 760 JUJC9, Atlanta, GA 30346, Telephone 1-800-544-1987 or 1-800-223-7399.

BC/BE OBSTETRICIAN/GYNECOLOGIST TO JOIN THREE other OB/GYNs in very successful group practice located in Blue Ridge mountains of Southern Virginia. Lush scenery year round, combined with numerous cultural activities existing in historic area, creates dream-like atmosphere. Generous starting salary with exclusive fringe benefits. Full partnership after one year. Contact John Couvillon, Jackson & Coker, 400 Perimeter Center Terrace, Suite 760 JUJC9, Atlanta, GA 30346. Telephone 1-800-544-1987 or 1-800-223-7399.

OBSTETRICS/GYNECOLOGY: PARTNERSHIP OPPORTUnity available for individual who has interest in joining thriving practice. Lovely community in Northern Virginia is combination of old charm of yesteryear and modern ambiance of today. Practice offers utilization of one hospital, good coverage, paid malpractice and health insurance, paid vacation, CME allowance, generous salary and partnership. Contact John Couvillan, Jackson & Coker, 400 Perimeter Center Terrace, Suite 760 JUJC9, Atlanta, GA 30346. Telephone 1-800-544-1987 or 1-800-223-7399.

OBSTETRIC/GYNECOLOGY OPPORTUNITY TO JOIN ESTablished practice in resort community of Florida. Fully-equipped office; hospital just few minutes away. Community is rich in tradition and charm and provides numerous recreational amenities. Excellent schools, shopping and housing. Exceptional financial package includes excellent salary with incentive bonus, paid malpractice, overhead and interviewing and relocation expenses. Contact Michael Lindsey, Jackson & Coker, 400 Perimeter Center Terrace, Suite 760 JUJC9, Atlanta, GA 30346. Telephone 1-800-544-1987.

OBSTETRICIAN/GYNECOLOGIST: ELEGANT FACILITY located directly across from medical Center offers immediate opening for BE/BC OB/GYN in an established 25-year, two physician incorporated practice. Ultrasound, laser and Colposcopy expertise required. Guaranteed benefits include early full partnership, competitive salary, professional liability, paid vacation, holiday, CME, sick leave and bonus. Fully paid reasonable recruitment and moving expenses. Excellent location and environment for cultural, social and business activities. Send your CV to: SGS Placement, Route 4, Box 92BB, Lake Dixie Springs, MS 39666. (FAX) 601-684-9872.

NORTH CENTRAL OHIO — BC/BE — OB/GYN — FOR COMmunity of 23,000 0 within an hours' drive of four metropolitan cities — well-equipped hospital. Contact Mary Packard at Garofolo, Curtiss & Co., 326 W. Lancaster Ave., Ardmore, PA 19003, 1-800-441-0996, in PA (215) 896-5080.

CENTRAL CONNECTICUT — OB/GYN — BC/BE — JOIN A 20 year old practice with partnership potential. Good coverage provided, teaching option available. Contact Mary Packard at Garofolo, Curtiss & Co., 326 W. Lancaster Ave., Ardmore, PA 19003, 1-800-441-0996 in PA (215) 896-5080 collect.

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FINALLY, A WAY TO PRACTICE MEDICINE WITHOUT ALL the red tape. Now you can practice your specialty without third party payers, malpractice premiums and administrative hassles. CompHealth, the nation's leading locum tenens group, is looking for physicians to practice as independent sub-contractors for one to five years at military facilities across the country. As a CompHealth physician, your income is overhead-free and many of your expenses are paid. For important information, call Tracy Zelenka or Christy Phifer toll-free at 1-800-453-3030. In Utah, call 1-801-532-1200.

OCCUPATIONAL MEDICINE. JOIN HOSPITAL-BASED OCcupational health clinic on beautiful Monterey Peninsula of Northern California. BE/BC, F.P. or Occupational Health with minor surgical and trauma skills. Salary range $67,900-$84,150 with full benefit package. CV with letter of reference to: Anthony Sforza, MD, Natividad Medical Center, P.O. Box 81611, Salinas, CA 93912-1611.

Ophthalmology

TEST THE WATERS. IF YOU ARE A PHYSICIAN OF EXcellent caliber and don't want to settle into one practice until you've examined all your options, consider joining CompHealth as a locum tenens physician. You'll have the chance to practice from the Atlantic to the Pacific. You also set your own schedule and the duration of your assignments. What's more, you'll earn an excellent income and we'll take care of your malpractice premiums and major expenses. Immediate openings available. Call now at 1-800-354-4050 toll-free (in GA, 1-404-391-9876).

OPHTHALMOLOGIST TO JOIN ESTABLISHED DEPARTment of larger, prestigious multi-specialty group. Lovely community located on the Ohio River conveniently located to several universities and major metro areas. Search conducted by: Physician International, 4-J/OPH Vermont Street, Buffalo, NY 14213. 1-800-622-4062.

Otolaryngology

OTOLARYNGOLOGIST, VIRGINIA — MODERN 153 BED acute care hospital has an excellent opportunity for a Board Certified/Eligible Otolaryngologist. Medical service area population of 55,000. Partnership/association available with coverage. New office building available. Very competitive financial package and relocation. Beautiful mountainous plateau area 50 miles from Roanoke, with exceptional cultural, educational and recreational opportunities. Contact: Assistant Administrator, P.O. Box 759, Pulaski, Virginia 24301, 703-980-6822.

ENT (BC/BE) TO JOIN A MULTISPECIALTY GROUP IN A lovely community of 34,000 with 100,000 referral area in Eastern Iowa on the Mississippi River. Excellent practice opportunity with modern hospital facilities (300 bed). Solid industrial base. Outstanding educational system. Chicago 3 hours via expressway. Generous first year guarantee plus bonus incentive and fringe benefits. Full member after 1 year. Contact Phil Sayles, Adm., Bluff Medical Center, P.C., 240 North Bluff Blvd., Clinton, IA 52732. Phone (319) 243-5600.

OTOLARYNGOLOGIST — SARATOGA SPRINGS, NY — EXcellent opportunity for BC/BE otolaryngologist to develop successful practice in a cosmopolitan, growing community, thirty minutes north of Albany, one of the nation's finest capital cities. Strong medical staff support. Competitive guarantee. Contact: Denise Romand, Saratoga Hospital, 211 Church Street, Saratoga Springs, NY 12866.

OTOLARYNGOLOGIST (BC/BE) NEEDED FOR BUSY PRACTICE in suburban Long Island, N.Y. All aspects of otolaryngology including head and neck, facial plastics. Excellent salary and benefits. Send CV to P.O. Box 298, Syosset, NY 11791.

ENT PHYSICIAN — WESTERN MASSACHUSETTS ("THE Berkshires") BC/BE ENT to join 55-physician multi-specialty medical P.C. group. Competitive salary, comprehensive benefits, full malpractice coverage, early opportunity to become shareholder at reasonable price. Area offerings: beautiful recreational area; cultural activities include arts/theatre (Tanglewood); located near VT, NY, CT borders. Send CV to: Linda Smith, P.O. Box 4759, Pittsfield, MA 01202.

ENT — BOARD CERTIFIED OR BOARD ELIGIBLE NEEDED immediately to join 23 physician multi-specialty group. Minimum guaranteed salary with incentive bonus program. Excellent fringe benefit program. Family oriented community. Send curriculum vitae to John Reed, Administrator, Weber Medical Clinic, 1200 N. East St., Olney, IL 62450.

Pathology

LARGE, MULTISPECIALTY PATHOLOGY GROUP IN northern California seeks excellent surgical pathologist. Board certification in A/P, C/P, and dermatopathology desired. Other subspecialties considered. Excellent opportunity, outstanding benefits. Send CV, including references to: Reply Box 5851, c/o JAMA.

ANATOMIC & CLINICAL PATHOLOGY RESIDENCY UNexpected vacancy. Fully accredited 8 position program in N.E. Ohio. Strong medical school affiliation; 7 full-time Board certified Pathologists. Must have FMGMS or ECFMG certification and permanent visa. Apply with 3 letters of recommendation to Box 5832, c/o JAMA.

Pediatrics

BOULDER, COLORADO . . . PEDIATRICIAN NEEDED FOR Kaiser Permanente Medical Care Program at the foot of the Rocky Mountains in Boulder. Competitive salary and benefits. For additional information, please contact: V. A. LaFleur, M.D., Associate Medical Director, Colorado Permanente Medical Group, P.C., 2045 Franklin St., Denver, CO 80205; (303) 861-3262. EOE.

PEDIATRICIAN — BC/BE TO JOIN MULTI-SPECIALTY practice 15 minutes from Minneapolis, MN. Practice involves both primary and consultative practice. Call (612) 560-3450 or send CV to: Tom Behrend, Columbia Park Medical Group, 6200 Shingle Creek Parkway, Suite 480, Brooklyn Center, MN 55430.

PEDIATRICIAN — WESTERN NEW YORK — BUSY SINGLE specialty group of 4 BC Pediatricians adding a 5th. Guaranteed salary with incentive plan. Benefits include: malpractice, health, life insurance, pension plan. CME and paid vacation, dues, licensure. New modern offices. Community offers recreational, cultural and professional conveniences. Low cost of living. Excellent schools. Contact Durham Medical Search Inc., 6300 Transit Rd., PO Box 478, Depew, NY 14043. 800-633-7724 (USA), 800-367-2356 (NYS).

PRACTICING MEDICINE CAN BE A LOT SIMPLER!

Would you like to leave petty politics, administrative entanglements and crippling overhead costs behind? If you qualify as a CompHealth locum tenens physician you can select where, when and how long you work. You won't be encumbered by tedious administrative duties or irritating disputes with third party payers because we only ask you to do one thing . . . practice good medicine. Call CompHealth, the nation's largest locum tenens group, today at 1-800-453-3030 toll-free (in Utah, 1-801-532-1200).

PEDIATRICIAN, VIRGINIA — MODERN 153 BED ACUTE care hospital has an excellent opportunity for a Board Certified/Eligible Pediatrician. Medical service area population of 55,000. Partnership/association available with coverage. New office building available. Very competitive financial package and relocation. Beautiful mountainous plateau area 50 miles from Roanoke, with exceptional cultural, educational and recreational opportunities. Contact: Assistant Administrator, P.O. Box 759, Pulaski, Virginia 24301, 703-980-6822.

PEDIATRICS: VERY ATTRACTIVE AND DESIRABLE COMmunity in Northern South Carolina needs second Pediatrician. Partnership opportunity with existing BC physician. Excellent financial package and benefits including income guarantee. Contact Todd Hill, Jackson & Coker, 400 Perimeter Center Terrace, Suite 760 JUJC9, Atlanta, GA 30346, Telephone 1-800-544-1987 or 1-800-223-7399.

ANOTHER MHA EXCLUSIVE OPPORTUNITY
ROCKY MOUNTAIN—WEST

Assume Solid PEDIATRIC practice. No investment, hospital backed. This community practice has all the amenities, college town, resort skiing. Minimal call and coverage. Guarantees established, beautiful high-tech medical facility. Call Jeffrey Gowan at (800) 288-1210 or (714) 757-7750 or send your CV to Merritt, Hawkins & Associates, 17300 Redhill Avenue, Suite 250, Irvine, CA 92714.

PEDIATRICS — OPPORTUNITY AVAILABLE TO JOIN three pediatricians in expanding multispecialty group practice. Midwestern location offers fine living environment for family with excellent schools, recreational opportunities. Reply Box 5767, c/o JAMA.

MONTANA, BC/BE PEDIATRICIAN TO ASSUME SEMI-RUral practice in unique NW Montana Community. Fully equipped office with excellent staff support in place; part-time Pediatric coverage available. Near Glacier Park with year-round recreation. Local hospital with full compliment of subspecialists. Reply to Whitefish Pediatric Clinic (406)862-4506.

PEDIATRICIAN (BC/BE) TO JOIN CONGENIAL MULTIspecialty group in a lovely community of 34,000 with 100,000 referral area in Eastern Iowa on the Mississippi River. Excellent practice opportunity with modern hospital facilities. Solid industrial base. Chicago 3 hours via expressway. Generous first year salary plus incentive bonus and fringe benefits. Full member after 1 year. Contact Phil Sayles, Administrator, Bluff Medical Center, P.C., 240 North Bluff Blvd., Clinton, Iowa 52732. (319)243-5600.

Psychiatry

ANOTHER MHA EXCLUSIVE OPPORTUNITY
PSYCHIATRY — HOUSTON, TEXAS

USA Today recently identified Houston as one of the fastest growing cities in the United States. One of the top five places to live as we enter the 90s. This partnership opportunity is with one of the most successful Psychiatrists in Texas. This physician is guaranteeing a minimum salary of $120,000 plus fair bonus and partnership. Lot of opportunity to grow and create. If you desire an excellent inpatient/outpatient practice, and want to join an established team of professionals, please call Jeffrey Gowan at (800) 288-1210 or (714) 757-7750 or send your CV to Merritt, Hawkins & Associates, 17300 Redhill Avenue, Suite 250, Irvine, CA 92714.

ANOTHER MHA EXCLUSIVE OPPORTUNITY
2 PSYCHIATRISTS — MEDICAL DIRECTOR

of inpatient unit needed to aggressively expand programs and grow facility in area of tremendous need. This 101-bed hospital will guarantee physician $150,000 base income, and complete medical staff support for in/out patient practitioners. Beautiful new medical offices available. Total financial potential unlimited. This rapidly growing city has a beautiful SOUTHWESTERN climate and more sunny days than Southern California. Call Jeffrey Gowan or Gerry Weipert at (800) 288-1210 or (714) 757-7750 or send your CV to Merritt, Hawkins & Associates, 17300 Redhill Avenue, Suite 250, Irvine, CA 92714.

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A unique opportunity for a BC/BE psychiatrist to join a growing practice located in South Eastern Virginia with a true mix of rural and urban amenities close to ocean, beaches, and other cultural, social, and recreational facilities. We are within 2 blocks of hospital opening a new psychiatric floor and within 20 minutes of tertiary care center. Call John McGlynn (804)399-5977 or write c/o Damsey & Associates, Ltd. 444 Crawford Street, Portsmouth, VA 23704

IMMEDIATE OPENING. ONE PSYCHIATRIST AND ONE Child Psychiatrist at a 250-bed acute treatment psychiatric hospital, JCAH approved, Medicare Certified, affiliated with the University of Iowa Medical College. Forty-hour work week. No night or weekend on call. Situated in picturesque northeast Iowa near large cities with cultural advantages. Ideal for family living. Golf club, hunting and fishing area, good schools, etc. Salary to $93,225. State law protects employees against malpractice. State pension plan. Unique deferred annuity plan. Generous sick leave and vacation. Write or call collect: B.J. Dave, M.D., Superintendent, Mental Health Institute, Independence, IA 50644. Phone 319-334-2583.

PSYCHIATRISTS

needed immediately for a number of high-quality practice opportunities in desirable locations across the country. As a retained search firm, all fees & expenses are covered by our clients. To explore your options, please submit your C.V. or call Julie Woolsey at 1-800/356-2237.

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WHY DID YOU GO INTO MEDICINE IN THE FIRST PLACE?
Have you had enough politics, paperwork and pressure? If you'd like more time to focus on quality health care, consider practicing with CompHealth, the nation's largest locum tenens group. If you qualify, you'll determine the setting: From Maine to Hawaii . . . and the duration: From a week to a year or more. We relieve you of the time-consuming administrative duties, provide a competitive income, and take care of housing, transportation, licensure and malpractice premiums. Call now: 1-800-453-3030 toll-free (in Utah, 1-801-532-1200).

Pulmonary Disease

SOUTHERN MICHIGAN. PULMONOLOGIST TO JOIN AS third associate of growing Pulmonary/Critical Care Medicine practice. Office located near 500 bed hospital. Mid-size community offers superior lifestyle; short distance to two major university centers. Search conducted by: Physician International, 4-J/PU Vermont Street, Buffalo, NY 14213. 1-800-622-4062.

PULMONOLOGIST. BC/BE TO DIRECT ACTIVE PROGRAM at newly remodeled Dean's Committee V.A. Medical Center located on the beautiful gulf coast, 80 miles from New Orleans, LA. Must have excellent bronchoscopy skills. Send CV to Paul S. Rosenfeld, M.D., Chief, Medical Service, V.A. Medical Center, Biloxi, MS 39531 or call 601-385-5795. The V.A. is an equal opportunity employer.

Radiology

PREFER PRACTICING TO POLITICS? TIRED OF THE ENDless meetings and cutthroat competition? If you qualify as a CompHealth locum tenens physician, you can distance yourself from medical politics and set your own schedule. With CompHealth, the nation's largest locum tenens group, you can practice from Maine to Hawaii, for a week, a month or more. You'll earn a competitive income while your housing, transportation, licensure, and malpractice premiums are provided. So get away from the politics and administrative drudgery; call today 1-800-453-3030 toll-free (in UT, 1-801-532-1200).

RADIOLOGIST WANTED. EXPERIENCE IN ANGIOGRAphy and Interventional essential. To join hospital based 4-person group in Northeast. Send C.V. to Box 5841, c/o JAMA.

RADIOLOGIST wanted to join 225 physician multi-specialty group with an adjacent 447 bed hospital. New clinic building recently completed. Gundersen Clinic, Ltd. is located in a progressive community with expanding university and private college. Population 50,000. Cultural and recreational facilities. Beautiful setting; good schools. Excellent pension program, no investment required. Service organization. Write: Philip J. Dahlberg, M.D., Chairman, Personnel Committee, Gundersen Clinic, Ltd., 1836 South Avenue, LaCrosse, WI 54601. An Equal Opportunity Employer

Puget Sound Needs Radiologists

as independent sub-contractors for area naval hospital. Competitive earnings package includes paid malpractice premiums. The community, an outdoorsman's paradise, is located on Puget Sound and is surrounded by beautiful state and national forests. Perfect opportunity to escape the hassles of third party payers, soaring malpractice rates and grueling work schedules. For important information, call Tracy Zelenka at 1-800-453-3030 toll-free (in Utah, 801-532-1200).

RADIOLOGIST NEEDED IN SOUTHWEST!! RADIOLOGIST is needed for an out-patient office facility. Facility performs general radiography, sonography, and mammography. Hours 8am-5pm, Monday through Friday. Attractive compensation package. Must be board certified. Please submit letter and resume to: PO Box 80886, Albuq., NM 87108-9998.

TWO POSITIONS OPEN FOR DIAGNOSTIC RADIOLOGIST. Duties include general diagnostic radiology, mammography, nuclear medicine, computed tomography, ultra sound, magnetic resonance imaging, angioplasty, interventional radiology. Will work at one base hospital and seven outlying hospitals on a rotation basis with employer's other 3-4 radiologists. Will work generally 48 hrs/week with a rotation of weekends with employer's other radiologists. Requirements: M.D. Degree, completion of approved residency in diagnostic radiology, board certified in radiology or must have become board eligible within the past 3 years. Must have training or experience in all duties listed above, must be recognized by peers as having high moral and ethical standards in this profession. Salary: $110,000.00 with no post-residency experience to $150,000.00 with two years or more post-residency experience. Send resumes to Nebraska Dept. of Labor, Job Order #NEO512617, P.O. Box 94600, Lincoln, NE 68509-4600, (402) 475-8451.

HOW TO TURN YOUR PRACTICE INTO PLEASURE. NOW you can have a challenging medical practice without the endless hours of private practice. CompHealth, the nation's leading locum tenens group, is looking for physicians in all specialties to practice as independent sub-contractors for one to five years at military facilities across the country. There are numerous locations to choose from, and with more flexible weekend and call schedules you have the free time you've always wanted. For important information, call Tracy Zelenka or Christy Phifer toll-free at 1-800-453-3030. In Utah, call 1-801-532-1200.

RADIOLOGIST WANTED TO JOIN SOLO PRACTITIONER IN SE Iowa. State of the art practice will include mobile MR. An interest in angiography and interventional radiology desirable. Attractive salary and benefits. Ample free time. Contact R. Kimmel, M.D. 319-524-1299 evenings.

RADIOLOGIST — SARATOGA SPRINGS, NY. FOUR MEMber hospital based group is seeking board eligible or certified radiologist. Interventional training or experience is required. This progressive practice includes CT, Ultrasound, Nuclear Medicine, and special procedures. Excellent compensation leading to early partnership plus comprehensive benefit package. Saratoga is an historic, close-knit community, a half hour drive from Albany, one of the nation's finest capital cities. Forward C.V. to Saratoga Radiological Associates, c/o Miss Denise Romand, Saratoga Hospital, 211 Church Street, Saratoga Springs, NY 12866. (518) 584-6000 ext. 465.

RADIOLOGIST — BOARD CERTIFIED OR IN PROCESS TO join two member group servicing two small well-equipped hospitals in the Florida Keys. Recent training or experience in CT, MR, and some interventional procedures required. Association leading to partnership. Contact R. H. Chase, M.D., 403 Harbour Drive, Duck Key, FL 33050.

Surgical Specialties

A CHANCE TO FOCUS ON WHAT'S IMPORTANT. IF YOU'RE an Orthopaedic or General Surgeon who qualifies as a CompHealth locum tenens physician, you can leave onerous paperwork and overhead costs behind. With CompHealth you'll enjoy practice in different locations throughout the U.S., for variable lengths of time. Earn an excellent income in a variety of practice settings. CompHealth takes care of all of the major expenses like malpractice premiums, housing and transportation. You'll find yourself free of administrative duties, with more time to take care of the patients who need you. Call today: 1-800-453-3030 toll-free (in Utah, 1-801-532-1200).

NORTH CAROLINA: EXCELLENT PRACTICE OPPORTUnity for a BC/BE Orthopaedic Surgeon 45 minutes from Charlotte. Either solo or group opportunity available. Friendly, thriving community with modern 200+ bed hospital. For more information call Tony C. Rasberry or Leonard Graivier, M.D., Physician Network of America, Inc., 1-800-336-2575, 8505 Freeport Parkway, Suite 130, Irving, Texas 75063, FAX 214-929-4568.

WESTERN PACIFIC, COMMONWEALTH OF THE NORTHern Mariana Islands. Seeking BC/BE Surgeon to join multi-specialty medical staff; modern 74-bed government hospital, on beautiful hospital, on beautiful island of Saipan, U.S. Commonwealth, 120 miles north of Guam. Superb climate, island lifestyle, recreational and travel opportunities and tax advantages. Dr. Jose T. Villagomez, Director of Public Health & Environmental Services, Commonwealth Health Center, Saipan, MP 96950, FAX number 011 (670) 234-8930.

BC ORTHOPEDIC SURGEON SEEKS PARTNER IN VERY busy practice in North Carolina. First year salary with paid interviewing and relocation expenses. Contact Terry Irwin, Jackson & Coker, 400 Perimeter Center Terrace, Suite 760 JUJC9, Atlanta, GA 30346, Telephone 1-800-544-1987 or 1-800-233-7399.

GENERAL SURGEON — BC/BE — TO JOIN A WELL ESTABlished General Surgeon. Excellent salary, full benefit package, with opportunity to become a partner. Location, Southwestern PA, 45 miles east of Pittsburgh, PA. Send CV to Medical Affairs Office, FCHC, 508 South Church Street, Mt. Pleasant, PA 15666.

EXCELLENT OPPORTUNITIES FOR GENERAL SURGEONS IN Alabama, Georgia, Idaho, Iowa, Kentucky, Texas, and Virginia. Call 800-255-4419.

BC/BE GENERAL SURGEON TO JOIN ESTABLISHED SURgeon in private practice with outpatient surgery facility located in the east Tennessee suburb or major metropolitan area of 35,000 with best and highest income in the south. Send CV to Box 5845, c/o JAMA.

SOUTHERN CALIFORNIA, ORTHOPEDIC SURGEON — AN Orthopedic Surgeon with training in Spine Surgery is needed to join two busy, well-established Orthopedic Surgeons in Los Angeles County. For more information about this private practice opportunity, call Toll-Free 1-800-626-1590, or send your curriculum vitae to: Gordon Crawford, Professional Relations, Humana Inc., Dept. A 602A, 500 West Main Street, Louisville, KY 40201-1438.

BC/BE VASCULAR SURGEON WITH THORACIC EXPERIence willing to do some general surgery in a busy practice in Southern West Virginia. No certified vascular surgeon within 100 miles. Active vascular lab with Angiodynography capabilities. Fully accredited JCAH Level II hospital has 211 total bed capacity, 18 bed ICU-CCU. Send CV to Box 5852, c/o JAMA.

GASTROINTESTINAL SURGEON: WE SEEK AN ACADEMIC surgeon with research training who has expertise in the digestive disease field. This is a full time, tenure track position with rank at the assistant professor level. The starting date is no later than September 1, 1989. In order to ensure full consideration, applications must be received by June 1, 1989. Contact David L. Nahrwold, M.D., Northwestern University Medical School, 250 East Superior Street, Suite 201, Chicago, IL 60611. Northwestern University is an affirmative action/equal opportunity employer. Hiring is contingent upon eligibility to work in the United States.

TRANSPLANT SPECIALIST: WE SEEK AN ACADEMIC surgeon who has training in hepatic transplantation and in research related to transplantation. The position is full-time, tenure track at the assistant professor level. Salary is negotiable. The starting date is no later than September 1, 1989. In order to ensure full consideration, applications must be received by June 1, 1989. Contact David L. Nahrwold, M.D., 250 East Superior Street, Suite 201, Chicago, IL 60611. Northwestern University is an affirmative action/equal opportunity employer. Hiring is contingent upon eligibility to work in the United States.

GENERAL AND COSMETIC SURGERY PRACTICE — Clean surgical practice, 20 years. Extensive referral from local physicians and surrounding communities. Established office, equipment and furnishings available. Central southern Illinois. Universities, recreational facilities, metropolitan areas easily accessible. Excellent opportunity. E. F. Stephens III, M.D., P.O. Box 1225, Centralia, IL 62801.

SURGICAL HOUSE PHYSICIAN NEEDED FOR N.E. OHIO and Buffalo area hospitals. F.T. 70-95K, paid malpractice, no on-call, BE/BC preferred. Physician Staffing, Inc., 3628 Walnut Hills Road, Cleveland, OH 44122. (216) 292-7445.

THORACIC-VASCULAR SURGEON — BOARD CERTIFIED/ Eligible Surgeon wanted to join very active non-cardiac thoracic vascular practice in small community with referral base of approximately 125,000. Salary leading to full partnership. Advantages of living in a small community in Eastern Ohio less than one hour from large, desirable metropolitan area. Will also consider applicants primarily interested in vascular surgery. Please respond with curriculum vitae to Box 5654, c/o JAMA.

NEURO-SURGEON. RAPIDLY GROWING COASTAL NORTH Carolina hospital seeks one or two Neuro-Surgeons to develop surgery program and Neuro Unit. Service area of 130K plus, moderate climate, low malpractice rates, wide range of recreational opportunities, excellent schools, and strong local economy. Median population age of 24 with high rate of head trauma. An excellent chance to start your own department. Contact: David W. Spangler, Administrator, Onslow Memorial Hospital, P.O. Box 1358, Jacksonville, N.C. 28540. EOE M/F.

GENERAL SURGEON — NEVADA'S OLDEST MULTI-SPECialty clinic seeks a Board Eligible/Board Certified Internist to join one other General Surgeon in a very busy practice. All fee for service with excellent collection ratio. Guaranteed salary for six months leading to full partnership. Comprehensive benefit package including malpractice insurance. Elko is a thriving community surrounded by mountains and wilderness areas. Recreation year round. Please send C.V. to Cherie Atwood, Administrator, Elko Regional Medical Center, 762-14th Street, Elko, Nevada 89801. (702) 738-3111.

WELL ESTABLISHED SURGICAL PRACTICE SEEKING third Surgeon to join busy surgical practice in Southeast, population 50,000. Apply to Box 5785, c/o JAMA.

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RECRUITING THORACIC/VASCULAR SURGEON, VA MEDical Center, Clarksburg, West Virginia. Affiliated with West Virginia University. Full surgical residency rotation. Dual appointment. Respond to: Gordon Murray, M.D., Professor and Chairman, Department of Surgery, West Virginia University Medical Center, Morgantown, West Virginia 26505. Phone (304)293-4869, Equal Opportunity Employers.

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OR

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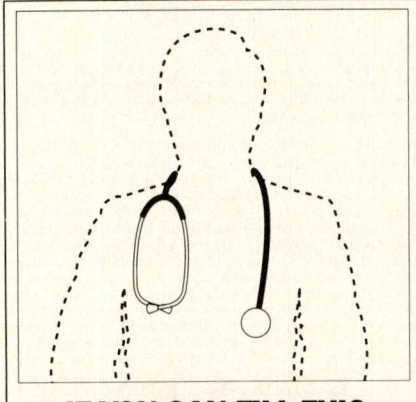

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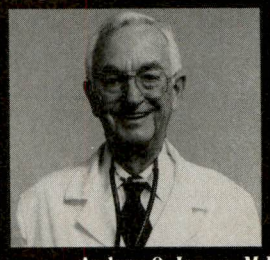

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THE UNIVERSITY OF FLORIDA IS SEEKING AN INDIVIDual to be Chief, Division of Otolaryngology at its major teaching unit in the University Hospital of Jacksonville. Responsibilities involve teaching of undergraduate and graduate education programs, a diverse clinical program, patient care and research. Requirements include specialty board certification with experience in trauma surgery. Academic appointment at the Assistant/Associate Professor to Professor level, a tenure accruing position. Application recruiting deadline is August 1, 1989. Anticipated starting date, January 1, 1990. Applicants are invited to forward curriculum vitae and names and addresses of three references to: Daniel Mollitt, M.D., Chairman, Otolaryngology Search Committee, University Health Science Center/Jacksonville, 655 W. 8th Street, Jacksonville, Florida 32209. Affirmative Action/Equal Opportunity Employer.

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Minimum qualifications requirements include the following: a degree of Doctor of Medicine, Doctor of Osteopathy, or a bachelor's or higher degree in an academic field related to the health sciences pertinent to the work of the position. In addition, candidates should possess progressively responsible experience in the scientific administration of basic research. Professional background and/or education must also include an extensive knowledge of research methodology, and a knowledge of one or more scientific disciplines that are relevant to research on alcohol abuse and alcoholism. Candidates must possess experience in the management of programs, demonstrating competence to assume leadership in planning, staffing, directing, coordinating and allocating resources, and other responsibilities associated with executive leadership of a major national program. All candidates must have had responsible professional experience at the senior level (GS-15 or equivalent).

Further information about the position and qualifications may be obtained by contacting Ms. Leslie Everheart at (301) 443-5030. Applications (Application for Federal Employment, SF 171) accompanied by a current curriculum vitae and bibliography should be submitted to Ms. Everheart at the Division of Personnel Management, Alcohol, Drug Abuse, and Mental Health Administration, 5600 Fishers Lane, Room 15C26, Rockville, Maryland 20857. Complete application material **(including the SF 171)** must be postmarked by July 21, 1989.

Applications from women and minority group members are especially solicited.

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THE DIVISION OF MEDICAL ONCOLOGY, DEPARTMENT of Internal Medicine at the University of South Florida College of Medicine is accepting applications for an Assistant Professor of Medicine Board Certified in Internal Medicine, Board Qualified or Certified in Medical Oncology or Hematology with Bone Marrow Transplant experience. The closing date for this appointment is June 16th. Send inquiries and current vitae to: Gary H. Lyman, M.D., M.P.H., Professor of Medicine and Chief, Medicine Service, H. Lee Moffitt Cancer Center and Research Institute at USF, 12902 Magnolia Drive, Tampa, FL 33612. USF is an AAEOE.

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DIRECTOR, CLINICAL AIDS ACTIVITIES: THE INFECtious Diseases Unit of the Department of Medicine of the University of Rochester Medical Center is seeking a full-time faculty member whose primary responsibility would be to direct, coordinate, and provide clinical care for patients with AIDS and related problems. An NIH-AIDS treatment/evaluation unit and an NIH-vaccine development unit are both in place at the University of Rochester, and active clinical and laboratory research programs relating to HIV infections are underway. In addition, the Medical Center is a designated New York State AIDS Center. The individual would have ample opportunity to participate in ongoing research programs, as well as to develop additional programs of his/her own. The faculty rank would be commensurate with the individual's qualifications. The projected start date is July 1, 1989. Please address inquiries to: Dr. R. Dolin, Box 689, University of Rochester Medical Center, 601 Emwood Avenue, Rochester, NY 14642 (716) 275-5871. An equal opportunity employer (M/F).

DIRECTOR OF MEDICAL EDUCATION, THE CHILDREN'S Hospital, Saint Paul, Minnesota. 116 bed Children's Hospital with active teaching program for residents in pediatrics and family practice and for medical students. Private hospital associated with pediatric teaching program of University of Minnesota. Strong general pediatric and sub-specialty medical staff. Large level III NICU. Tertiary center for pediatrics, including intensive care. Contact: F. Blanton Bessinger, Jr., M.D., Vice President, Medical Affairs, The Children's Hospital, Inc., 345 North Smith Avenue, St. Paul, MN 55101. (612) 298-8314.

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Required readings from the June 2, 1989, issue

1. Knowledge, Attitudes, and Reported Practices of Medical Students and House Staff Regarding the Diagnosis and Treatment of Alcoholism, p 3115.
2. Drug and Neurotransmitter Receptors: New Perspectives With Clinical Relevance, p 3126.
3. Forty Years of Medical Genetics p 3155.

Additional recommended readings

1. Blehar MC, Rosenthal NE. Seasonal affective disorders and phototherapy. *Arch Gen Psychiatry*. 1989;46:469-474.
2. Offer D, et al. Adolescence: What is normal? *AJDC*. 1989;143:731-736.
3. McKhan GM. The trials of clinical trials. *Arch Neurol*. 1989;46:611-614.

If you have any questions or wish information on forming a local *JAMA* Journal Club, please contact Michael I. Gannon at (312) 645-4670 or write: *JAMA* Journal Club, Division of Continuing Medical Education, American Medical Association, 535 N Dearborn St, Chicago, IL 60610.

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Pamelor *3182A-B**
Tavist-D *3090A-B*

G.D. Searle & Company
Corporate *3094-3095*

SmithKline & French Laboratories
Tagamet *3065-3066*

Syntex Laboratories
Naprosyn *3066A-D**

Upjohn Company
Micronase *3073*

*Demographic/Geographic Insert

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Rocephin® IV·IM

ceftriaxone sodium/Roche

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep. pneumoniae, Streptococcus* species (excluding enterococci), *Staph. aureus, H. influenzae, H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *E. coli, E. aerogenes, Proteus mirabilis* and *Serratia marcescens*.

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus, Staph. epidermidis, Streptococcus* species (excluding enterococci), *E. cloacae, Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*.

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli, Proteus mirabilis, Proteus vulgaris, M. morganii* and *Klebsiella* species (including *K. pneumoniae*).

UNCOMPLICATED GONORRHEA (cervicalurethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains.

PELVIC INFLAMMATORY DISEASE caused by *N. gonorrhoeae*.

BACTERIAL SEPTICEMIA caused by *Staph. aureus, Strep. pneumoniae, E. coli, H. influenzae* and *K. pneumoniae*.

BONE AND JOINT INFECTIONS caused by *Staph. aureus, Strep. pneumoniae, Streptococcus* species (excluding enterococci), *E. coli, P. mirabilis, K. pneumoniae* and *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS caused by *E. coli* and *K. pneumoniae*.

MENINGITIS caused by *H. influenzae, N. meningitidis* and *Strep. pneumoniae*. Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph. epidermidis* and *E. coli*.

SURGICAL PROPHYLAXIS: Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (*e.g.*, vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (*e.g.*, during coronary artery bypass surgery).

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery. When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure.

SUSCEPTIBILITY TESTING: Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*.

Mild cases of colitis respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated.

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should also be considered.

Rarely, shadows suggesting sludge have been detected by sonograms of the gallbladder in asymptomatic and symptomatic patients. This appears to be reversible on discontinuation of therapy. In a few symptomatic patients receiving higher than usual doses, who underwent surgery, sludge containing traces of ceftriaxone was recovered from surgical specimens. Discontinue therapy in patients who develop signs or symptoms suggestive of gallbladder disease; consider conservative management.

PRECAUTIONS: *GENERAL:* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.*, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum

duration of animal toxicity studies was six months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

PREGNANCY: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

NURSING MOTHERS: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section. *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Exercise caution before administration to hyperbilirubinemic neonates, especially prematures.

ADVERSE REACTIONS: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration.

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESTINAL—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia.

HEPATIC—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

RENAL—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%).

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%).

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours.

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days; in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone; piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone; bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION).

Also supplied as a sterile crystalline powder as follows:
ADD-Vantage Vials®* containing 1 gm or 2 gm equivalent of ceftriaxone.

Also supplied premixed as a frozen iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose plastic containers,† as follows:

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.9 gm dextrose hydrous, USP added.

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.2 gm dextrose hydrous, USP added.

NOTE: Rocephin in the frozen state should not be stored above -20°C.

*Registered trademark of Abbott Laboratories, Inc.

†Manufactured for Roche Laboratories, Division of Hoffmann-La Roche Inc., by Travenol Laboratories, Inc., Deerfield, Illinois 60015.

P.I. 0587

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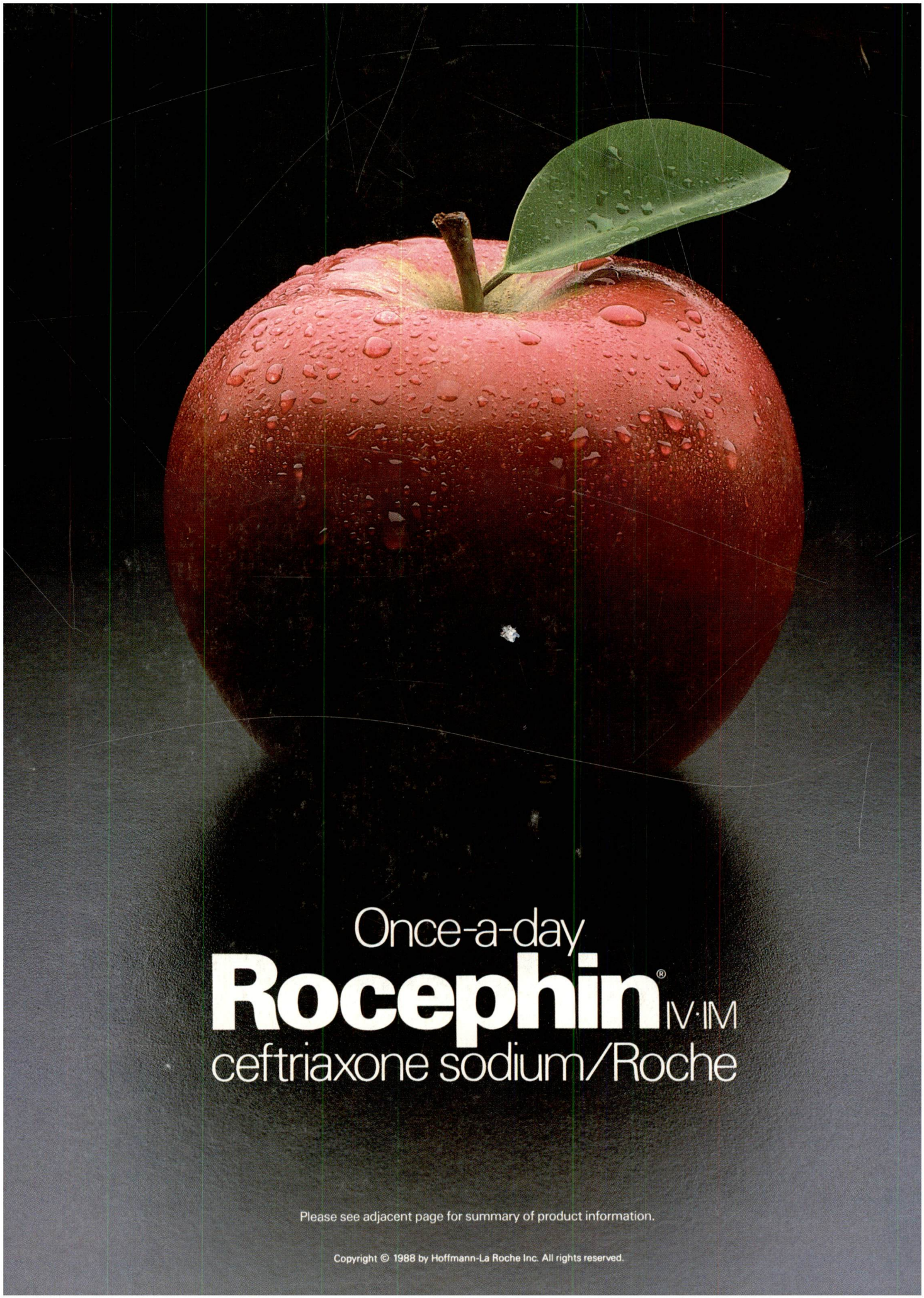

Please see adjacent page for summary of product information.

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