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# OUTLOOK MAGAZINE

Washington University School of Medicine

Winter 1981





*The inventor of the telescope, Laennec, was born 200 years ago and the medical community in Paris, France, celebrated the achievement of one of its own. Above is a statue of Laennec examining a young patient. Writer Marion Hunt was in Paris and shares the story of Laennec and the bicentennial celebration of auscultation. The story begins on page 16.*

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Washington University School of Medicine Winter 1981 Volume XVIII, Number 4

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**On the cover:**

Duotone treatment of the poster of Laennec applying his new invention to diagnosis. The poster was prepared under the auspices of the mayor of Paris and was widely displayed in the city.

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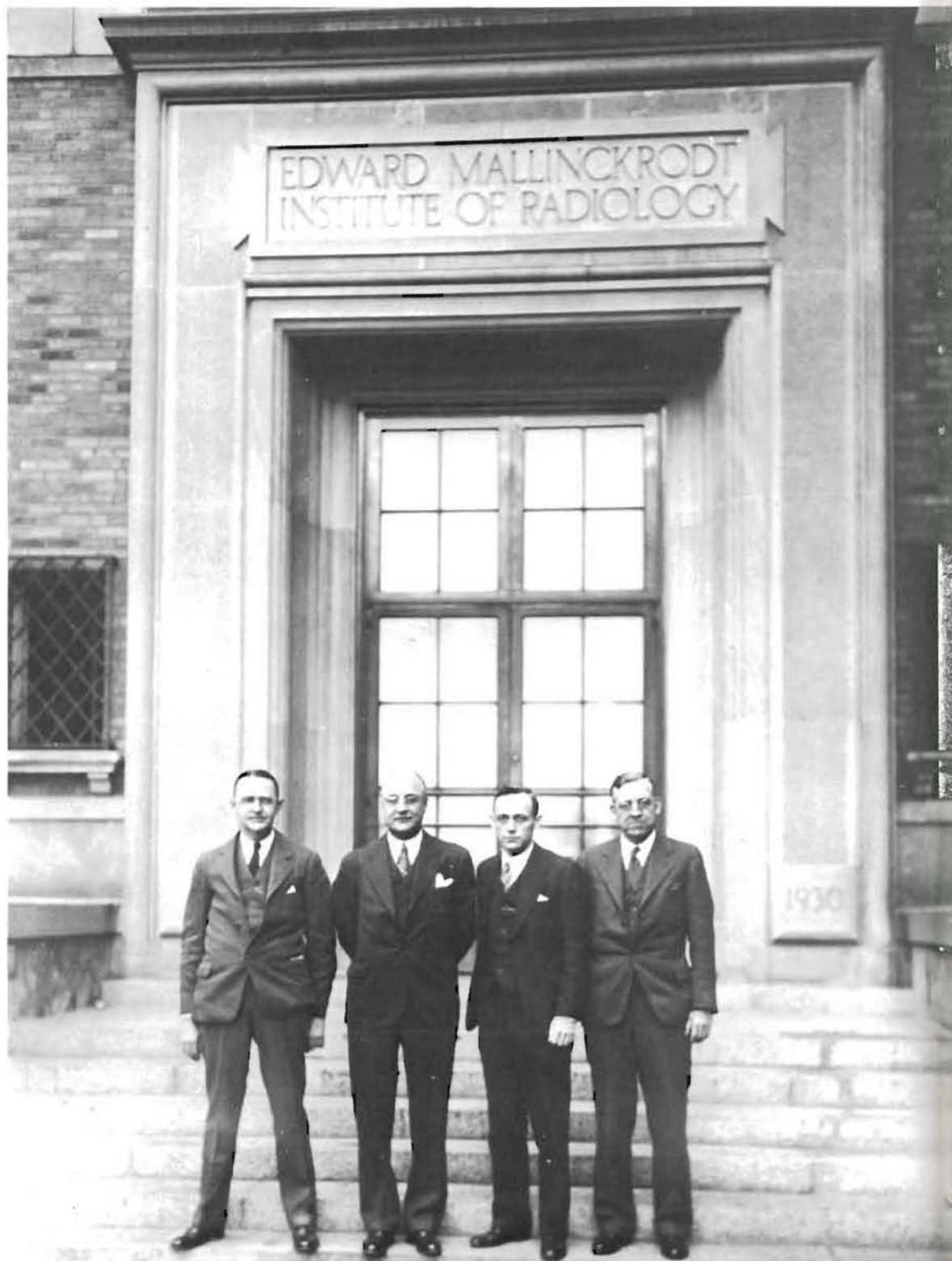
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# The Roots of Radiology

by Marion Hunt

**O**n the first three days of October, the Mallinckrodt Institute of Radiology celebrated its 50th anniversary with a three-day symposium; 28 sessions on every major aspect of modern radiology attest to the remarkable flowering of this specialty during the last half-century. Although such new technological developments as computers, CT scanners (originally called CAT scanners), and positron emission tomography have transformed the field, Mallinckrodt Institute enters its second half-century on the same firm foundation with which it began in 1931: private and scientific research, medical philanthropy, and clinical excellence. To this combination has been added the established prestige of radiology as a distinct and highly complex specialty, best symbolized by the Nobel prize awarded to the inventors of the CT scanner in 1978. As Ronald Evens, M.D., Director of the Institute, points out, Sir Godfrey Hounsfield, its inventor, had been collaborating with colleagues in St. Louis for some years before his international recognition. What attracted him to the Mallinckrodt Institute was its tradition of innovation and excellence. Evens notes that "the necessary resources for the next fifty years are the same as in 1931: a great medical school, private philanthropy, high standards of excellence, and strong leadership." Yet in order to appreciate the growth of radiology in general and of the Mallinckrodt Institute of Radiology in particular, it is important to understand the roots from which they both sprang.

*The team of surgeons and radiologists who developed cholecystography standing outside the newly completed Mallinckrodt Institute building: (from left to right) Drs. Glover Copher, Everts Graham, Warren Cole, and Sherwood Moore.*



# Mallinckrodt Institute of Radiology Celebrates 50 Years

**O**n November 11, 1931, the Mallinckrodt Institute was officially opened for service with the note that it was "sufficiently complete to permit its full clinical operation." At this time, the building was still more than half empty; only four of its nine floors were occupied. Still, these four floors were a great increase from the two rooms in which radiology had operated from 1915 until 1930. All necessary services in the new institute were to be provided by a staff consisting of four radiologists and one physicist. Until 1937, when housestaff training in the specialty began at Washington University Medical School, there were no supporting interns or residents. Not until three years after the Institute opened its doors was the American Board of Radiology formally incorporated. The first candidates for certification in the new specialty were examined in June of 1934. Thus, the construction of a nine story building designated as an Institute of Radiology had been accomplished before the specialty itself had organized its certifying board. To a great extent, this fact testifies to the vision and faith of those who saw the need for such an institute: Evarts Graham, M.D., Sherwood Moore, M.D., and businessman-philanthropist Edward Mallinckrodt.

**G**raham, like many a surgeon of his day, was quick to see the importance of radiology's development for the success of his work. It is of interest to note that neurosurgeon Harvey Cushing, M.D., was responsible as a young house officer for buying the first "x-ray machine" put in use at Massachusetts General Hospital in 1896. When he moved to Johns Hopkins, he took his so-called 'gas tube' with him. The famous Dr. Osler had not yet

*Edward Mallinckrodt (1845-1928),  
the Institute's first benefactor.*

persuaded the hospital in Baltimore to buy one. But by 1900 radiology in some form was in use in most major hospitals; x-rays were being used for therapy as well as diagnosis. In 1910 the invention of a more reliable tube with tungsten filament improved the quality of the results obtained. This innovation and the enormous clinical demands of World War I increased the number of doctors practicing radiology from a few hundred in 1913 to over a thousand in 1931.

**I**n addition to surgeons' interest, another major element in the growth of the specialty was the development of contrast radiography. By 1898, Walter B. Cannon, M.D., had reported the result of his visualizing animal digestion. He first fed a button to a dog and with a fluoroscope watched it pass into the stomach. In later experiments he used salts of heavy metal to watch the activity of the entire intestinal tract. Another step in this direction occurred at Johns Hopkins in 1918 when a young surgical resident, Walter E. Dandy, M.D., first used air injections to visualize the brain. At the Mayo Clinic between 1921 and 1922, two other researchers reported a different type of contrast radiography to visualize the kidneys. The next major breakthroughs to be reported were from Washington University medical school and Barnes Hospital where Barney Brooks, M.D., injected sodium iodide into a leg artery and made x-ray pictures showing the major vessels in hitherto unseen detail. That same year, Evarts Graham, M.D., collaborated with a young surgical resident, Warren Cole, M.D., to develop a contrast medium for the visualization of the gall



bladder. The brilliant success of their efforts is considered a key element in the conception of the Mallinckrodt Institute of Radiology, sometimes called "the house that cholecystography built."

**B**ut the roots of radiology at Washington University medical school go deeper still; twenty-one years before the Institute's creation, in 1910, Russell D. Carmen, M.D., was listed as a "lecturer in roentgenography" in the Department of Surgery. He alone represented the fledgling specialty. On Carmen's departure for the Mayo

Clinic in 1913, R. Walter Mills, M.D., took over this position and served as Director of the X-Ray Laboratory until his untimely death, from unprotected exposure to radiation, in 1926. Like most early victims of the x-ray, he was in the prime of life — only 47 years old. His superb clinical skills and the tragic circumstances of his death may well have speeded plans for an institute of radiology at Washington University School of Medicine. At a special joint meeting of the St. Louis Medical Society and the medical school on March 16, 1924, Evarts Graham

Dr. R. Walter Mills (1877-1924) whose brilliant achievements and early death helped speed the establishment of a radiological institute at WUMS.



gave Mills a heartfelt eulogy, in which he spoke of his colleague's achievements: "I can still vividly remember with what amazement I heard him say . . . that a patient of mine whom he had been studying had an adenoma of the stomach. I regarded x-ray diagnosis of such a condition as impossible and I can well remember my skepticism. But that was because I did not know Mills and his capabilities. To those of you who knew him and his work it will be no surprise to hear that a few days later at operation I found an adenoma . . . To me the most fascinating characteristics of Mills were his scientific spirit, his thoughtfulness of others, and

his versatility. An uninformed observer who watched Mills at the fluoroscope making examinations with lightning speed would be perhaps justified in thinking either that there was something of the magician about him or that his diagnosis must rest on a very insecure foundation . . . Despite the astonishing speed with which he seemed sometimes to arrive at a diagnosis his methods in reality were most laborious. The thousands of carefully kept routine records bear witness to the painstaking character of this work . . . Mills had the truly scientific spirit . . ."

Concluding his talk, Graham noted how Mills' work could best

be commemorated: "He often discussed with me his ardent wish that some day Washington University would be able to enlarge its x-ray facilities and create a Roentgenological Institute. Could anything be a more fitting memorial to our beloved colleague . . .?"

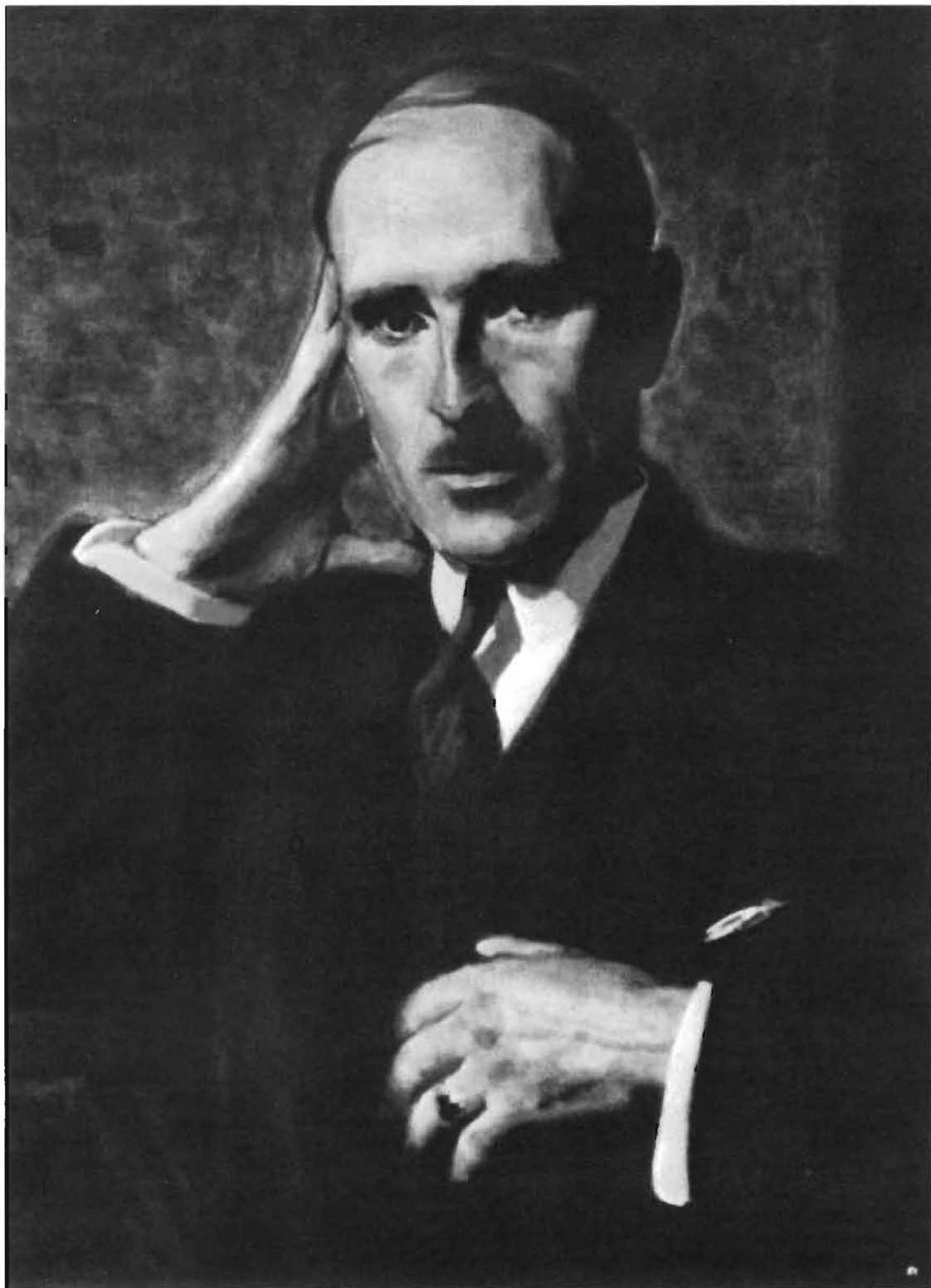
Before a decade had passed, this hope was accomplished.

A crucial element in its realization was the success of the technique Graham perfected in 1924, the visualization of the gall bladder. It is of interest to note that Mills played a role in that success. The experiments on this problem had begun in 1922. The personal interest of Edward Mallinckrodt, in the development of a compound to be used in this process, led the company to assign a chemist, Dr. Drake, to work with Graham and his team. In the course of his collaboration, more than 90 compounds were developed and injected before success was finally attained. After nearly five months of work and over 200 failures in experimental animals, Dr. Warren Cole had obtained a single film on which was visible what seemed to be the shadow of a dog's gallbladder. After the next six dogs injected showed no similar outline, Cole returned to the Radiology Department to look once more at his only successful visualization, fearful that he had been misled by "some round bone or other object the dog might have swallowed accidentally." Mills happened to walk by the viewing area, and Cole explained his misgivings about the film. Mill's reply was unequivocal; "Don't be silly young man; this is the shadow of the gallbladder." In a footnote to their 1928 book *Diseases of the Gall Bladder and Bile Ducts* (dedicated to Edward Mallinckrodt) the authors

(Drs. Graham, Cole, Moore and Copher) noted that their first efforts at gall bladder visualization might have been their last had it not been for another fortunate accident. Unable to explain the success in the first dog and the subsequent failures in other animals, Cole turned in desperation to the animal caretaker to ask if there had been any difference in their treatment; the caretaker admitted he'd forgotten to feed the first dog. As the authors later noted, "If it had not been for our initial success, we probably would have given up the whole idea as a fruitless one." The collaborative nature of this achievement — involving scientists, physicians, and industry — has characterized the Institute of Radiology which grew from this innovation.

According to Dr. Wendell Scott's account, "as a result of the epochal success with cholecystography, Mr. Edward Mallinckrodt . . . asked Dr. Graham to determine the most critical needs of the Medical School." Graham knew that Sherwood Moore and Walter Mills "wanted and urgently needed a new department and that they had even prepared tentative sketches and plans for an Institute of Radiology that would serve all of the affiliated hospitals in the Medical Center." When informed of this fact, Mr. Mallinckrodt notified the Corporation of Washington University in 1927 that he and other members of his family would provide a gift of \$750,000 for the erection and endowment of an institute and department of radiology. Prior to that year, Dr. Graham and Dean Marriott had approached Abraham Flexner of the Rockefeller-funded General Education Board for a similar grant. From its inception, the Board did not make large gifts unless they were

*Dr. Sherwood Moore (1880-1963), first director of the Mallinckrodt Institute and first chairman of radiology at WUMS.*



*Edward Mallinckrodt, Jr. (1878-1967), who followed his father's distinguished tradition of medical philanthropy.*





matched by local funds. Thus Mallinckrodt's generosity insured a gift of double the size. An additional \$20,000 gift from John and Edgar Queeny brought the total investment in the new institute and department to \$1,220,000.

**T**wo years of careful planning preceded the groundbreaking in 1929. The disastrous Cleveland Clinic fire made the safe storage of x-ray films a major priority and added to the building's cost. Neither the death of Edward Mallinckrodt, Sr., in 1928, nor the onset of the Great Depression the next year, deterred its completion. In fact, the building's size was increased to nine stories with additional funds provided by Edward Mallinckrodt, Jr., in fulfillment of his father's wishes. Thus Sherwood Moore, M.D., the first Director of the Mallinckrodt Institute and the first chairman of the new Department of Radiology, was able to move from two

rooms in Barnes Hospital to a multi-story building. While only four of its floors were occupied in 1931, Moore wisely foresaw the inevitable need of radiology for expansion. His careful planning was evident throughout the completed project; as the Washington University Alumni Magazine reported in November of 1931: "The building and equipment . . . represent the highest point yet attained anywhere in efficiency, economy, and design." Nor was Dr. R. Walter Mills forgotten; a room in his memory was set aside on the first floor, containing "valuable collections of films and records which attest his great enthusiasm for the work that cost his life."

Sherwood Moore, only three years Mills' junior, had been appointed the first professor of radiology at the School of Medicine in 1927; he served as Director of the new Institute and chairman of the Department of Radiology from 1930 until 1949.

Trained like many of his generation through apprenticeship in his specialty, he presided over the establishment not only of an institute and a department, but over the formal training of future radiologists as well. As his former student, Wendell Scott, wrote of him at his death in 1963: "As a teacher he had an abiding faith and affection for the young physician . . . he believed in learning through experience and by guiding the receptive mind, as opposed to regimentation and formal didactic lectures. As a teacher, he was at his best as a preceptor. This method of training young radiologists proved more productive, for Sherwood Moore's 'boys' who are scattered across the country are in positions of importance in both academic radiology and private practice . . ."

Another generation of radiologists has been trained by Moore's "boys," now senior members of their chosen special-

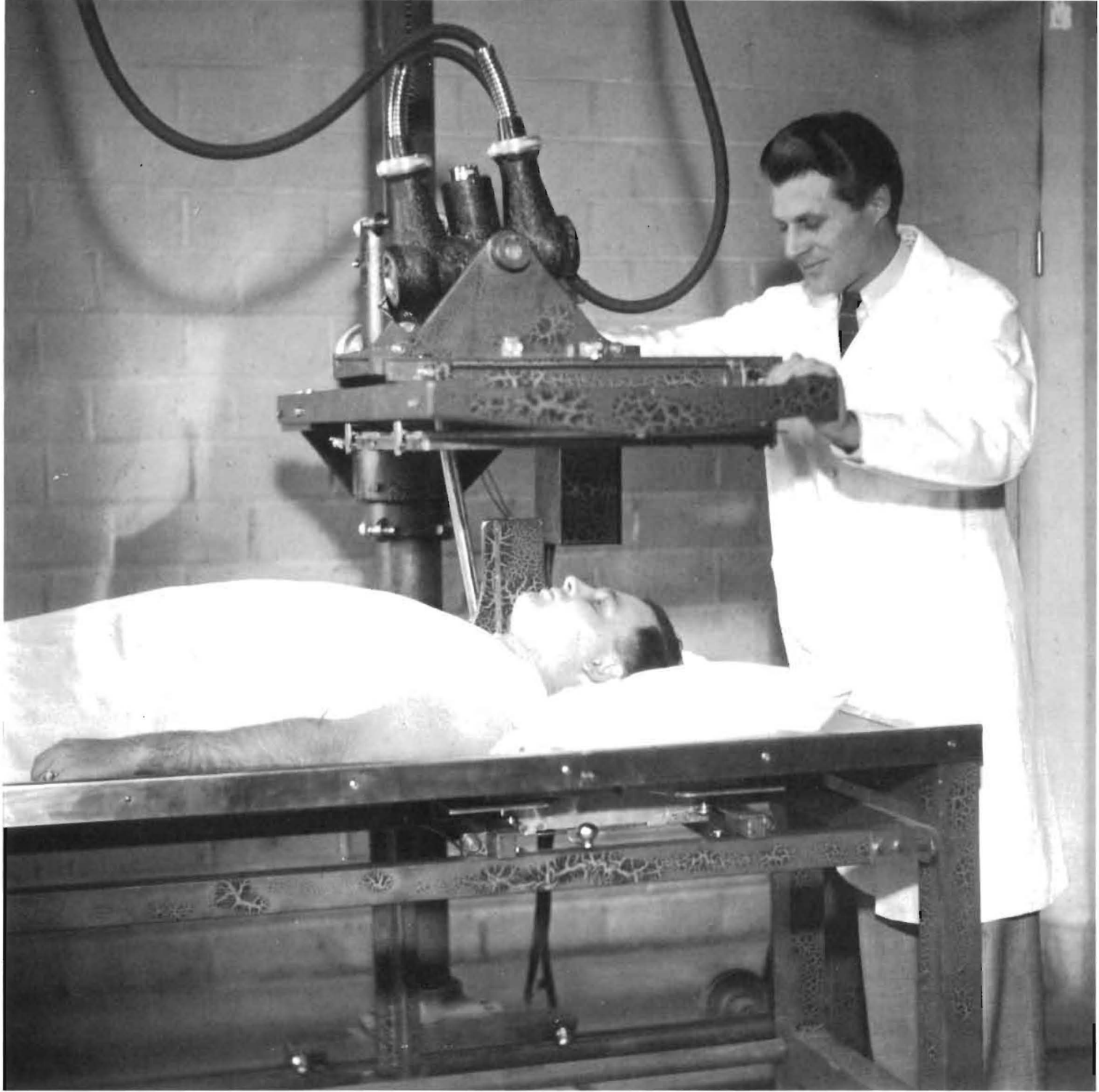
ty. And the Mallinckrodt Institute of Radiology, which he helped bring into being, has entered its second half-century committed to excellence in research, teaching, and patient care.

**J**ust as the roots of the Mallinckrodt Institute stand in excellence, so does its future. As Chancellor William H. Danforth, M.D., remarked at the 1981 Wendell Scott lecture: "There is no substitute for excellence. It starts an upward spiral. Excellence breeds excellence. Achievements inspire more achievements. Mallinckrodt Institute of Radiology is today, as in the past, an institution worth building, worth the time and effort of serious and talented people. Great leadership has kept this spirit alive and well and is continuing to do so." ■

(Left to right) Chancellor William Danforth, M.D., Ronald Evens, M.D., director of Mallinckrodt Institute of Radiology, and Eric Smith of Smith-Entzeroth, architects, designers of the MIR building. (Photo by Tom Murray, MIR).



Alexander M. Margulis, professor and chairman of the Department of Radiology, University of California at San Francisco, spoke on the new technique of nuclear magnetic resonance at one of the technical sessions. Margulis is a former professor of radiology at Mallinckrodt.



Modern x-ray equipment, circa 1930.

**Building opens,** September 14, 1931. Radiation therapy and a small film library were on the ground floor. The first floor contained physicians' offices. On the second floor was general radiology; on the third floor were cystoscopy and surgical radiology. The fourth floor housed gastrointestinal examination rooms and fluoroscopy. The fifth and sixth floors were for expansion. The seventh floor was partially equipped for research. Film storage and photography were on the eighth floor. There were four radiologists and a physicist on staff.

**Body-section radiography principles developed,** 1934. Self-taught technician Jean Kieffer joined the Institute staff and developed the principles involving synchronous movement of an x-ray tube and film in opposite directions to image a small slice of the body. Kieffer built his laminagraph in 1936 and produced the first successful radiographs in February 1937. His tomography approach was the seed of today's computed tomography.

**Roentgen kymography developed** by Wendell Scott, 1936. He was chiefly responsible for developing this method of recording the movements of various organs and structures on a single x-ray film.

**House staff training began,** 1937. The first two residents accepted for training were William Burton, M.D., and Allan B. Phillips, M.D.

**First cyclotron funded,** 1938, by a Rockefeller Foundation grant and endowment at the Institute. University and Institute leaders had decided that the rapidly expanding field of nuclear physics held promise for advancements in radiology and medicine. Building of the cyclotron began in 1940 on the main campus.

**Isotopes delivered for medical research,** 1942. Carl Moore's laboratory received the cyclotron-produced isotopes in March; the first injection of radioactive phosphorus was given to a patient in April.

**Cyclotron "goes to war,"** 1944, producing plutonium for the Manhattan Project.

**Co-discoverer of Carbon 14 joined Institute,** 1945. Dr. Martin Kamen was appointed as research chemist. He developed a laboratory of basic research in intermediary metabolism.

**Cobalt 60 unit installed,** 1948, making higher energy radiation therapy available.

**Changing of the guard,** 1949. Sherwood Moore retired, and Hugh Wilson, M.D., became the second director of Mallinckrodt Institute. Wilson established subspecialties based on age and anatomy — pediatrics, chest, gastrointestinal, genitourinary, bone and joint.

**School Of X-ray Technology** established, 1950. Enrollment in 1981 is 35 students of x-ray technology, four in nuclear medicine, and 11 in radiation therapy.

**First pediatric radiologist** joined Institute, 1954. Peter Humphrey, M.D., demanded high quality examinations despite cramped quarters and shared equipment. He successfully eliminated overuse of fluoroscopy, which was common in the 1940's. The Pediatric Radiology division now occupies its own floor at the Institute, employs 19 people, and produces approximately 50,000 examinations per year, serving St. Louis Children's Hospital, Shriners Hospital and private physicians in the bi-state region.

**Cardiac radiology academic program begun,** 1957, by Erik Carlsson, M.D., who came from Sweden and continued on the faculty until 1964. The cardiac radiology section, now on the ninth floor of Barnes West Pavilion, includes three special procedure rooms, cine and fluoroscopy rooms, ultrasound and support facilities, plus three cardiac catheterization suites. Section chief is Robert McKnight, M.D.

**Successful experiments carried out** in 1958 on cyclotron radioactive oxygen to study oxygen distribution in malignant tumors. This work, by Michel Ter-Pogossian, Ph.D., and William Powers, M.D., resulted in support by the Atomic Energy Commission for more detailed studies, leading to acquisition of the medical school's own cyclotron.

**The medical center's first 24 MeV Betatron** installed, 1962. The Betatron was the first therapy equipment to produce electrons and photons of extremely high energy for cancer therapy.

**The medical center's first electron microscope** installed, 1963.

**America's first medical center cyclotron** installed and began operating, 1964, to produce short-lived radio isotopes for medical use. A strong radio chemistry group was assembled at the Institute, now recognized as one of the finest centers in the world. Two scientists in the Division of Radiation Sciences, Michel Ter-Pogossian, Ph.D., and Michael J. Welch, M.D., are among only nine recipients of the Society of Nuclear Medicine Education and Research Foundation Paul C. Aebersold Award for Outstanding Achievement in basic science.

**Changing of the guard, 1964.** Hugh Wilson, M.D., retired, and Juan M. Taveras, M.D., became the third director, succeeding acting director Marvin Friedenber, M.D. During Wilson's leadership, the divisions of nuclear medicine and radiation therapy were established, and much progress recorded.

**Abdominal Radiology section established,** 1965. P. Ruben Koehler, M.D., was the first director; the present director is Robert Stanley, M.D. The section is responsible for all gastrointestinal and genitourinary radiology, including ultrasound, computed tomography, arteriography, lymphangiography and percutaneous diagnostic and therapeutic procedures involving the biliary tree, genitourinary tract and other abdominal organ systems.

**Division of Nuclear Medicine formed**, 1966, with E. James Potchen, M.D., as the first director. In 1973, Barry A. Siegel, M.D., became director of the division which now occupies 9,000 sq. ft., housing seven scintillation cameras and four nuclear medical computer systems. The division's four full-time physicians, four nuclear medicine residents, three diagnostic radiology residents, 15 technologists and student technologists, and the radiopharmacist perform 12,000 studies a year. The division also employs a computer systems analyst and support personnel.

**Elizabeth Elliot Mallinckrodt (1885-1973) endowed a chair** in 1972 in radiology to be occupied by Ronald G. Evens, M.D., fourth director of the Institute. Evens had become director the previous year, at age 31 the youngest radiology department head in the world.

**Chest Radiology section established**, 1972. Today, the section includes three or four radiology residents, a pulmonary fellow and a medical student and provides 25 percent of all the radiology exams at the Institute.

**Musculoskeletal section organized**, 1972.

**Abdominal ultrasound unit installed**, 1973, in new diagnostic laboratory. The ultrasound unit now utilizes advanced gray-scale signal processing.

**Whole-body CT scanner installed**, 1975. This prototype of EMI, Ltd.'s (London, England) CT scanner was one of two in the U.S. Especially useful in evaluating the larynx, mediastinum, adrenal glands, liver and biliary tree, pancreas, kidneys and intra- and reticuloendothelial system, the new equipment was tested at MIR and improved. The newest generation of CT scanners now obtain a high-spatial, high-contrast resolution scan in three seconds and perform approximately 20 patient exams per day.

**Institute-wide computer system begun**, 1975, to handle patient registration, billing and research support data. Now the largest radiology computer center in the world, Mallinckrodt Institute's center includes seven computer systems with 13 high-speed disc drives and a dozen terminals. Applications include patient monitoring, film library management, scheduling, reporting, room utilization studies. The center is linked with Barnes Hospital computer systems. This year, two new systems were added, primarily devoted to imaging projects and linking various imaging equipment throughout the Institute.

**Division of Radiation Sciences formed**, 1975, to apply radiological sciences to the study of physiology and pathophysiology, continuing work first started by Sherwood Moore, M.D., three decades previously. Michel M. Ter-Pogossian, who had received his Ph.D. in nuclear physics from Washington University in 1950, joined the staff of the Institute, becoming increasingly responsible for expanding radiation physics activities, is now director of the division. In collaboration with colleagues and with the EMI company of London, Ter-Pogossian is developing a series of positron emission transaxial tomograph (PETT) scanners.

**Innovative double-contrast techniques developed**, 1976, in gastrointestinal radiology, for evaluation of esophagus, pharynx, colon, etc.

**Abdominal radiology fellowship established**, 1977.

**Bedside ultrasound capabilities added**, 1979, with the purchase of a high-resolution linear array real-time scanner.

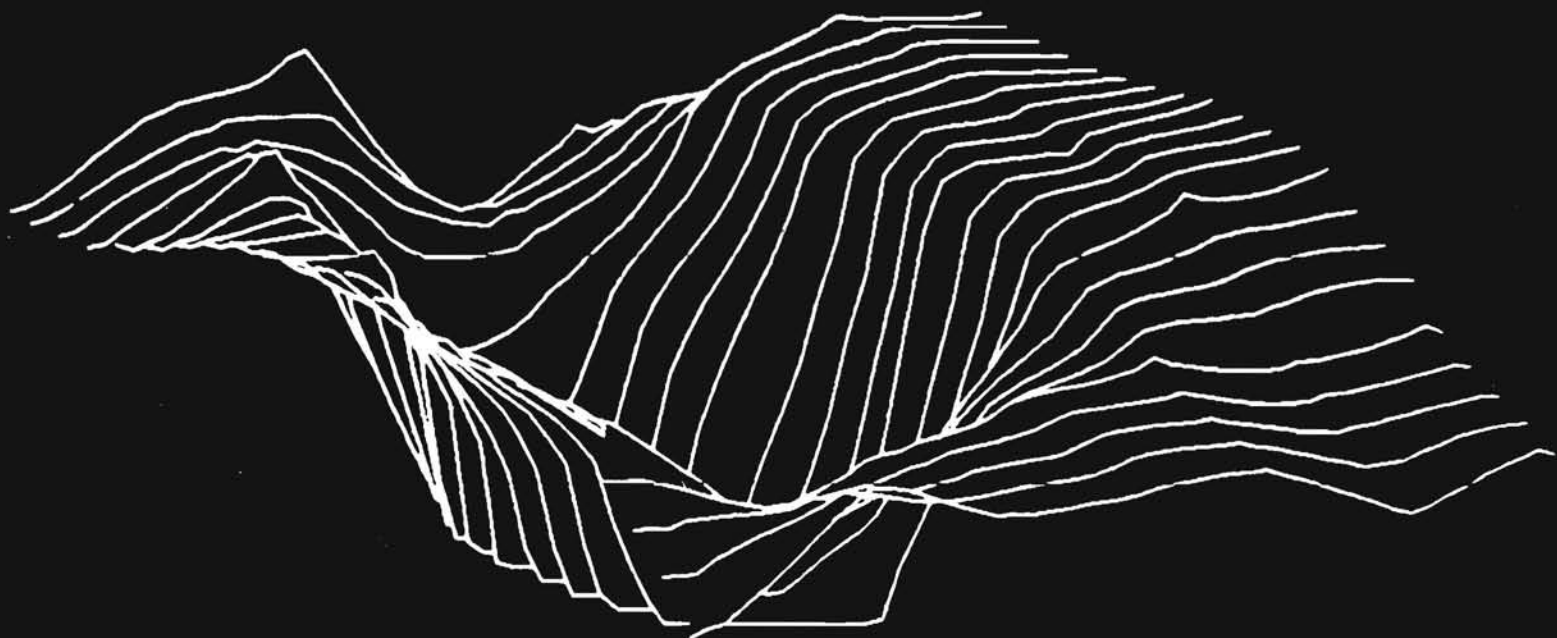
**Neonatal diagnostic radiology enhanced**, 1980, with addition of a high-resolution real-time scanner, digital B-scanner and other equipment.

**Fellowships established**, 1981, in ultrasound, computed tomography, and genitourinary radiology.

**M**allinckrodt Institute of Radiology was the first, and is today the largest, radiology institute in the world. The 500 employees, including 150 physicians or Ph.D. holders, continue to carry out the Institute's charter — research, teaching, and diagnostic and therapeutic radiology. Sixteen former MIR students or faculty members now chair academic radiology departments throughout the United States. Research conducted at MIR or by its graduates and former affiliates, based on the priorities of accuracy, safety and comfort, has resulted in rapid technological advancements. Nearly a fourth of the kinds of radiologic examinations now considered commonplace could not be done only a decade ago. Many of the newest procedures and equipment can often minimize the need for painful, invasive actions such as surgery.

In his Wendell Scott Lecture, Chancellor William Danforth reviewed some of the traditions of the Mallinckrodt Institute of Radiology: application of science to medicine; close cooperation with clinical departments and with University departments of physics, engineering, computer sciences, chemistry and with private industry; concentration on teaching, learning and service; continuing private philanthropy, especially from the Mallinckrodt family; and the traditional feeling among MIR people that they are an important part of an exciting place, "literally the best there is." Danforth continued: "The work of many of you in this room, plus others too numerous to name, has made it all possible. The challenge, of course, is to do better in the future so that the accomplishments of the past may be dwarfed and really appear only as prologue. The acceptance of that challenge is the mark of a great institution." ■

# Computer Applications in Visual Field Examinations



*This piece of equipment, the Goldmann Perimeter, has been modified for use with the computer system.*

by R.R. Smith

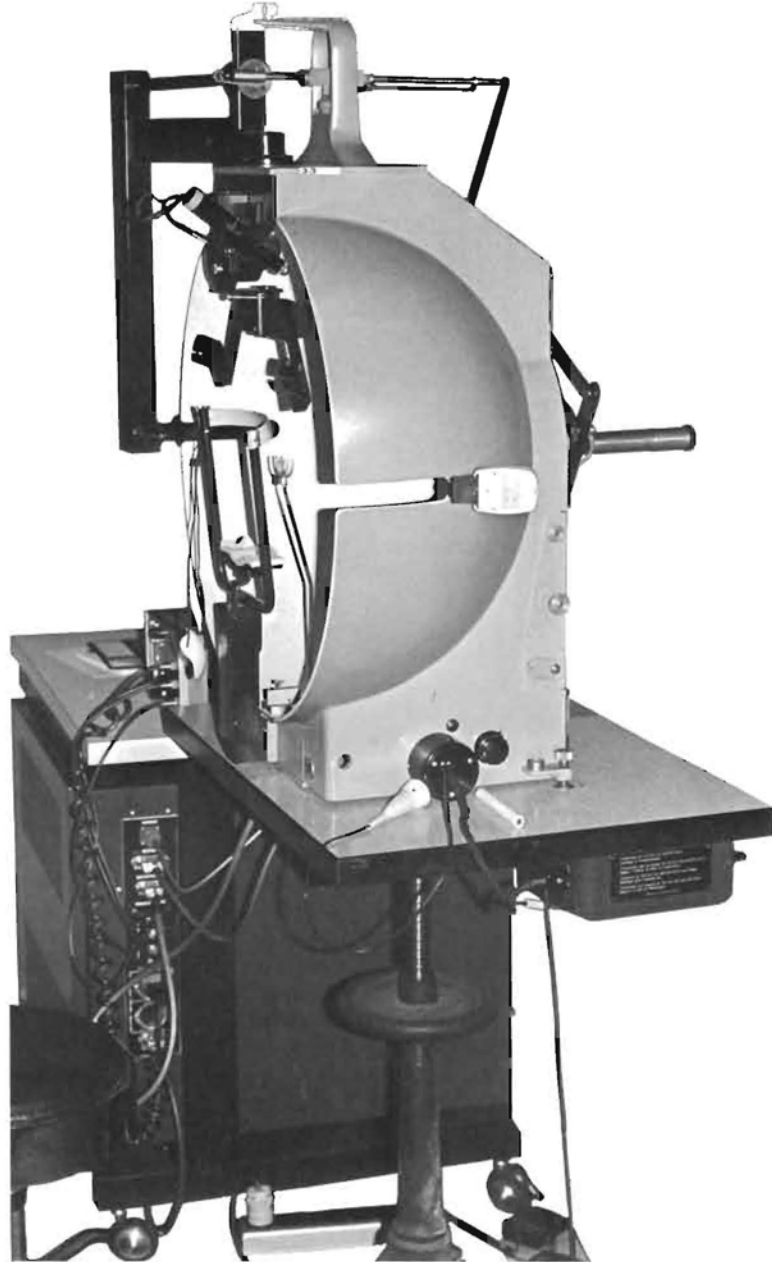
**G**laucoma is, perhaps, the most feared eye disease. Undetected or left untreated, it will always result in blindness — partial or total. People with a family history of glaucoma, diabetes, vascular disease or irregularly shaped optic nerve cups are at high risk for developing glaucoma, a progressive disease which results in gradual loss of vision and damage to the optic nerve. Many advancements have been made in treatment to retard or halt damage once the diagnosis is made. However, the loss of vision or damage to the optic nerve which occurs before the diagnosis is made is, unfortunately, irreversible. Now, progress is being made to enable ophthalmologists to make more accurate and earlier diagnoses, thus reducing the damage that occurs in the early stages of the disease. William M. Hart, Jr., M.D., Ph.D., Assistant Professor of Ophthalmology at the School of Medicine, is developing a new computer-based diagnostic tool, and testing it at the Barnes Hospital Eye Clinic.

**W**hile much of Hart's research has, indeed, centered on glaucoma, the diagnostic and prognostic applications of the computer-based system are not limited to glaucoma alone. "What we have," said Hart, "is a very valuable system for diagnosing any disease that affects the health of the retina, the optic nerve, or the visual pathways in the brain behind the eye. This includes all manner and variety of ocular diseases, including retinal and optic nerve disorders, as well as neurologic diseases including stroke, multiple sclerosis, brain tumors and encephalitis. Every imaginable neurologic disease that can affect the visual system can either be detected or actively

diagnosed by computerized visual field examination."

The visual field examination identifies the eye's sensitivity to light. Clinically, the visual field is expressed and recorded as an abstract map. The "kinetic" technique for examining visual field plots the threshold of the subject's detection of targets as they are moved from the periphery towards the center of visual space. While kinetic visual field examinations are essential to understanding an individual's vision and any visual defects, they do, however, have limitations. As a result, "static" visual field examinations have become widely accepted as a superior tool for examination of the central visual field (the portion within the central 30 degrees, measured 15 degrees in either direction from the eye's center of visual direction). The static technique plots the threshold at which the subject first perceives stationary targets within the central visual field as the brightness of the targets is increased from below the level of perception to a just-barely-perceived level. The resulting visual field maps from both static and kinetic tests represent three-dimensional surfaces. The static test map is not necessarily compatible with the kinetic test map. These maps accurately define an individual's field of vision.

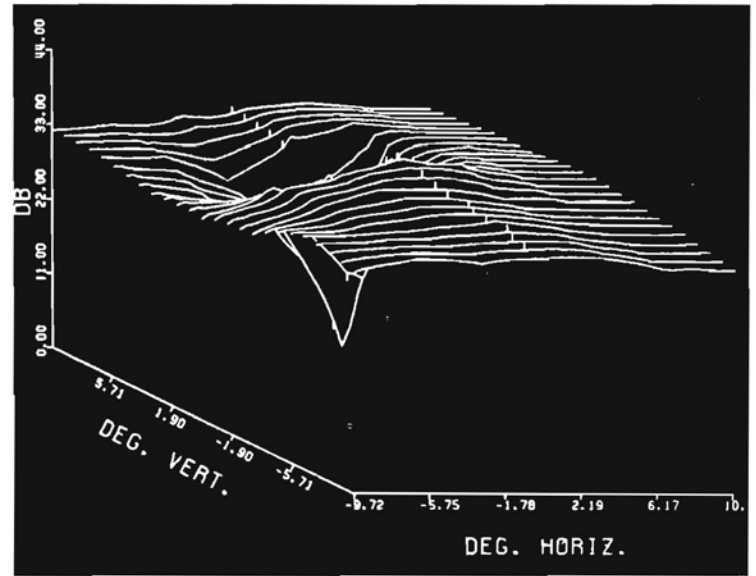
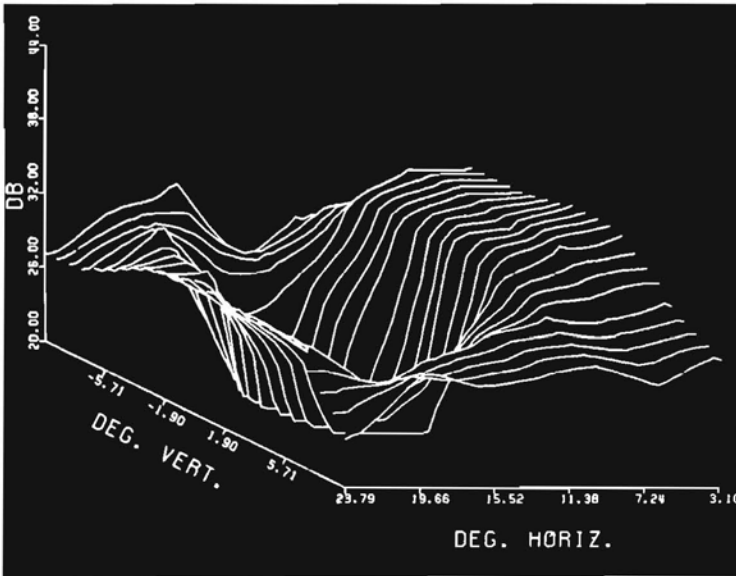
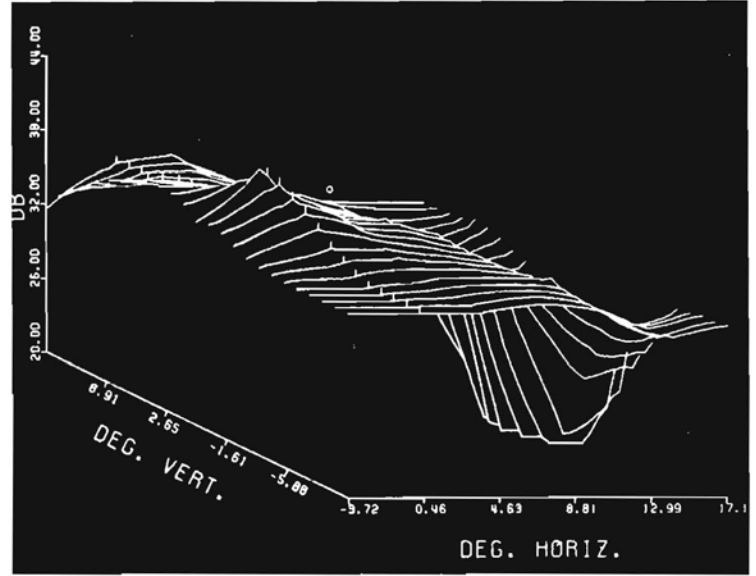
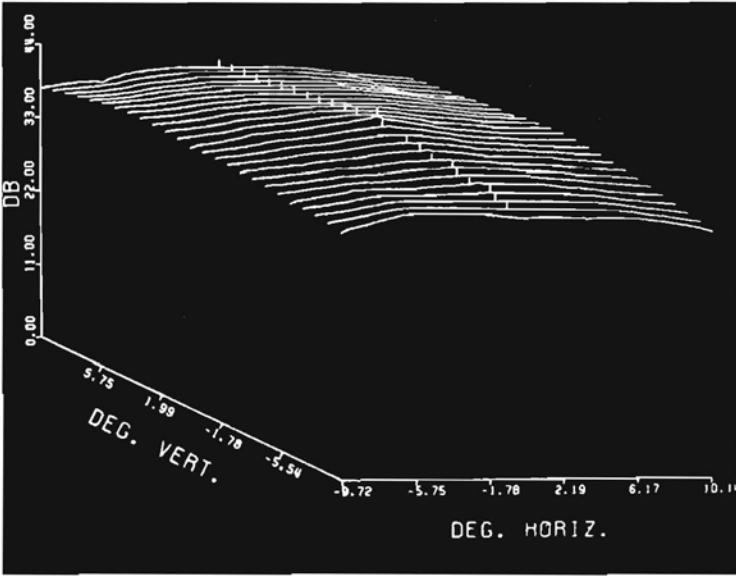
A traditional static test has two primary limitations. First, it is very demanding of both the examiner and the patient; so the examination must be limited to the area most likely to demonstrate pathologic findings. Second, it is difficult to record and display all three variables (two for position and one for threshold) which are generated for each target in the test pattern. It is in this area that Hart's new computer-based system is proving its merits, especially in the simulation of dimension.



**S**ince 1976, when Hart completed his medical residency in ophthalmology at Barnes Hospital, he has been interested in the use of computers to store, manage and analyze data obtained from eye examinations, particularly the type of data generated from visual field examinations. Computer applications to visual field examinations were nothing new. Much attention had historically been devoted to the use of computers in data collection, such as computer-controlled testing strategies. The general goals had been to relieve both the patient and the examiner of much of the tedium involved in manual testing techniques, and to standardize test parameters and results. Little had been accomplished, however, in computer storage, retrieval, analysis and display of data. As Hart explained, "In the past, the re-

sults of three-dimensional visual field examinations had always been recorded by manually drawing two-dimensional images on charts," Hart explained. "The examinations were interpreted qualitatively by trained people inspecting the charted data. But there was, to my way of thinking, often quantitative, rather than qualitative, information contained within these hand-drawn records. Quantitative information was not easily determined by qualitative inspection. So, I began seeking ways of transferring the data from a visual field examination to storage in machine-readable form so that the information could be examined with any one of a series of automated techniques."

Because of previously limited knowledge of data processing techniques in visual examinations, Hart first began by entering existing examination results into



Hart's computer system draws dimensional maps of patients' visual fields. Top left: A normal central visual field with the point of maximum visual sensitivity represented by the peaks in the center of the series of lines. Top right: Everyone has a normal physiological blind spot, represented on this map by the bucket-shaped depression. The peaks on the left of the map show the point of maximum visual sensitivity. Bottom left: The computer's map of the visual field surface of a normal but nearsighted eye shows the blind spot as a depression. Bottom right: The visual field map of a person with glaucoma shows an abnormal blind spot very close to the center of the visual field. This kind of test result, plus intraocular pressure and the appearance of the optic nerve combine to verify the suspicions of glaucoma.

the computer, using the magnetic graphic tablet. Then, various computer analyses of the resulting two-dimensional representations of visual field data were performed. "We got some interesting information about the quantitative nature of the visual field changes produced by increases in intraocular pressure in people with known or suspected eye abnormalities," Hart said.

Subsequently, the project grew to the point where the National Eye Institute awarded Hart's program a grant for the installation of a computer in the Department of Ophthalmology specifically to enable Hart to pursue his research on a larger and more elaborate scale. That computer has been operating for slightly more than three years. Currently, an established and reliable system for conducting eye examinations is combined with a recently developed minicomputer system for programmed manipulations of the data.

The basic equipment used in the examination is the Goldmann Perimeter, modified for generating data directly into the computer. To minimize costs, Hart decided against using automated examination techniques. "We have found," he said, "that the most direct way of getting good, reproducible, high-quality examinations is to use skilled human perimetrists." Highly trained in the technical aspects of the examination as well as in the anatomy and physiology of vision, the perimetrist confirms the patient's responses before the data is captured locally on a magnetic flexible disk drive. Full editing, via the display screen of a small oscilloscope, allows removal or change of any recorded data. Following the examination, all data are transferred to the minicomputer for storage.



*Perimetrist Kathy Jones prepares a patient for a visual field examination by placing a patch over the left eye. Each eye is examined individually.*

**T**he second major component is the minicomputer system with temporary and permanent disk memory which stores and retrieves data from examinations. Examination data is entered by means of a magnetic graphics tablet, operated like a tracing device, which is interfaced to one of the graphic display terminals. The time for retrieval and display of a single examination varies according to the complexity of the examination. For a normal record, the time is approximately two seconds; for an abnormal record showing irregularities in vision, the time is from three to five seconds. Various features of normal and/or abnormal visual exams

are coded to allow matching of equivalent features. This system gives Hart the ability to perform rapid cross-sectional statistical analysis of visual information obtained from large populations, as well as to explore in more detail some of the results attained from individual examinations. The system can search a thousand records in 40 minutes.

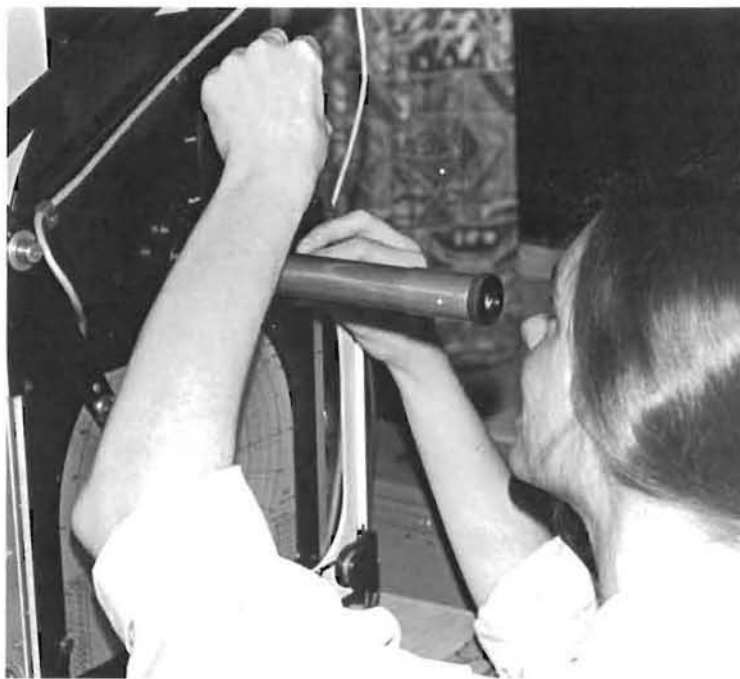
**F**or visual field data to be retrievable efficiently, a means was needed for detecting and extracting from the data specific features thought to be characteristic of patterns of glaucomatous visual field loss. The data base had to be made

accessible to search for individual records containing the defects of interest. Rather than relying on interpretive verbal descriptions, a completely generalized method was developed. Said Hart, "This approach gives us the flexibility to define or redefine, and to search for, any type of visual field defect or combinations of defects. It also gives us the objectivity inherent in the necessarily rigid criteria defining the objects of the search."

First, a set of seven primitive-level features was defined and used to encode and distinguish individual levels of sensitivity, such as the isotopers or contours on a two-dimensional kinetic visual field test. After deriving these primitive features, each resulting contour



*As the patient peers into the Goldmann Perimeter, the perimetrist operates the controls on the back of the device.*



was examined for the presence of any of six intermediate-level features. Logical combinations of primitive-level and intermediate-level features were then used to derive any of a set of thirteen higher level features. These were separately determined for non-defective or defective contours and varied from nonspecific features to those more specific for glaucomatous visual field loss. The computer could then be commanded to search the data from recorded examinations for instances of a specific type of visual field defect contained in any of the higher-level features.

**A**fter devising the computer programs, in cooperation with Ross Hartz of the University's Biomedical Computer Laboratory, which encoded the Goldmann perimeter values and produced the two-dimensional display, Hart began work to improve the system by achieving more flexible analyses and improved visual display. "What we often need

to know about an individual's visual field," Hart said, "is not along a single line or along a single circular contour, but rather involved examination of a whole contiguous area of the visual field. One of the more recent developments in the use of our system has been to exploit the capacity of the computer to produce high quality graphic images obtained from these visual fields in such a way that we can examine the field in a fashion that was not previously practical. This involves looking at the data as if it represented a three-dimensional construct. The computer is quite capable of producing this three-dimensional image so that the topography or shape of the data can be immediately appreciated by the examiner."

In the display of visual field examination data, Hart's computer now simulates dimension while solving the problems inherent in managing all three variables of the static visual field test. (There are two variables for position and one for threshold.) Both

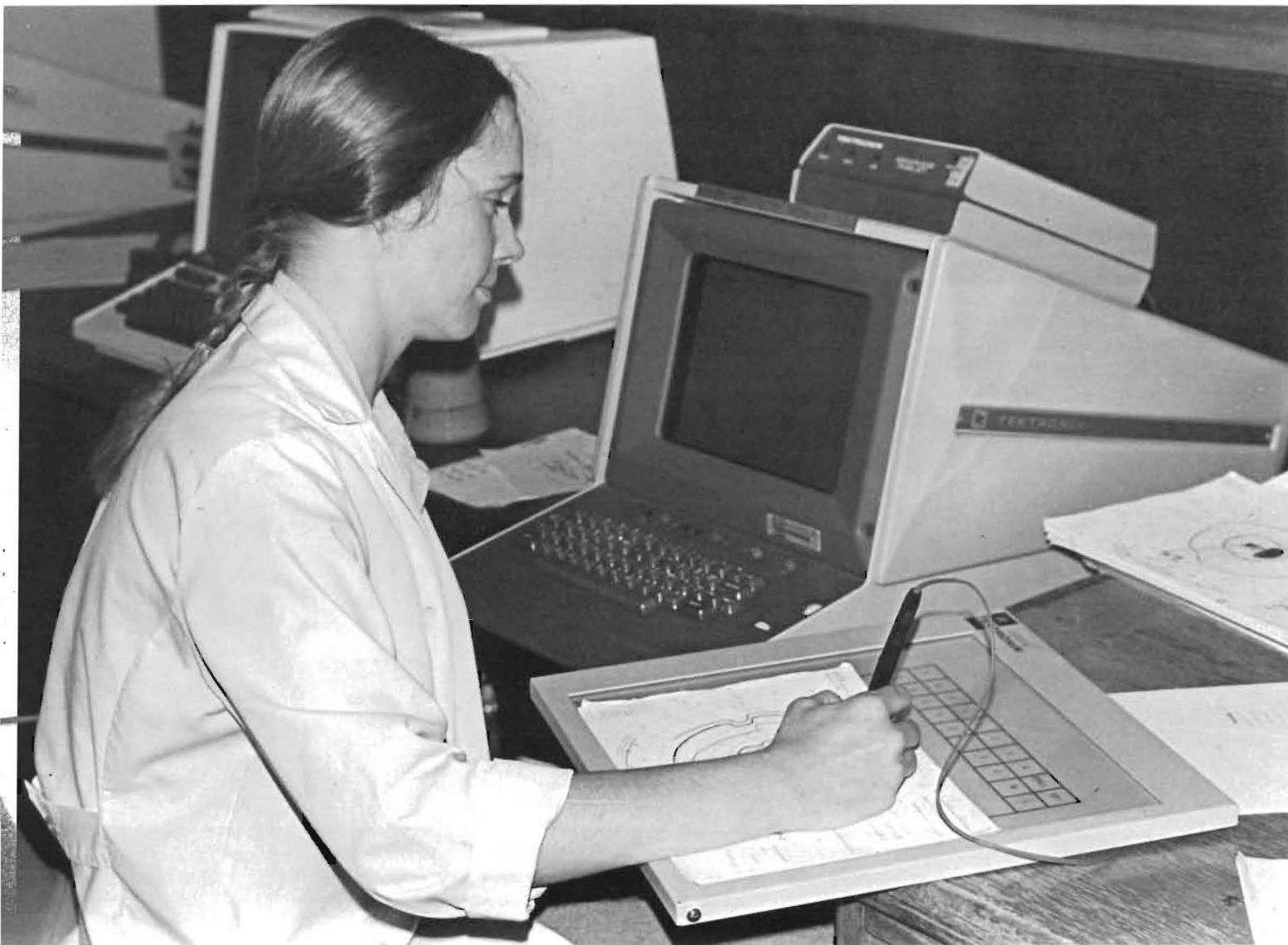
the detectability and the resolution of visual field defects are improved when the test area is blanketed by evenly spaced grids of points. This grid makes it possible to use targets to test contiguous areas of the visual field at small angular separations — down to 1.0 degrees if necessary. In order to display the data in an intuitively understandable format, raw data points representing the many points of the visual threshold are used to indicate the contour of a three-dimensional surface, which is then drawn in two dimensions. The illusion of depth is achieved by superimposing foreground elements over those in the background. The surface consists of 1,250 points arrayed as a series of 25 lines, each containing 50 points connected by straight line segments. The square surface of the display screen is matched in size and position to the pattern of raw data points. Imaging employs a "hidden line removal algorithm" which suppresses parts of the lines so that elements of the surface that should not be visible appear to be hidden. A second, smoothing algorithm is used to eliminate the rough edges produced by the lines being generated between raw data points. The result is a display surface that is smoothed while being constrained in position and shape by the raw data points. Because sharp elevations or depressions, or other irregularities in the display surface, can cause substantial portions of the image to lie in the "hidden" area, an interactive rotation algorithm has also been used to allow simultaneous inspection of the data from two opposite directions. This three-dimensional display allows for more finely detailed mapping of abnormalities in all dimensions for determining the degree of abnormality and the location of the abnormality in the visual field.

**A**s with any software design, improvement is a constant undertaking. Improved speed of operation and detection of specificity are the primary goals. Said Hart, "Specificity is by far the most important objective and it refers to the identification of defects contained in the higher level features in a manner that closely mimics the way a human observer would describe them. To forestall incorrect diagnoses which might originate from two similar patterns, such as a specific glaucomatous defect versus an innocent but apparently similar effect," Hart explained, "requires that the computer identify critical features of shape, size or position that can then be used to make a distinction between the two patterns."

**T**he next logical step in the development of the system is dissemination to clinicians in private practice. However, two major stumbling blocks currently prohibit this use. As Hart explained, "While costs of computer technology have been reduced considerably in the past decade, they still remain substantial. Combined equipment costs for our system amount to approximately \$75,000 to \$100,000. Additional costs of development time, and the skills necessary to design and operate the increasingly complex programs which will perform more elaborate analysis will limit application of these techniques to research-oriented institutional practices with large patient populations. We anticipate, however," Hart continued, "that commercial development of suitable graphic systems for clinical practice will be available in the future." While a widespread practical application may be years away, the present research points to a tantalizing future. ■



*William Hart, Jr., M.D., Ph.D., Assistant Professor of Ophthalmology.*



*Data entry and retrieval can be accomplished using the keyboard and display screen and the magnetic graphics tablet at the lower right.*

# A Celebration of Auscultation



## LAENNEC inventeur de l'auscultation 1781 - 1826

MAIRIE ANNEXE DU VI<sup>e</sup> ARRONDISSEMENT  
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MAIRIE DE PARIS

*"Every physician throughout the world  
who auscultates any part whatsoever of  
a human being is, by this act alone, a  
disciple of Laennec."*

*(Letulle)*

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A poster, showing Laennec using his stethoscope, announced an exhibition in his honor this past winter, sponsored by the Mayor of Paris.

# The Bicentennial of Laennec's Birth, Paris 1981

by Marion Hunt

**A**uscultation, according to the Oxford English Dictionary, comes from the Latin verb "auscultare," to hear with attention. In medicine, it is the act of listening with the ear or stethoscope to the sound of the movement of heart, lungs, or other organs, in order to judge the condition of health or disease. While Hippocrates himself was the first to describe the use of auscultation in medicine, his observations were largely ignored by later generations of physicians. The man who gave new meaning to this term, and to the use of this technique in modern medicine — René Theophile Hyacinthe Laennec — was honored in ceremonies throughout France and particularly in Paris this winter.

Born in 1781 at Quimper, in Brittany, Laennec was raised by an uncle who was himself a physician and professor of medicine. He arrived in Paris in 1801 to begin his formal medical studies. Soon recognized as a brilliant student, he prepared more than 400 case histories in his last three years of training and gained the first prizes in both medicine and surgery. Forced by economic circumstances to enter private practice in 1804, Laennec did not have a hospital appointment until 1816 when he became physician at l'Hôpital Necker. That very year he improvised a new instrument — the stethoscope — to diagnose diseases of the heart and lungs.

Though medical technology has given physicians many new tools since then, the stethoscope remains a basic instrument, auscultation a basic diagnostic procedure. Laennec's term "râle" (from the French, râler: to rattle) entered English because of his careful description of the sounds his new instrument



made accessible. "For want," he wrote, "of a better or more generic term, I use the word *râle* . . . to express all the sounds, besides those of health, which the act of respiration occasions."

**D**espite his remarkable achievements, Laennec's name — unlike the instrument he invented — is little known. In Paris, there is a hospital devoted to pulmonary diseases which still bears his name, and his stern visage may be seen in a small park on the Boulevard St. Germain as well as in the

courtyard of the Collège de France — where he served as professor of practical medicine from 1822 until his death in 1826.

The French have a special passion for their nation's history; honoring those who have made France great is a high art — centennials and multicentennials are done with style. Laennec's anniversary is no exception to this rule. Though the celebration is a year long and national in scope, the day-long colloquium held at the Collège de France in his honor had particular meaning because of Laennec's connection with this unique institution.

*A memorial tablet outside the hospital in which Laennec first performed mediate auscultation; the institution is now called L'Hôpital Laennec and specializes in the treatment of pulmonary disorders.*

**F**ounded in 1530 by François I, the Collège de France has served for more than 450 years as the site of innovative research and free public instruction. Originally called the "College of Four Languages" because of its emphasis on Greek, Hebrew, and Arabic, it now has fifty-two chairs in disciplines ranging from art history and archaeology to international law and cellular genetics. Medicine has been taught here for over 400 years. Many of France's most distinguished scholars have served as its faculty, a tradition which continues to this day. The present occupant of the chair of experimental medicine, which succeeded the chair of practical medicine occupied by Laennec and Claude Bernard, is Professor Jean Dausset, who received the Nobel prize for his medical research in 1980. The Collège's motto "Docet Omnia" refers to the fact that since the 16th century, each professor has been required to give an annual series of free public lectures. There are no students in this remarkable college, other than those who choose to attend. While the King himself used to make appointments to the Collège, it is now a national institution; the faculty elects its members. The specific mission of a professor at the Collège is that of research and the teaching of that research; his or her course program must be new each year. (The first woman professor was elected in 1972.) Distinguished visiting professors from other countries are invited each year to

A bas-relief of Laennec in a small park off the Boulevard St. Germain; his innovations there are noted in the background.



The front gate of the Collège de France, where Laennec held a chair from 1822 to 1826; the statue is of Claude Bernard, also a professor there, often called the "father of experimental medicine."



give lectures; thus the Collège de France maintains an international outlook.

Because Laennec was a son of France and a member of the Collège's faculty, the colloquium held in his honor was an exceptional occasion. Scholars and physicians from several countries participated; appropriately, the opening discourses were given by two professors from the Collège itself: Yves Laporte, professor of neurophysiology (a former postdoctoral fellow of George Bishop at WUMS) and Jean Dausset, professor of ex-

perimental medicine. Each participant spoke of the importance of Laennec's work to modern medical research and practice. Laporte recalled his own medical training during the second World War when the most senior physicians were in charge of teaching students: "We passed quite naturally from the hospital rooms to the amphitheatres of dissection. There is no doubt that the anatomo-clinical method, more than a century after its birth, represented again for many hospital physicians the sole solid base of medicine."

Medical historians agree on the importance of Laennec's work to the practice of modern medicine. In the 17th and 18th centuries, physicians had to rely largely on visual and verbal means to make their diagnoses; they observed the patient and listened to his or her complaints. New manual techniques such as percussion were developed in the 18th century to supplement these findings. Laennec's contribution in the early 19th century was seminal; as one historian has remarked: "The effects of the stethoscope on physicians were analogous to the effect of print on Western culture . . . auscultation helped to create the objective physician, who could move away from involvement with the patients' experiences and sensations, to a more detached relationship, less with the patient but more with the sounds from within the body . . . Laennec devised a method in which nonverbal sounds became the signals of diseases and a new instrument, the stethoscope, became essential to broadcast their presence . . ."

Stanley Joel Reiser, *Medicine and the Reign of Technology*, Cambridge University Press, 1978

This was no mere technological change, but a basic transformation of medical practice. Diagnostic judgments could henceforth be made on objective, as well as subjective, criteria. To patient symptoms and physician observations were added objective evidence such as the sounds Laennec described as characteristic of heart and lung disease.

Laennec's findings were based on the use of a new instrument, the stethoscope (from the Greek "stethos" for chest and "skopein" to examine); they were contained in his exhaustive 928-page treatise, *On Mediate Aus-*

*cultation and the Diseases of the Heart and Lungs*. The stethoscope was the mediating instrument between the patient's body and the physician's ear. Previously, physicians had to apply their ears directly to the patient's chest. Given the modesty of most female patients and the limitations of hospital hygiene, the stethoscope was of immediate practical, as well as diagnostic, use. It preserved a sense of propriety and kept the doctor at some distance — while allowing him improved access to internal body sounds. In 1816 Laennec described his first examination performed with the new instrument: "The age and sex of the patient forbade me the direct application of the ear to the precordial region. I then remembered a well-known acoustic phenomenon . . . if one puts his ear at the end of a beam, he hears quite distinctly a needle scratching the other end. I took a blue book, formed a tight cylinder of it, put one end to the precordial region, and the other to my ear. And to my great surprise and satisfaction, I heard the sounds of the heart much more clearly and distinctly than I had ever done by applying my ear directly. I then presumed that this method could be useful not only in the study of the heart, but in examining respiration, voice, and rattles, and perhaps even the fluctuation of liquids in the pleural and pericardial cavities . . ."

With typical modesty Laennec wrote, "At first I did not feel it was necessary to give a name to such a simple instrument." Others disagreed, and he chose the name we know today.

In the years after 1816 he continued to refine his invention and his descriptions of diagnostic findings; he differentiated a variety of ailments including pneumothorax, hemorrhagic pleurisy, pulmonary gangrene, infarct, and

# TRAITÉ DE L'AUSCULTATION MÉDIATE

ET DES MALADIES  
DES POUMONS ET DU COEUR,

PAR R.-T.-H. LAENNEC,

Médecin de S. A. R. MADAME duchesse de BERRY, Lecteur et Professeur royal en Médecine au Collège de France, Professeur de Clinique à la Faculté de Médecine de Paris, Membre de l'Académie royale de Médecine, des Sociétés de Médecine de Stockholm, Bonn, Liège, et de plusieurs autres Sociétés savantes nationales et étrangères, Chevalier de l'ordre royal de la Légion-d'Honneur, etc.

Μεγά δὲ μέρος ἡγεῖσθαι τῆς τέχνης  
εἶναι τὸ δύνασθαι σκοπεῖν.

Pouvoir explorer est, à mon avis, une  
grande partie de l'art. Hipp., Epid. iii.

SECONDE ÉDITION ENTièrement REFONDUE.

**TOME PREMIER.**

**Paris,**

J.-S. CHAUDE, LIBRAIRE-ÉDITEUR,

RUE DE LA HARPE, n° 56.

1826.

emphysema. As his great contemporary, Broussais, remarked, Laennec used the instrument with such facility that "it seemed he had been in the very interior of the body and of its ailments." But not all physicians were able to use the new instrument with such success. Some continued to support earlier techniques; others were suspicious of the new instrument and disliked giving up familiar procedures. They questioned the value of precise physical diagnosis, given the limited nature of medical therapeutics. They feared the pronouncement of an incurable disease after auscultation would make both physician and patient lose hope. The stethoscope's supporters argued no less vehemently that more exact diagnosis would

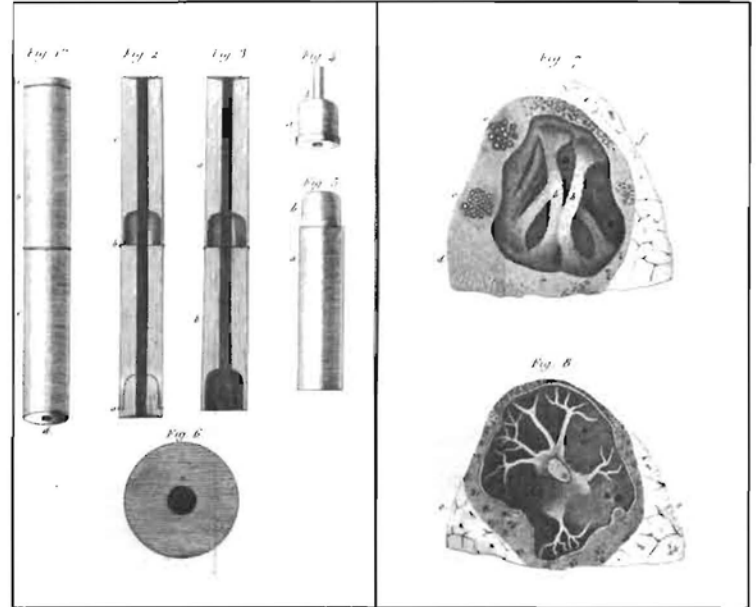
make vigorous and effective treatment more likely.

So heated was the debate over the stethoscope in the early 19th century that Oliver Wendell Holmes, professor of anatomy at Harvard, made the over-enthusiastic advocate of auscultation the subject of a satirical poem in which a young physician, recently returned from study in Paris, is deceived into false diagnoses by insects nesting in the instrument. He drew this moral:

*Now use your ears, all you  
that can  
But don't forget to mind  
your eyes,  
Or you may be cheated, like  
this young man,*

Title page from the 2nd edition (1826) of Laennec's *Treatise*, quoting an epigram from Hippocrates in Greek and French. ("To be able to explore in my opinion is a great part of the art.")

Two plates from Laennec's 1826 edition, showing a diagram of his stethoscope and cross sections of the heart.



*By a couple of silly,  
abnormal flies.*

Laennec refined his invention in the years after 1816 and manufactured several versions himself. His instrument was a wooden cylinder, 16 mm. in diameter and one foot in length; its shortness and rigidity required both patient and doctor to change positions frequently. By 1829 the first flexible monaural stethoscope was made in Edinburgh. While a binaural version appeared in 1851, it did not entirely replace the earlier monaural model in general use until the 1890s. Thus, the stethoscope was to become symbolic of latter-day physicians just as the urine glass had once been of the medieval physician. It is a basic piece of medical equipment which no health care professional can afford to do without. Laennec would no doubt be surprised to learn that the best current model of his invention now sells for nearly \$100. While patient reaction to the new instrument was mixed (some feared it as the prelude to a surgical operation), its popular success was such that by

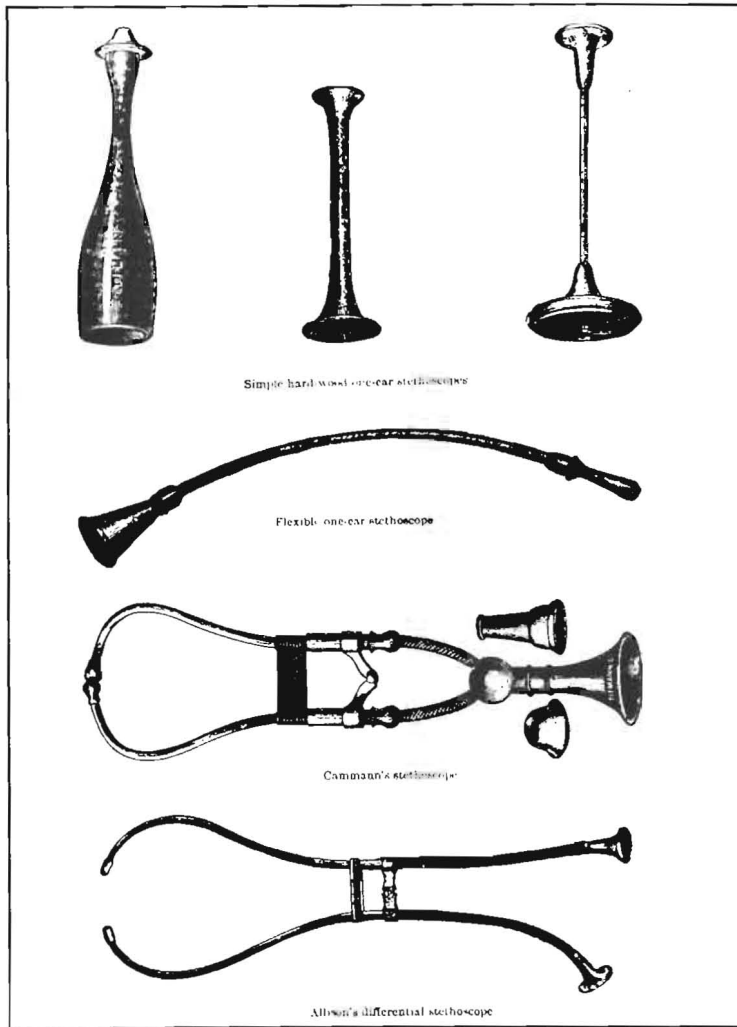
the 1830s doctors who refused to use it put their professional reputations in doubt. As today, incorporating the instrument into their daily dress was something of a problem; in the 19th century some physicians wore a stethoscope in their top hats.

Laennec's brilliant achievement was not an isolated phenomenon but part of the flowering of a remarkable period in French medicine (from about 1790 to 1850) which made Paris a magnet for foreign medical students. Born out of political and intellectual revolution, the Paris School represented a whole epoch in medicine; its central element was the hospital. This new hospital medicine (as opposed to earlier bedside medicine or modern laboratory medicine) was based on fresh ideas many of which have a distinctly modern ring. Public health measures, statistics, specialization, thorough physical examinations and frequent autopsies were its hallmarks. The correlation of clinical findings with those at autopsy

A characteristic shop on the Rue de L'Ecole de Médecine advertising "didactic material since 1822" — the year Laennec took his chair at the Collège de France.



A selection of 19th century stethoscopes reprinted from an 1880 handbook of physical diagnoses.



were characteristic of the French school's passionate interest in "anatomie-pathologique" or the anatomo-clinical method. The hospital became the center of this research and of a new kind of medical education. No other European city could rival the number of hospitals in Paris.

After the French Revolution, old hospitals were enlarged and improved; new, smaller hospitals oriented towards certain specialties were founded. The hospital's particular mission as a medical institution was separated from its older function as a prison or hospice. By Laennec's time a

number of Paris hospitals were identified with specialty practice: La Salpêtrière with psychiatry, the Saint Louis with dermatology, the Necker (where he first used the stethoscope) with chest diseases. In 1802, l'Hôpital des Enfants Malades became the first modern children's hospital in the world, a place where clinical care was refined by new ideas and methods. Nor were the elderly neglected; as early as 1833 a note "On the Conditions Necessary for Hospitals for People of over 60" was published in the *Annals of Public Hygiene*.

It was in the crucible of the Paris hospital that Laennec invented, applied, and refined the stethoscope and the technique of auscultation. In the three years between his first use of the instrument in 1816 and his publication of the treatise *On Mediate Auscultation* in 1819, he used it extensively on patients suffering from diseases of the heart and lungs, making careful notes on the distinctive sounds he heard. More important, he correlated them as frequently as possible with findings at autopsy. This wealth of data was contained in 928 pages of his book. The first 200 pages were devoted to his observations on pulmonary tuberculosis; so accurate were they that little can be added to what Laennec described 160 years ago.

Yet Laennec's work was better received abroad than in his homeland. This was in large part due to his conservative religious and political convictions, highly unpopular with medical colleagues and students. So many foreigners flocked to his Paris lectures that he had to give them in Latin. His great treatise on auscultation was available in English by 1821 in a translation by Sir John Forbes. It was much abridged from its original 928 pages; Forbes himself wrote to Laennec about this in 1823:

"My apologies for the great liberties which I have taken with the manner and matter of your treatise. The only substantive reason I can offer is the conviction . . . that a simple translation of so voluminous a work would not have met with any encouragement in this country and, if attempted, therefore, would have frustrated the great and important object of making your immortal work known to the great body of British practitioners . . ."

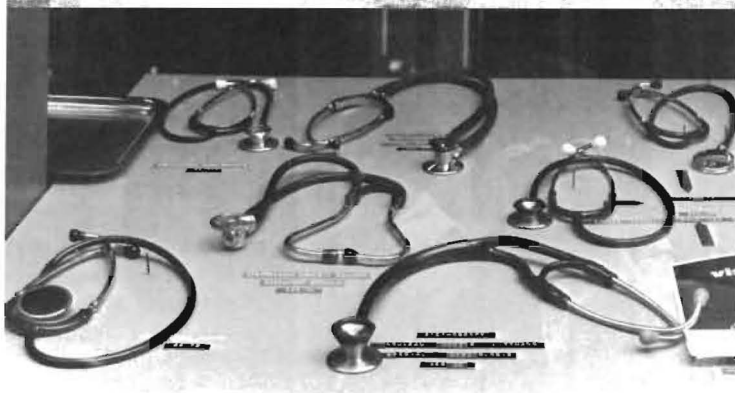
Laennec's fragile health suffered from his devotion to

teaching, writing, research, and clinical care. On completing the first edition of his book in 1819, he had to retire for several years to his family's estate in Brittany. Laennec later wrote: "I know that I risked my life, but the book I am going to publish will be, I hope, useful enough sooner or later to be of more value than the life of a man."

He had become a victim of the very disease he had so well described: pulmonary tuberculosis. In 1822 he returned to Paris and became professor of clinical medicine at the Charité Hospital, professor of practical medicine at the Collège de France, and physician to the Crown Princess, the Duchesse de Berry. It is ironic to note that despite all Laennec's careful study of tuberculosis, its contagious nature had not yet been firmly established. Thus, a distinguished physician suffering from the disease was appointed to treat the French royal family. Laennec himself denied that it was contagious, though he described his own infection while performing an autopsy.

On April 1, 1826, he finished the second edition of this *Treatise on Auscultation*; on August 13th of that year he died at the age of 46. Far more important than his invention of the stethoscope or his remarkable clinical observations was the fact that they laid the basis for a new kind of medical practice. Last February *Le Monde*, the leading newspaper of France, summarized his work in a simple sentence: "He placed clinical medicine, for the first time, at the level of an objective and rigorous science." ■

A typical window display on the Rue de L'École de Médecine, showing modern models of Laennec's invention.



The corner of the "Street of the School of Medicine" (Rue de L'École de Médecine), Paris, where the main Faculty of Medicine is located.



The imposing gates of the Salpêtrière, where Laennec attended patients in 1814; it is still one of the major hospitals in Paris.



# Research Update: Raising the Ceiling on Growth



by Casey Croy



**W**ashington University School of Medicine, for nearly 25 years one of America's leading centers in the study and treatment of growth disorders in children, has just begun testing a new synthetic growth hormone. WUMS is one of ten medical centers in the U.S. to test the hormone, which is produced by recombinant DNA technology at the Genentech Company in San Francisco. The synthetic hormone had previously been tested for efficacy and toxicity in animals, and for toxicity in healthy, normal adult volunteers. The current tests will determine if the synthetic hormone succeeds in inducing growth in growth hormone deficient (GHD) youngsters. Principal investigator in the study is Sandra L. Blethen, M.D., Ph.D., assistant professor of pediatrics and St. Louis Children's Hospital physician. If the tests are successful, the new synthetic growth hormone promises to increase dramatically the supply of growth hormone and, eventually, to lower the cost of therapy.

Human growth hormone is one of many hormones which regulate growth, including thyroxine, cortisol and adrenal androgens, testosterone, estrogen and insulin. Human growth hormone is one of several hormones secreted by the pituitary gland. Growth hormone deficiency (GHD) is only one cause of short stature. While most cases of GHD are of unknown origin, it may be caused by an injury at birth requiring resuscitation or oxygen, or, less commonly, it may be inherited. Idiopathic GHD is four times more common in boys than in girls. Studies indicate a possible link between breech births and GHD, and some researchers suspect that fetal GHD may cause the breech position. Other causes of short stature, in addition to GHD, include chromo-

some disorders, bone disease or other serious disease, malnutrition or malabsorption of food, or metabolic imbalances leading to dwarfism. A variety of tests are used to determine the exact cause of short stature. In the 1970's, Virginia V. Weldon, currently professor of pediatrics and assistant vice chancellor for medical affairs, developed and refined a test, using arginine and L-dopa, which identifies growth hormone deficiency.

Unlike some children who suffer from severe short stature, GHD children are usually healthy, of normal intelligence and proportions, and are sometimes chubby. Frequently their poor growth goes unnoticed until a younger sibling surpasses them in height or until they attend school and can be compared with their peers. In some cases, a child's deficient growth becomes apparent earlier if the child shows signs of hypoglycemia. Hypoglycemia indicates deficiency in the hormone ACTH and in growth hormone as well. Parents and physicians should suspect a medical problem for any child in the lowest two percent of height for his or her age group.

**L**eft untreated, a GHD child will attain a height of only four feet, six inches. In the past, treatments consisted of three intramuscular injections per week of human growth hormone extracted from the pituitary glands of cadavers. Much of the early work leading to growth hormone therapy was accomplished at Washington University and St. Louis Children's Hospital. By the 1950's it had been discovered that an extract from human pituitary glands stimulated growth in GHD children, although the mechanisms of that stimulation were not completely understood. In 1957, William H. Daughaday, M.D., Director of

the Metabolism Division and Professor of Medicine, with a research fellow, William Salmon, M.D., found a substance in human serum which facilitated incorporation of  $SO_4$  into epiphyseal cartilage which is part of the process leading to skeletal growth. Daughaday and Salmon called the substance "sulfation factor." Their research indicated that HGH does not act directly on cells or tissue, but acts through the sulfation factor. Subsequent research built on that foundation and identified the sulfation factor as a peptide found in quantity in plasma. Later, the peptide was traced to its point of origin, the liver. In 1972, Daughaday and other researchers suggested that the peptide be named "somatomedin," or mediator of somatotropin, the growth hormone which acts on cartilage.

**O**nly human growth hormone will work in humans, although other hormones derived from animals, such as ACTH and insulin, are effective in treating people. The obvious difficulties in acquiring human pituitary glands — from 80 to a hundred or more were required to treat one child for one year — limited treatment in the past. The general rule was that children would be treated, sometimes intermittently rather than weekly, until they attained a height of five feet. The National Pituitary Agency, which Daughaday helped establish, was the central agency for collecting pituitaries, processing them and distributing the extract to medical centers in the U.S.

Until the new recombinant DNA technique was applied by scientists at Genentech, human growth hormone could not be synthesized. Natural growth hormone consists of 191 amino acids and was considered to be too large and complex a molecule to

synthesize affordably. Now, however, the DNA of a human growth hormone cell is spliced into a common bacteria, *E coli*, which is found in the human intestinal tract. After the splice, about one percent of the protein which the bacteria produces is synthetic human growth hormone. The synthetic hormone is then purified in Genentech's biochemical laboratories and made available to clinical investigators for their patients. The promise of the new synthetic growth hormone is a bountiful supply from which children will receive continuous therapy until they achieve all of their potential growth.

**T**he synthetic growth hormone acts exactly like the natural human growth hormone secreted by the pituitary. The pituitary secretes growth hormone intermittently during a 24-hour period, and at a peak approximately an hour to an hour and a half after the person is asleep. Sometimes growth hormone is secreted in response to exercise or to anxiety, although too much stress can prevent secretion. The peak-level secretion of HGH triggers production of enough somatomedin to raise the blood levels of it for 24 hours, providing a constant supply to cartilage cells at the ends of the bones.

GHD children usually have, in addition to short stature, delayed skeletal maturity and delayed puberty. For example, a 14-year-old GHD boy might have the skeletal maturity of a normal eight year old. While normal 14 year olds are entering puberty, a GHD child of the same age is far from it. Normal boys, on the average, have attained their full growth by the age of 17 or 18. But even a 16-year-old boy has more than a year to receive growth hormone therapy because of slower skeletal matu-



*Sandra Blethen, M.D., Ph.D. prepares the first injection of synthetic hormone for the testing program.*

rity rate and delayed puberty. During the first year of growth hormone therapy, patients can experience up to four or five inches of growth, called "catch-up" growth. During subsequent years, growth is continuous and accelerated, but less spectacular. During growth hormone therapy, the rate of skeletal maturity increases, and puberty approaches more rapidly. Growth can continue until the production of sex hormones at puberty finally eliminates the growth plates.

The Growth Clinic in St. Louis Children's Hospital has successfully treated hundreds of HGH-deficient children, and cur-

rently has 60 patients receiving conventional human growth hormone therapy. The synthetic growth hormone testing program began in November with one patient, a four-year-old boy who is 33 inches tall. Patients for the testing program must be previously untreated for their GHD, although no adverse affects are anticipated in changing a patient from natural to synthetic growth hormone. "We can accept many more new patients for the test program," Blethen reported. "I'm looking for all the hypopituitary cases I can find." Blethen is also planning a major study of the effects of synthetic growth hor-

none therapy on children of short stature due to other than HGH deficiency. Washington University Medical Center is one of the first to describe children who may make biologically inactive growth hormone. These children show normal or high levels of growth hormone but low levels of somatomedin. Under old criteria, they would have been excluded from growth hormone therapy. Blethen and other researchers are continually alert to the possibility that certain very short children may respond to growth hormone therapy although they do not meet the usual criteria. ■

# The Alumni Report

Washington University  
Medical Center  
Alumni Association

## '30s

**I.D. Newmark, M.D., '30s**, was honored upon his retirement as Chief of Medical Staff of Memorial Hospital in Chester, Illinois and as co-founder of the town's first hospital. As a gesture of appreciation, Newmark was named Honorary Mayor of the City of Chester for a day. During his 48 years of medical service to Chester, he also served as physician for Illinois Security Hospital (Chester Mental Health Center). Newmark and his wife plan to move to St. Louis in the near future.

**Harry B. Stauffer, M.D., '31**, has been breeding and selling Simmental cattle since his retirement in 1971. He still lives in Jefferson City, Mo., and owns a ranch, the Two Bar, in Chase County, Kansas.

**Robert Elliott, M.D., '36**, toured China in 1979, inspecting hospitals, medical schools and clinics, and visiting historical sites in China. He toured with a group of American College of Physicians. In 1980, he went to Hamburg, Germany to attend a conference of the International Society of Internal Medicine, and went on a North Cape cruise.

**D. Elliott Ursin, M.D., '36**, received the Distinguished Service Medal upon his retirement from the United States Army in 1970, after 33 years of service as an army medical officer. Since retirement, he has been working part-time in a mental health clinic near his home in San Antonio, Texas.

**James F. Nolan, M.D., '38**, was honored upon his retirement as medical director of the cancer program at California Hospital Medical Center and the Southern California Cancer Center (an affiliate of the hospital) since 1972. A member of both the California Hospital Medical Staff and the University of Southern California School of Medicine clinical faculty for 33 years, Nolan is now emeritus clinical professor of obstetrics and gynecology, and of radiology, at USC. Nolan completed his residency in gynecology at St. Louis Maternity Hospital and was a Special Fellow at the National Cancer Institute, Memorial Hospital, New York. His specialty is gynecological malignancies.

During his long and successful career, Nolan worked with the development of the first atomic bomb, was consultant to the Radiation Committee of the American College of Obstetricians and Gynecologists, the Advisory Council for Gynecology and Obstetrics of the American College of Surgeons, and the Advisory Committee for the California Tumor Registry. Nolan and his wife, Jane, will continue living in Laguna Hills, California.

## '40s

**Sydney T. Wright, M.D., '40**, recently retired as Selma, California's longest-practicing physician. He and wife, Wyn, plan to travel and return to school in their retirement.

**Parker R. Beamer, M.D., '43**, was named associate pathologist and director of the pathology resident training program at West Suburban Hospital, Franklin Park, Illinois. He is a life trustee of the American Board of Pathology and emeritus professor at University of Chicago Medical School.

**Mary D. Bubliss, '46**, received a Texas Panhandle Distinguished Service Award last year from Texas State University. She practices privately and is also associate clinical professor of Psychiatry at Texas Technical University School of Medicine in Lubbock, Texas.

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Alumni Association

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Fred D. Peterson, M.D., President

The alumni office is located in  
room 107 of Wohl Hospital.

## Letters

### Correct Errors

George J. Hill, II, M.D., wrote in response to the Summer 1981 OUTLOOK:

"I would call your attention to an error on p.23 that perpetuates the myth of Charles Best and the Nobel Prize, which he should have, but did not receive. Banting and Macleod won the prize (1923); Banting publicly acknowledged Best's contribution and shared the prize money with Best. The prize, itself, was not Banting's to share since the Prize Committee is the sole judge of recipients."

Hill and his wife, Helene, have moved from West Virginia to West Orange, New Jersey.

*(OUTLOOK welcomes letters from readers. If there is sufficient response from readers, we will begin a "Letters" feature.)*

Paul J. Goodnick, M.D., wrote that he delivered a paper, "Diagnostic Differences in Lithium Kinetics" at the American Psychiatric Association meeting in New Orleans. The last issue of OUTLOOK reported incorrectly that Andrew L. Carney had delivered the paper.

Goodnick reported that he has also delivered papers at the World Congress of Biological Psychiatry in Stockholm in June, and at the International Congress of Gerontology in Hamburg in July of 1981. Goodnick is now Director of the Affective Disorders Clinic of the Illinois State Psychiatric Institute and will be joining the faculty of the Department of Psychiatry at the University of Chicago. He had been at Wayne State University in Michigan.

## '50s

**M. John Epp, M.D.**, '50s, is director of the Ladies Center of Nebraska in Omaha. The clinic is a full-service women's medical center specializing in pregnancy counseling and responsible parenthood advocacy.

**Joe Le Blanc, M.D.**, '56, is medical director for Phillips Petroleum. In 1981, he completed a trip around the world for Phillips, visiting the Phillipines, Indonesia, Singapore, Bombay, and other "far-away places with strange-sounding names." He and Shirley live in Bartlesville, Oklahoma.

**William F. Hejna, M.D.**, '58, is the new chairman of the Board of Trustees of the ANCHOR Organization for Health Maintenance at Rush-Presbyterian-St. Luke's Medical Center in Chicago, Illinois. Dr. Hejna, Senior Vice President of the Medical Center, is also a professor of surgery at Rush Medical College and a senior attending surgeon in the Department of Orthopedic Surgery. Formed 10 years ago, ANCHOR is an alternative health care system which combines "group practice" with pre-payment financing. This organization sponsors programs to lose weight, stop smoking and control hypertension in addition to regular outpatient services. A staff of 40 physicians works under the auspices of ANCHOR to provide health care in six medical facilities in Chicago and its outlying suburbs.

## '60s

**Drs. Ronald and Elizabeth Sowa, M.D.**, '63, have recently received appointments at the Evansville Center for Medical Education in Indiana University's School of Medicine. Ronald Sowa has been named a clinical instructor in Orthopedic Surgery and an adjunct instructor in Anatomy, while his wife, Elizabeth Sowa, has been named a clinical instructor in Ophthalmology.

**Captain John R. Fletcher, M.D.**, '64, was awarded the distinguished Legion of Merit on June 11, 1981 for "exceptionally meritorious conduct in the performance of outstanding services" in the United States Navy Medical Corps. Formally presented to Capt. Fletcher by the Secretary of the Navy acting for the President, the Legion of Merit generally signifies the highest personal decoration given by the Navy in peacetime.

Capt. Fletcher received this award for organizing and directing a research program designed to improve the survival rate of combat casualties dying from septic shock. Induced by bacterial infection, septic shock had been long associated with a 60-80% mortality rate despite previous extensive research.

Initially, Fletcher based his research on a hypothetical relationship between prostaglandins and septic shock which had been suggested by animal studies but not confirmed by human clinical studies. In early experiments, he established the existence of high blood-prostaglandin levels in septic shock patients at the National Navy Medical Center. Insufficient in itself, this finding led Fletcher to develop an animal model duplicating the septic shock condition in humans. The animal model enabled him to establish a correlation between changes in hemodynamics (cardiac output, systemic blood pressure and pulmonary artery pressure) and plasma prostaglandin levels in the baboon.

Through subsequent experiments, Fletcher demonstrated that certain prostaglandin inhibitors successfully improved the survival of animals after the onset of septic shock. Such experimentation gave Fletcher the insight to speculate that stabilizing the cell membranes producing prostaglandins would achieve another means of preventing their cellular formation. A result of Fletcher's research was the identification of lidocaine, a widely used and clinically acceptable anesthetic compound, as a stabilizer of cell membranes capable of successfully improving the survival rate of baboons from 50 to 100 percent.

As an extension of his research, Fletcher organized a clinical trial comprised of American and foreign hospitals to test intravenous lidocaine as a treatment for septic shock. Each hospital now uses lidocaine in addition to its standard treatment for septic shock.

**B. Leonard Holman, M.D., '66**, is director of clinical nuclear medicine services at Brigham and Women's Hospitals in Boston and professor of radiology at Harvard Medical School.

**Larry A. Schafer, M.D., '66**, is presently clinical instructor in the Department of Medicine at the University of Colorado Health Sciences Center. He specializes in medical oncology and infectious diseases, and is also in private practice. In 1976, he was one of ten Americans who went to Russia for a week's exchange of research information in cancer immunology.

**James P. McCulley, M.D., '68**, has been named professor and chairman of the Department of Ophthalmology at The University of Texas Health Science Center in Dallas, Texas. As head of Ophthalmology, McCulley has done extensive research in the area of corneal transplantation and his collaborative work with a group of Stanford researchers on corneal endothelial transplantation has been cited in the *Journal of the American Medical Association*, (JAMA), as one of the most exciting ophthalmology research developments of the eighties.

According to McCulley, it might be possible in certain corneal diseases to transplant the endothelial layer (which prevents the eye from swelling) rather than the standard eye bank cornea. Some of the many potential advantages to this approach include a greater availability of donor tissue and a decreased risk of subsequent rejection. In experiments with rabbits, McCulley has shown that a tissue-cultured corneal endothelium can regain normal structure and function when transplanted in the rabbit eye. To culture the corneal endothelium, McCulley explained that a transplantable gelatin membrane was developed to serve as a carrier for endothelial cells. The cellular membrane has been transplanted successfully in rabbits with good results and McCulley's researchers hope the technique can be developed ultimately for routine use in man.

After interning on the Harvard Medical Service, Boston City Hospital, McCulley completed a residency in Ophthalmology and two years of fellowship in corneal and external ocular diseases at Massachusetts Eye and Ear Infirmary, Harvard Medical School. He has written several publications and worked extensively in an advisory capacity with the National Eye Institute, a part of the National Institutes of Health. McCulley joined The University of Texas Health Science Center at Dallas last year as an associate professor.

## '70s

**Dennis Cooper, M.D., '71**, was guest lecturer at the 1981 Australian-New Zealand Ophthalmology Congress. He and his wife, Linda, live in Scottsdale, Arizona, where he is in private practice. He is active in astronomy, rock-hounding and intermittent dieting.

**Larry J. Shapiro, M.D., '71**, has been honored for outstanding research, receiving the Outstanding Investigator Award from the Western Society for Pediatrics Research. He also received an NIH career development award. Shapiro is associate professor of pediatrics, specializing in genetics, at the UCLA School of Medicine.

**Bob Seale, M.D., '72**, reports that his "biggest accomplishment" was finally getting married, to Audrey Jean Sheridan, in November 1980. He is in private practice in Seattle, Washington, started and played with a band called "The Iron Lung," is starting a computer business on the side, and worked for several years as Medical Director of the local Mountain Rescue Council.

**Marshall N. Cyrilin, '75**, has been appointed Director of Glaucoma Service and assistant professor of Ophthalmology at the University of Florida College of Medicine in Gainesville, Florida.

**Bruce A. Molitoris, M.D., '79**, has moved to Denver, Colorado. He is presently a renal fellow at the University of Colorado Health Sciences Center.

## Library Slide Show Available

Christopher Hoolihan, Rare Book Librarian at the Library Annex, now has a slide-illustrated lecture describing the rare book collection of the Medical Library. Forty-five slides show the primary figures involved in formation of the rare book collections (since 1912) and highlights from the rare book collections. Hoolihan invites inquiries about the illustrated lecture from departments and other groups within the Washington University Medical Center. Out-of-townners might be able to make special arrangements. For more information, contact Christopher Hoolihan, Medical Library, 4580 Scott Avenue, St. Louis, Mo., 63110. The phone number is (314) 454-3711.

## In Memoriam

- Morris Weiner, M.D., '19 .....  
date unknown
- Alton Ochsner, M.D., '20 .....  
September 24, 1981
- David M. Skilling, Jr., M.D., '28  
July 15, 1981
- Calvis S. Drayer, M.D. '31 .....  
May 2, 1981
- Lewis S. Ent, M.D., '31 .....  
August 14, 1981
- Garrett Pipkin, M.D., '30 .....  
August 14, 1981
- Albert Thomson Hume, M.D., '31  
October 25, 1981
- Louis Pellegrino, M.D., '32 .....  
May 29, 1981
- Robert Minton, M.D., '33 .....  
December 30, 1980
- William E. Patton, M.D., '34 ...  
February 15, 1981
- Edward J. Simon, M.D., '34 ...  
March 1981
- Col. Charles H. Talbott,  
M.D., '34 .....  
June 19, 1981
- Erwin S. Wallace, M.D., '35 ...  
August 25, 1981
- Robert D. Wright, M.D., '35 ...  
April 16, 1981
- Frank McDowell, M.D., '36 ....  
July 3, 1981
- Malvern T. Bryan, M.D., '38 ...  
September 8, 1981
- Donald A. Corgill, M.D., '39 ...  
September 15, 1981
- Allen H. Tigert, M.D., '39 .....  
May 4, 1981
- James K. Van Deventer,  
M.D., '39 .....  
March 3, 1981
- J.F. Henry, M.D., '41 .....  
April 1981

- Lucien I. Arditi, M.D., '54 .....  
April 13, 1981
- Frank R. Attridge, FHS .....  
June 9, 1981
- Harry Ballou, FHS .....  
April 7, 1981
- John C. Colbert, FHS .....  
December 31, 1980
- Warren Hempel, FHS .....  
April 18, 1981
- Joseph C. Hinsey, FHS .....  
March 25, 1981
- David N. McClure, FHS .....  
July 3, 1981
- David Pohlman, FHS .....  
December 19, 1979

## Deferred Giving Seminar Slated For March 13

The deferred Giving Committee of the University's Alumni Board of Governors will hold a daylong seminar on Saturday, March 13, 1982, in the Edison Theatre at the Mallinckrodt Center on the Hilltop campus. Led by outstanding experts in various fields of investment and money management, these annual seminars usually attract many alumni and friends. Complete details will be announced early in 1982.

### Hold That Tiger!

"While walking through the hippo house one day, I captured on film a snapshot of the world-renowned ferocious beast, *Felis Americana*," writes Richard M. Ratzan, M.D., formerly chief resident, internal medicine, at Jewish Hospital of St. Louis. Ratzan is now an internist working in the emergency room at John Dempsey Hospital of the University of Connecticut Health Center.

Alumni, alumnae, former house staff, students — you are all encouraged to send in your photographs for use on this page. Share your flair for beauty or your eye for the interesting or humorous with the 17,500 readers of OUTLOOK! Black-and-white prints or negatives, or color slides are all welcome. Slides and negatives will be returned. So will the prints if you request. Send your photos to Casey Croy, Editor, Outlook Magazine, 660 S. Euclid, Box 8065, St. Louis, Mo. 63110.





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