The Expansion Of Knowledge And The Limits Of Space:

by Marion Hunt

The Washington University School of Medicine Library is facing the consequences of the modern explosion in biomedical knowledge: it is running out of space, and at an ever increasing rate. The library’s collection doubled in size between 1960 and 1978 and can be expected to double again in a shorter interval if the current rates of information gathering, dissemination, and acquisition hold true. This library’s growth reflects the overall expansion of biomedical knowledge in the last three hundred years. Every century since 1750, the number of scientific periodicals has increased five-fold. By 1950, over 100,000 were published annually. Their number has continued to increase in the last thirty years, making retrieval of past information and keeping up with the current literature major tasks. No one library can possibly hold all the biomedical information now available. With the development of electronic storage and retrieval of information, the modern medical librarian has had to become expert in information management.

In addition to the space and information crises, the Medical School library is involved in a race against time. The high acid content of paper in books and journals printed in the last century has caused many of them to disintegrate. Deterioration has been hastened by conditions under which these volumes were, and to some extent still are, housed; exposure to dust, dampness and dirt hastens their destruction. Management of this triple threat, as well as the day-to-day administration of the library for the past two decades, has been the responsibility of Estelle Brodman, Ph.D., Librarian and Professor of the History of Medicine.

A graduate of Cornell, Brodman holds three advanced degrees from Columbia University in librarianship and the history of medicine, as well as an honorary D.Sc. which she received from the University of Illinois Medical Center in 1974. She came to St. Louis in 1961 from the National Library of Medicine where she served as head of the Reference Division. Edward Dempsey, M.D., then Dean of Washington University School of Medicine, invited Brodman to St. Louis with the understanding that she would teach medical history and carry on research, in addition to her responsibility for the administration and expansion of the medical library’s services. For twenty years Estelle Brodman has met this multiple charge; she will retire as Librarian of the Medical School in the spring of 1981. A search committee which includes Oliver Lowry, Ph.D., M.D.; Bernard Becker, M.D.; and Virginia Weldon, M.D., has been appointed to advise Dean King on a successor.

Brodman will be a tough act to follow. A pioneer in the use of computers in health sciences libraries, her dual training in librarianship and medical history has given her a sophisticated perspective on library development. Her twenty-year career here has brought this medical library to national prominence. Estelle Brodman has been recognized nationally and internationally as "a rare breed of both historian and automator." These roles might seem contradictory, but an interest in the history of medicine and in the most advanced methods of information management coexist comfortably in Brodman’s life and work. More sentimental souls have called the medical library, "the heart" of medical education. Ever pragmatic, she sees the medical library primarily as "a problem-solving device." Its value is not in its holdings per se, but in how efficiently those holdings can be brought to bear on a given medical or scientific problem. As she noted in a 1974 speech:

...medical libraries contain the recorded experiences of mankind in its attempt to study and take action on the problems of health and disease. Their goal is the desirable one of bringing the information gathered in the past to bear on the questions of the present and the future ...

Under Brodman’s leadership, and with the support of the medical school’s administration, the medical library has indeed produced knowledge through research, in addition to offering an ever-expanding array of services to faculty, students, and visitors from all over the world.

In particular, the last twenty years in the library’s development have seen the application of new computer-based systems for information management and access. Credit for this innovation goes in large part to Brodman’s reorganization of the library in the early 1960s. As her close colleague, Irwin Pizer, now Librarian at the University of Illinois Medical Center, has noted:

"Four of us from the National Library of Medicine joined her in the reorganization ... the first tasks were physical reorganization and initial remodeling ... then Dr. Brodman was instrumental in moving into the field of library automation .... By 1963 Washington University’s School of Medicine Library was in the forefront of library automation ...."

There has, in fact, probably been more research done on computer applications for health sciences libraries than at any other medical library except the National Library of Medicine. A complementary development was the training of librarians in these new techniques. A number of them, like Pizer, now have prominent positions in the profession.

This successful reorganization of the Washington University School of Medicine Library has brought Brodman numerous invitations to serve as an advisor to medical libraries across the country and around the world. She has served on the President’s National Commission on Library and Information Science, as a consultant to the United Nations and to the World Health Organization in Southeast Asia, and as a Visiting Professor at Keio University, Tokyo. Her publications include numerous articles on the history of medicine, and her monograph on the development of medical bibliography (published in 1954) is still the standard work in the field — and is about to be issued in a new edition.

This year the Medical Library enters its eighth decade of existence and Dr. Brodman will retire next June. It is, therefore, an appropriate time to take a retrospective view of its development. The Library was first organized after Abraham Flexner’s evaluation of the Medical School in 1909. In 1910 a Library Committee, composed of members of the new Executive Faculty, was appointed to oversee its development. According to Dr. George Dock, who headed the group:

"There was a simple list of some 3000 volumes in the back rooms of various teachers in the medical school ... but no librarian and no plan for development. In the fall of 1910 the medical faculty was given $15,000 for the immediate assistance of the Library, the promise of an adequate annual
budget, and a room large enough for shelving, cataloguing, and circulation . . ."  

Dr. Brodman herself has described the crucial decision the Library Committee made that year:  

"Instead of purchasing classics, such as Galen . . ., the Library Committee emphasized the modern journal, where new advances could be reported promptly . . . they especially emphasized the relations between good research and access to new findings as reported in the literature. One of their earliest decisions was that if the library were to subscribe to a journal, it should obtain (it) from the first issue of its first volume, on the theory that medical knowledge was a continuum, with no breaks at convenient dates . . ."

This choice was significant, for it indicated the important role medical research would play in modern medical education. The decision had another effect: it allowed the Medical Library to amass a valuable collection of journal sets seldom found at other libraries in the Middle West.

However, the wealth of these holdings was soon to lead to problems of storage space — problems which have plagued the library for eighty years. The 1912 annual report noted:

"Owing to the crowded condition of the library, all books published before 1880 have been removed to an adjoining room . . ."

By that time, the volumes on hand numbered 9,700. With the opening of the new medical school buildings on Euclid Avenue in 1915, the library was established in the west wing of the first floor, North Building. This still forms the central core of its space. By 1922 it held over 33,000 volumes and employed a librarian, Miss Ella B. Lawrence, with two full-time assistants. In an article he published at this time Dr. Dock expressed a pragmatic view of its function:

"It is essentially a working library. It was founded and is conducted for the benefit of medical teachers, students, and investigators."

Though medical librarians at this time generally had little advanced training, Dr. Dock realized their importance; he wrote:

"I know of no place in which experience gives such a large return to its employer, not only in service, but in financial economies . . . If I had my way all such people would have adequate salaries, with heavy bonuses to the husbands of women, who, though married, would continue to carry on their library work . . ."

Fortunately, Miss Lawrence stayed for twenty-five years and provided the library with a steady hand; her successor as Librarian was Miss Marian Murphy who came from the Rockefeller Institute Library and held the position from 1943 to 1958.

The Depression and the Second World War caused decreases in the Medical Library's staff and services, but in the post-war era federal funds for medical research expanded. As Brodman remembers, "Many members of the faculty began to realize that their ability to obtain grants, or to carry out their research satisfactorily if they did get a grant, was being hampered by the low level of service the library was able to provide to them. As a result, as in the Flexner days, a reorganization of the entire area was decided upon." To restore the library to its former pre-eminence, she attacked the antiquated physical plant and set to work on research and application of computer techniques to implement machine systems for serials and circulation.

When Estelle Brodman arrived in 1961, the medical library was lit with its original 1915 fixtures, had never been painted, had no air conditioning in its stacks, and functioned largely as a repository for books and periodicals. Under her direction, the library became an innovative research and service organization, which gained it early access to the National Library of Medicine's national automated bibliographic data base, MEDLINE. She convinced the Library Committee to invest in a copying machine, though in 1961 its worth had yet to be proved. As Barbara Halbrook, Associate Director
of the Library says, simply: "She brought Washington University’s medical library into the 20th century."

Dr. Jessie Ternberg, Chief of the Division of Pediatric Surgery, was a medical student here in the 1950s; she comments: "The present administration of our library can only be appreciated by someone who has spent hours of research trying to put together a bibliography in the pre-Brodman era... It never ceases to astonish me how the same cramped, inadequate quarters have been made to work..." Ternberg’s remarks underline the fact that while many aspects of the library’s services have been transformed by Brodman’s innovations and the physical plant has improved in many ways, the space in which the Library is housed is inadequate for the dramatic increase in services, supporting staff and users which have marked the period from 1961 to present. In addition, the expansion of the Library collections to more than 175,000 bound volumes with 2500 journals received annually, has put an already antiquated physical plant under ever-increasing pressure. The only solutions thus far have been stop-gap measures: removing older journals to the Library’s Taylor Avenue Annex and to the Tyson Valley storage area. Twenty thousand volumes have been in storage since 1971 and an equal number have been put in storage since then. The result is that less and less of the library’s holdings are actually “in the library.” This undermines the idea of medical knowledge as a continuum, since a researcher might have to request early journals from two other locations in order to reconstruct the history of a particular treatment or problem. While some of these holdings could be converted to microfilm, many of the library’s older journals are quite valuable as hard copy. The library feels it has an obligation to the whole society, as well as to its own users, to retain these materials and make them available in the original form. This may not be possible if the Tyson Valley storage area continues to be used for the library’s older holdings. A constant problem with dampness and mold growth is causing damage to these journals.

To make maximum use of available space, Brodman and her staff have developed a coherent policy for collection-building, which includes both acquisitions and weeding. Few libraries have such policies, and even fewer libraries with such written policies revise them at intervals. Brodman notes that “acquisitions policies must change over time with changes in library personnel, in groups served, and in concepts of professions and libraries.” The staff has published “Selected Acquisitions Manual” in several editions, which serves many other medical libraries. Brodman envisions updating and change as constant; as she wrote, “Good as this document is...we are under no illusion that it will remain immutable.” Fitting the library’s collections to the needs of its users is a never-ending task.

Innovative computer applications have brought the library into particular prominence. For approximately seven years, under a pre-doctoral training program financed by the National Library of Medicine, Brodman and her staff trained twenty-five post-master’s-degree individuals in one-year computer-librarian programs. They published some 20 research papers under the general title “Machine Methods for the Medium-Sized Medical Library” five symposia on machine methods were mounted, and a consulting and service program began to emerge.

This development has continued steadily through the 1970s. The oldest computer-based serials control system network was devised under Brodman’s supervision in 1962; it is called PHILSOM, an acronym for “Periodical Holdings in Libraries of Schools of Medicine.” The purpose of the system is to provide libraries with an automated serials control system without the need for resident computer experts. Started as a small serials control mechanism for Washington University only, using the primitive computers of the early 1960s, PHILSOM has had several metamorphoses and is now run from here for twenty medical libraries throughout the country and replicated for another 15 libraries in New York City. Four libraries joined the network this year and the membership group stretches from Oregon to Texas, from Illinois to Maryland. In addition to PHILSOM, Brodman has used computers in many other parts of the library including cataloguing, indexing, circulation, and administration.

Though computer technology has been a major influence in libraries for two decades, it has been a mixed blessing. As Brodman noted in 1978:

"Many... librarians came to automation as new converts, often without being completely sure of the basis for library automation; some... came only after being pushed into it by their administration. Automation, for them, had to be the truth and the way... Uncertain development is the characteristic of newly developing fields, such as library automation, and the fact that some developments act as expected and others do not is a fact of life which must be accepted..."

Certainly, it is much easier to purchase machines than it is to use them efficiently. One of Brodman’s many strengths has been an ability to think about how technology can be intelligently deployed, and it is for this reason that she is a firm believer in the library as a research enterprise. An ongoing machine project is an integral part of the medical library; the project works with members of the staff on such questions as the feasibility of telecommunications and improvements of the PHILSOM system.

In addition to new technology, the 1960s brought new relationships between libraries and the federal government. Through the Regional Medical Library Program, cooperative regional networks were developed to bring medical literature to health professionals and to make the united collections of the largest and best biomedical librar-
A well-stocked library also needs storage space for the supplies which enable librarians to manage and disseminate information. Narrowing the storeroom aisles permitted installation of extra shelving.

ies accessible to all who needed them. The spiraling cost and number of periodicals made such networks an absolute necessity. Under this program, Washington University School of Medicine Library was designated a Resource Library in its region. The Medical Library Assistance Act of 1965 and the Health Sciences Library Assistance Act of 1978 brought medical libraries into a closer financial relationship with the federal government. Under this program, a number of major medical school libraries were built with matching federal funds including the Countway Library at Harvard, the Shiffman Library at Wayne State, and the medical center libraries at Chapel Hill and Utah. It was Washington University Medical School’s great misfortune that, at the time these federal funds were available for library construction, other needs appeared to be more pressing. The provisions which made such federal funds available for library construction have since disappeared from later versions of the acts.

The 1970s were a much bleaker period for such federal funding. Brodman and a faculty committee worked for a number of years in the 1960s and 1970s on plans for a new library building; on both occasions, either local funds or federal funds necessary for the project’s completion were not available. Ever pragmatic, she turned once again to making the best of the existing physical plant.

Downstairs in the stacks, little has changed since the library was built. A picture in the dedication pamphlet is almost identical to this scene, taken in November 1980.
The library is usually busy and full of students and faculty members.

(Top) Modern equipment enables fewer people to handle greater volumes of information.

(Bottom) The library staff in this office is a close-knit group.

In 1974, a small building at 615 South Taylor was designated the Washington University School of Medicine Archives and Rare Book Annex. The nucleus of its holdings is the Page Collection, purchased in 1912. Physician bibliophiles have continually enriched the collection. In 1975, for example, Bernard Becker, M.D., Professor and Head of the Department of Ophthalmology, presented 600 rare and early volumes to the School of Medicine Library. Another major gift came in 1977, when the Central Institute for the Deaf donated the rare book collection of Max Aaron Goldstein, M.D., noted otologist and founder of the Institute. It includes nearly all the important early works in the education of the deaf. The Medical School Archive contains the early records of the Medical School and the personal papers of physicians and professors who have played important roles in its development. An organized oral history project began in the late 1960s; Brodman herself conducted the first such interviews with Joseph Erlanger, M.D., (Nobel Laureate and Professor Emeritus of Physiology) in 1963. There is a computerized index to the interviews available to interested scholars, who come from many parts of the country to use these collections.

Of particular interest to the Washington University community is research on the medical school itself. Last year Dr. Louise Marshall, editor of the *Journal of Experimental Neurology*, presented a paper to the History of Medicine Club on the “Washington University Axonologists in the 1930s.” This group included such illustrious figures as Drs. Erlanger and Gasser, awarded the Nobel Prize in 1944 for their work on nature of the nerve impulse. A then junior member of the axonology group, Hallowell Davis, M.D., (now 82 years old) was able to contribute lively comments to the discussion following Marshall’s paper. Such occasions, which Brodman provides through the History of Medicine Club, create a sense of community and continuity at the Medical School. Kenneth Ludmerer, M.D., Assistant Professor of Internal Medicine, spends his research time in the Archives. He is writing a book on the history of reform in medical education and has recently received a
Generations of medical students, faculty and staff have pursued knowledge up and down the main stairway in the stacks.

In the library annex workroom, rare books are studied and preserved.

A three-year grant from the American College of Physicians for this work. Ludmerer notes:

"It would not be possible for me to conduct my research without the magnificent historical collection assembled and preserved by Dr. Brodman... her dual career as a distinguished historian and librarian has given her both a sense of what materials are crucial to historians of medicine and the motivation to collect and preserve these materials..."

As Brodman approaches retirement, she is particularly proud of the research and development in medical librarianship which has been accomplished through consistent support from the Dean. This allocation has been based on the theory that every department of the medical school should try to add to the sum of knowledge in its field. In Estelle Brodman's view, the Librarian of the School of Medicine must be able to do research in order to provide the best possible service to physicians, scientists, and other users. As a recent editorial in Science magazine noted, "We are in the early phase of major change in scientific communication... the electronics revolution has begun to influence many areas..." Brodman's expertise has kept the Washington University School of Medicine Library on the frontiers of that revolution. This is particularly remarkable in view of the constant crises she has had to deal with in the physical plant. Just this summer the library suffered one of the periodic floods which has plagued it for decades. Fortunately, no major damage was done to its holdings.

This flood is only the latest in a series of constant threats to the library's quality. As the Washington University School of Medicine Library enters its eighth decade and Estelle Brodman's innovative leadership comes to an end, there is reason for concern about its future. The constant expansion of biomedical knowledge and the already severe limits of library space will make it increasingly difficult to provide the level of service which Brodman and her staff have spent twenty years developing. She herself commented prophetically on the current situation in a 1974 address:

"... budgets of medical center libraries will continue to grow in the foreseeable future, if this great national resource is not to deteriorate. If they are not to go from crisis to crisis, the financing of such libraries will have to be considered sympathetically and in advance. Only when real planning occurs can we manipulate circumstances, and not have circumstances manipulate us..."

The 21st century is less than twenty years away, and the Washington University School of Medicine Library must have the space necessary to meet the challenges it will certainly bring.
Philip E. Cryer, M.D., Director of the CRC, and Barnes and St. Louis Children's Hospital physician, with Dennis Popp, M.D., a trainee in the Division of Metabolism.
The CRC On Its 20th Anniversary

by Mary Poluski

To trace the history of the Clinical Research Center (CRC) at Washington University School of Medicine is comparable to following one of several twisted roads that branch into smaller paths. The roads twisted by shifts in the direction of research, the smaller paths — individual projects or experiments. Some paths connect, some cross and others run without interruption and eventually end.

"Research, in general, doesn't go from a problem to a 'Eureka, I-found-it' type of cure for a disease or disorder," says Philip E. Cryer, M.D., Associate Professor of Medicine and Director of the CRC. "Occasionally that happens," he says, "but generally speaking, you ask a defined question and set up an experiment to answer that question. You may or may not answer it, but almost invariably the experiment will raise further questions" and require additional experimentation. This, in turn, may change the course of research and prolong the process.

"Research doesn't proceed from A to Z," continues Cryer. The process can span months — sometimes years. It is a daily fact of life, however, for the 140 investigators from 11 divisions of the School of Medicine who use the University's Clinical Research Center. And for some of them, it has been a 20-year marathon.

This year marks the 20th anniversary of the CRC at Washington University. It is one of the oldest, largest and most scientifically productive units in the General Clinical Research Centers Program (GCRC) which is administered by the Division of Research Resources of the National Institutes of Health.

The GCRC Program, authorized by Congress and initially administered by the Division of General Medical Sciences of the NIH, began in 1960. The program's purpose is to provide centers where investigators — representing many medical disciplines — can collaborate and study diseases and disorders in selected patients under highly controlled conditions not possible in a hospital. The desired end result? To develop methods of treatment.

When the program began, there were eight CRCs located in major medical centers across the nation. Washington University's CRC was one of these centers. Today, there are 75 CRCs and 613 beds in the program. There used to be more.

Inflation and the economy have trimmed the GCRC budget over the years, forcing some centers to close and others to reduce their size. Despite this, the CRC at Washington University has, for the most part, maintained its size.

Currently Washington University's CRC has 30 beds — 22 adult and 8 pediatric. The adult "ward" is located in the Barnard Hospital and the pediatric unit in St. Louis Children's Hospital. Both "wards" have their own nursing staffs; dietary and laboratory staffs are shared. As with all other CRCs, Washington University's maintains and operates its own kitchens, laboratories and support facilities separate from the hospital containing them.

"The CRC is like a specialized part of a hospital," adds Cryer, "except that it functions independently so that physicians who do research involving humans can use the space for inpatient and outpatient research." Approximately 1,200 patients are admitted to Washington University's CRC each year and an additional 1,800 participate on an out-patient basis. They represent a multitude of disorders from rare to common.

"Although we do study unusual diseases, research of that kind is really up to the scientific curiosity of the individual investigator, and many of the diseases and disorders they study are common," says Cryer.

"The most common, including diabetes, hyperglycemia, infertility, growth disorders, bone diseases, kidney disorders, hypertension, obesity and cancers including leukemia are among the disorders studied at the center."

"We approach these and all problems step by step," says Cryer. And, a lot of the things that we find exciting from day to day are answers to short-term questions which really just lead to more questions. And so," continues Cryer, "we perceive each puzzle piece by piece."

One of these puzzles is diabetes mellitus, a carbohydrate disorder resulting from insulin deficiency. Although it is chronic and incurable, "patients don't die from acute ketoacidosis (severe and uncontrollable diabetes). They live for varying periods of time and then develop complications. They die from complications," says Cryer. These complications include heart attacks and kidney failure.

"Studies in diabetes began shortly after the center started and still continue," says Cryer. But before attempting to develop methods of treating the disorder, investigators needed to know more about diabetes. This required preliminary studies and it is upon findings from these investigations that methods were eventually developed to treat diabetes. But the process to develop these methods demanded time and trial-and-error experimentation, and involved more than just a few investigators. It still continues.

Diabetic research at the CRC began in the early 1960s under the direction of David M. Kipnis, M.D., then Director of the CRC. (Currently, Kipnis is the Adolphus Busch Professor and Chairman of the Department of Medicine. He is also Physician-in-Chief at Barnes Hospital.) Kipnis, and investigators working on similar research elsewhere, measured insulin levels in healthy and diabetic patients and concluded that impaired insulin secretion is the basis of the metabolic abnormality in diabetes.

Later studies conducted by Joseph Williamson, M.D., and his...
associates in the Department of Pathology using biopsy specimens from a large pool of patients — including some from the CRC — identified thickening of the capillary basement membranes as the basic pathologic abnormality of diabetes. (Williamson is a Professor of Pathology and Barnes physician.) "This thickening is a characteristic feature of diabetes and is related to the duration of the disease," says Cryer. "It is also presumed to be secondary to the metabolic abnormality, insulin deficiency."

The pieces of the puzzle began to fit.

"Now we have the fundamental pathogenic mechanism, the common denominator in terms of the small vessel complications and the relationship of that common denominator to, at least, the duration of the disease. And we have identified what's wrong in terms of the cause of the metabolic abnormality and some of the common complications of diabetes," says Cryer. "Both seem to be related to insulin deficit. Now we want to replace insulin in a physiologic way so we can normalize these metabolic abnormalities and see if the complications are prevented."

Conventional daily injections with insulin — a protein made by the islet cells in the pancreas to burn off glucose — control symptoms but do not prevent complications. The injections do not mimic the body in achieving precise minute-to-minute control of glucose and other metabolic processes.

Currently, there are two new approaches under investigation for administering insulin. "One is transplanting healthy islet cells," says Cryer, "and Dr. Lacy (Paul E. Lacy, M.D., Ph.D., Edward Mallinckrodt Professor and Chairman of the Department of Pathology, Pathologist-in-Chief for Barnes and St. Louis Children's hospitals, and member of the staff of The Jewish Hospital of St. Louis) is certainly one of the leaders in that area. But islet transplantation has not yet reached clinical application."

The second approach is infusing diabetics with insulin through a machine called a Biostator. The Biostator uses a closed-loop system which measures the blood sugar in the diabetic patient and infuses insulin based on those measurements. "It was developed by Miles Laboratories," says Cryer, "but was field-tested here, and a lot of its initial problems were solved by Dr. Santiago (Julio V. Santiago, M.D., Associate Professor of Pediatrics and Medicine and member of the staff of St. Louis Children's Hospital and Barnes Hospital). The machine works; however, it is not practical for long-term treatment at this point," says Cryer. "The major obstacle is the lack of an implantable sensor which can measure the blood sugar. Presently, the machine withdraws blood and measures the blood sugar outside the body. As of yet, there is not an implantable sensor that works for any prolonged period of time. But that's a technical problem," says Cryer, "and it's reasonable to expect that over the not-too-distant future the technical problem will be handled. Once it is, the major obstacle to the use of a closed-loop system will be overcome. There are still some problems with miniaturization," he adds, "but I think this can be overcome."

"Presently, the machine is a very valuable research instrument," continues Cryer. "We can use it to answer a variety of questions about diabetes and it has given us a lot of insight about how to give insulin, for example, the timing."

"Because the machine cannot be used for the long-term, what can we do?" asks Cryer. — "infuse insulin in an open-loop system. In this system, the patient is given an arbitrary dose of insulin and his blood sugar is measured periodically. Dosages are adjusted on the basis of previous measurements," says Cryer. "And, to the surprise of some of us, this system works fairly well. It's not universal; not all patients can do this, but many can," says Cryer. "So, with insulin infusions, or perhaps with multiple injections of insulin, we think we can surpass the efficacy of previous systems."

Continues Cryer, "Now, what about the complications of diabetes? Complications take 10-20 years to develop, so you're talking about a very prolonged study if you consider the traditional complications of diabetes. But there may be some things that we can measure on a short-term basis. Those things include measuring the permeability of vessels in the eye with vitreous fluorophotometry. This technique was developed by an ophthalmologist in Spain and, shortly thereafter, was picked up by Washington University and Barnes ophthalmologist, Dr. Steve Waltman. (Waltman is also a member of the staff of St. Louis Children's Hospital.) Drs. Santiago and Waltman have shown that effective insulin therapy, using an open-loop system, returns vascular permeability to normal in the eye, a very encouraging finding.
"Another way of monitoring control is measuring what is called Hemoglobin A₁c. It has been observed that glucose hooks onto many proteins, including hemoglobin in the blood, in a manner that is directly proportional to the amount of glucose around. Once it hooks on to these proteins, it stays there for the life of the protein. And things like hemoglobin are around for a long time," says Cryer. "The hemoglobin A₁c level is a way to estimate the average, integrated plasma glucose concentration over several weeks. The importance of Hemoglobin A₁c was not discovered here, but a method to measure it was developed here," says Cryer. "Hemoglobin A₁c levels can also be normalized by aggressive insulin therapy." He believes the ability to measure short-term things indicates that research progress is headed in the right direction.

"Now we know what the fundamental defect of diabetes is and therefore, conceptually, how to treat it. We also know what the fundamental vascular abnormality of diabetes is and think it's related to insulin deficit," says Cryer. "We're developing better ways to give insulin, which presumably will be the way we will treat diabetes in the interim until transplantation becomes a reality or the machines become feasible on a long-term basis.

"So we are approaching common problems - such as diabetes - but we are approaching them step by step," says Cryer. "In order to have grown and maintained its size for 20 years, the CRC at Washington University had to go through periodic reviews, and that review process has to have concluded that this center has been a scientifically productive unit," continues Cryer, "particularly in these times when the budget for the CRC program nationwide has been restricted and has not kept up with inflation." At its peak, the program supported more than 1000 beds nationwide; now it supports approximately 600.

"The CRC is something that I run, that I take from and use," continues Cryer. "Because my research deals largely with humans, I need the CRC." He praised senior people who have dedicated a large portion of their lives to the CRC, such as Jane Hamilton, Nursing Administrator, and Norma Janes, Dietician-Nutritionist. "They, and many of their colleagues, make this place unique; their being here is probably one of the reasons why this CRC has been so productive. The success of this unit reflects not only the quality of the investigators, but also the dedication of the nursing, dietary and laboratory people who work here."

From left to right: Geoff Herzg, M.D., Associate Professor of Medicine and Barnes physician, with S. Asmar, M.D., and Joe Cole, M.D., assistants in medicine and house staff members.
Marcus E. Raichle, M.D., principal investigator at the WUMS Stroke Center
A New Look At Stroke

by Mary Poluski

"The big thrust in the area of stroke is trying to prevent it by identifying patients who have had a warning symptom — a transient ischemic attack. These are brief periods (usually lasting 5 to 30 minutes and no longer than 24 hours) during which you can’t speak, or your arm or leg becomes numb, or you become dizzy and lose your balance, or lose sight in one eye or see double. Although these symptoms don’t always presage stroke, if you are in an older age group and have high blood pressure, there is need for investigation. . . We must educate not only the public about these attacks, but physicians too. They need to realize warnings of a potential stroke and know that we have some things to offer people if we see them in time."

Marcus E. Raichle, M.D.
Professor of Neurology
Principal Investigator
WUMS Stroke Center

For years it remained an area of little or no research although its consequences then and now are severe and far reaching. Physicians, convinced that there was nothing they could do after it occurred, counseled the victims’ families about how to cope with the condition. Now, due to developing technologies helping to unearth its causes, they talk about how to prevent it.

Stroke is a layman’s term for a whole host of symptoms resulting from a malfunction in a blood vessel which prevents blood from reaching a region of the brain.

Glucose and oxygen — the only nutrients the brain needs — are contained in and transported by blood. When blood flow is obstructed and these nutrients are unable to reach a region of the brain, the cells in the affected region die. Subsequently, an event commonly referred to as a stroke occurs, stripping self-sufficient and independent people of their pride, the use of their limbs or speech, and sometimes, their lives.

Most strokes represent cerebrovascular disease and result from an accumulation of debris (cholesterol, calcium or platelet) or thrombus in the carotid artery in the neck, a principal supplier of blood to the brain. The stroke is caused by debris clogging the artery and preventing blood from reaching the brain, or by debris breaking off of the encrusted artery, traveling to the brain and blocking smaller blood vessels which supply blood for a specific neurologic function.

Washington University School of Medicine researchers have been intensively investigating the etiology of this condition which afflicts over 500,000 and kills almost 250,000 people each year in the United States alone, making it the third most common cause of death in the nation.

In 1966, the School of Medicine was awarded a grant by the National Institutes of Neurological Communicative Disorders and Stroke, an agency of the National Institutes of Health, to establish a stroke center. It was one of the first stroke centers in the nation and focused initially on the acute care and management of the stroke patient. Today, the center, a major facility for stroke research, is a tightly integrated multidiscipline effort that deals with the entire stroke process.

Although personnel and specific projects at the center have changed over the years, the undertaking has remained — interest in diagnosing the process of the disease in the blood vessels of the brain through improved radiologic techniques.

These techniques maintained researchers’ interest because the brain, obviously enough, cannot be felt, seen and biopsied as readily as other organs in the body. If the brain could be imaged and metabolic and biological processes observed, researchers contended, the process occurring in the brain could be better understood.

"The big problem we face in the management of a stroke patient is trying to understand what is going on in the brain that is making the patient ill," says Marcus E. Raichle, M.D., Professor of Neurology and principal investigator at the center. The inability to observe the processes of the brain has been a major stumbling block in this endeavor. "You may perform some sort of treatment that your biological and physiological colleagues say should change a certain chemical reaction in brain tissue," he says. "But it is very important to know whether, in fact, their predictions were correct and, furthermore, whether it made any difference to the individual patient."

When one wants to understand the whole process of stroke," continues Raichie, "one will want to know how the blood vessel looks, how it performs — i.e. how much blood is going up to a given region of the brain, and how much oxygen and glucose that area of the brain needs to survive. What we're now working on is a way of knowing what's going on in the brain so we can make some intelligent decisions about how to treat the patient to prohibit further damage, improve his condition and to minimize, if not prevent, the possibility of future stroke occurrences.

The use of short-lived cyclotron-produced radioisotopes and the development of positron emission tomographic devices (PET scanners) to plot the path of these radioactive substances once they have been administered to the patient, have greatly aided in this effort. The PET scanner provides in vivo a regional assessment of a number of biochemical processes in the body, including the metabolism, circulation and permeability of the brain, with minimum risk to the patient.

Washington University School of Medicine has pioneered both the use of these radioisotopes for biomedical research and the development of PET scanners. In the past few years, other institutions have begun work similar to the research that has been conducted at Washington University for the past 14 years.

Work in this area at the School of Medicine began in the late 1950s when Michel Ter-Pogossian, Ph.D., Professor of Radiation Sciences in Radiology, began using a cyclotron, which had been used by the University’s physics department, to produce short-lived radioisotopes. Initially,
Ter-Pogossian and his colleagues produced oxygen-15 to study oxygen metabolism in small animals following radiation therapy. Later studies conducted by them indicated the usefulness of this substance and other positron-emitting, cyclotron-produced short-lived radioactive isotopes in biomedical studies. Because of these findings, a cyclotron for producing these substances was installed in the basement of the Barnard Free Skin and Cancer Hospital in 1963. It was the first biomedical cyclotron to be installed in a medical center in the U.S.

"Of course, at that time," says Raichle, "there was no discussion of PETT-imaging devices and the like, but it was clear that if we could put these radioisotopes on molecules that were important to the brain, and then figure out how to analyze the data that resulted, we could observe its metabolism and circulation." Over the years, a team of investigators from the Division of Radiation Sciences and the Biomedical Computer Laboratory developed chemical procedures for labeling these molecules, the instrumentation to follow their fate and highly sophisticated strategies to interpret their data. As a result of their clinical usefulness, demand for the radioactive substances grew and, in 1978, a second cyclotron was added.

"The two cyclotrons are used by the Division of Radiation Sciences to label compounds for biomedical research," says Michael J. Welch, Ph.D., Professor of Radiation Chemistry in Radiology. "This research is in two areas — one is in the study of myocardial research and the other is in the study of stroke patients." Interestingly, many of the patients who survive a stroke will frequently have a heart attack in subsequent years. "And probably the thing they will die from is the heart attack and not the stroke," adds Raichle, "that is, if they survived the stroke to begin with."

The cyclotrons produce four radioisotopes, all of which have very short half-lives, requiring that they be produced in-house. The isotopes are oxygen-15, which has a 2-minute half-life; nitrogen-13, which has a 10-minute half-life; carbon-11, which has a 20-minute half-life; and fluorine-18, which has a 2-hour half life. "The fact that these isotopes are short-lived has enormous advantages for medical research," says Welch. Subsequent studies using different substrates can be performed in the same subject shortly after the initial test.

"Of the four isotopes mentioned, three of them are common to the major constituents of biomedical compounds," says Welch. "Almost everything that is used in metabolism physiology contains carbon, oxygen and nitrogen. And several compounds which behave in similar ways to natural metabolites, called analogs, contain fluorine," says Welch. "So with these four isotopes of four elements, one can label a whole host of compounds of biological interest. The sort of compounds that gained almost widespread use are labeled with oxygen, carbon and fluorine."

"We now make certain simple compounds with labeled oxygen, oxygen gas itself with which one can measure oxygen metabolism; labeled carbon monoxide, which one can use to label hemoglobin and end up with carboxyhemoglobin, and labeled water," continues Welch. "And with these three agents (labeled oxygen, carbon monoxide and water) our physiological colleagues can measure oxygen metabolism, regional blood volume and regional blood flow — all by non-invasive techniques."

Although carbon-11 is used to label glucose, "we have also developed the synthesis of an analog which is transported to the brain in a similar way to glucose but is labeled with fluorine," says Welch, "to measure glucose metabolism."

Initially, the isotopes were injected into the carotid artery or through a catheter which was inserted in the femoral artery and snaked into the carotid artery vein. "The process was risky and was done in conjunction with cerebral angiography," adds Raichle.

"The thing which has radically changed is the way in which we can look at the behavior of these special isotopes with a PETT system," continues Raichle. "Now the patient can inhale the isotopes, or be injected with them through a vein in the arm instead of in the neck."

"The simpler compounds can be administered by inhalation," adds Welch, "and the more complicated by intravenous injection." For inhalation, "we make the chemical in a small volume of gas between 15 and approximately 200 ccs. Then, we place it in a bag from which the patient inhales. Very simple," says Welch.

All the isotopes decay by a mode known as positron emission. As the isotope decays, it generates a very high level of energy radiation called annihilation radiation which is detected by the PETT scanner's detectors. This information is converted into electrical signals which are then fed to a computer that reconstructs the distribution of the isotope in three dimensions — transverse, coronal and sagittal.

This PETT system provides images of superior resolution and contrast, and are more quanti-
A patient is ready to be PETT-scanned in this view from the rear of the instrument.

PETT VI is the latest of the PETT series and is used in imaging the brain. (All of the PETT scanners at the School of Medicine have been developed by Ter-Pogossian who is considered the "father" of these tomographic devices.) PETT VI is a particularly fast positron-imaging device designed specifically for imaging the human brain and experimental animals. It provides seven image slices of the brain simultaneously and has a minimum scanning time of one second. The very high sensitivity of this device and its ability to provide these images simultaneously, permits the study of the dynamic processes of the brain.

"These radiologic techniques allow us to look at all of these processes (metabolism, circulation, biochemistry and permeability of the brain) which are at the heart of the problem of stroke," says Raichle. "It is disorders of these parameters that lead to stroke, and we need to be able to measure them in some satisfactory way in patients that are likely to have a stroke," he says.

Based on the findings provided by the PETT scans, physicians may be able to determine a course of treatment most suitable for the patient. These findings are potentially useful in determining which patients might benefit from surgical procedures that could improve brain blood flow and metabolism and, in effect, prevent future strokes.

But not all patients are candidates for these procedures. "There are some patients whose severe vascular disease involves not only the blood supply to the brain, but also to the heart," says Robert A. Ratcheson, M.D., Associate Professor of Neurological Surgery, "and these patients are at significant risk for almost any type of surgery." There are also patients whose cerebrovascular disease is so advanced that surgery would not help, he adds.

"Once someone has a stroke, there really is very little that one can do to reverse the symptoms unless treatment can be instituted within a very short time — a number of hours after the event," he says, "and even then treatment is not always successful."

Some patients who have had a mild stroke may be suitable candidates for preventive surgery, he says, "but these are people who still have significant neurological function left to lose if another stroke were to occur."

In Neurosurgery, Robert L. Grubb, M.D., Associate Professor of Neurological Surgery, and I are trying to determine in which patients surgery will be effective in preventing a stroke. We have been using the information obtained from these initial PETT scans to help assess the dynamics of the cerebral circulation and metabolism to aid in determining those patients who will benefit functionally from the operation," says Ratcheson.

Interest in the surgical management of stroke has been inspired by Henry G. Schwartz, M.D., August A. Busch, Jr. Professor of Neurological Surgery, who is a leader in the treatment of cerebrovascular disease.

There are a number of different operations currently being performed at the medical center to prevent stroke and the procedure selected depends upon the anatomy of the patient. Two procedures are most frequently performed, and while neither operation is totally unique to the University, the neurosurgery department was one of the first to recognize their value in the prevention of stroke.
Robert A. Ratcheson, M.D., with a patient who benefited from surgery to improve blood flow to the brain.

The Positron Emission Transaxial Tomograph or PETT scanner.

"One of these procedures is a straightforward and direct operation called carotid endarterectomy," says Ratcheson. "In this operation, a blockage of an artery, referred to as a plaque, is removed. The carotid artery can be approached directly in many instances, and opened, and the plaque, which is often ulcerated with rough irregular areas on which platelets and debris may accumulate, can be removed leaving a relatively smooth inner surface. Soon after the operation, the interior of the artery will form an almost normal surface.

"If the obstruction lies in an inaccessible area or in one of the intracranial vessels, an operation to bypass the obstruction can be performed," he says.

"Using microsurgical techniques, we are able to dissect an artery — usually no greater than one and one-half millimeters — from the scalp, free it and then, with very fine suture materials, connect it to a small artery — no larger than a millimeter — on the surface of the brain. This bypasses the obstruction and provides additional blood flow to the brain.

Following this operation, the vessel can enlarge dramatically. "It can grow from less than a millimeter to three or four millimeters in diameter and carry almost as much blood as a normal carotid artery in the neck," adds Ratcheson. This enlargement is one of the criteria that we use to say that an operation is successful. We believe this indicates a demand for that blood supply by metabolic factors in the brain.

"In our own studies here, we feel that the incidence of stroke following surgery is far less than what we would expect if these people were left untreated or treated with anticoagulants," says Ratcheson. "There is no question that some strokes can be prevented.

"Stroke is a major problem in this country with far reaching social and economic effects," continues Ratcheson, "but I feel that one has to look at it and deal with it very directly. It is a disease that not only damages the body, but damages the mind," he says. "It is one of the most debilitating processes which can affect an individual.

"Even though we feel relatively successful in treating the people who reach this institution without having suffered a major stroke, efforts such as this have not greatly altered the overall impact of stroke in this country," says Ratcheson. "And we feel that it must be approached not only from an aggressive therapeutic point of view but through an aggressive intellectual process in which we can learn far more about stroke so we may be able to understand how to prevent them entirely."
Soviet Scientists Visit The School Of Medicine

by Casey Cray

Four Soviet medical research scientists visiting research institutions in Maryland, Missouri, Florida and Washington as part of a joint US-USSR cooperative agreement, spent eight days at Washington University School of Medicine in November. The joint US-USSR program in cardiovascular diseases is one of five programs of cooperation between the two governments. Cardiovascular diseases are of significant importance in both countries, being the major cause of death in both, and having extensive social and personal consequences involving not only death but also chronic illness, decline in productivity and increase in the costs of care, and a decrease in the general quality of life — consequences which know no geographic boundaries.

Informal direct relationships between scientists in the US and in the USSR began in 1955. In 1956, Soviet specialists visited the US to study the control of poliomyelitis, and US microbiologists and epidemiologists visited Soviet medical institutions and organizations. In 1972, the original health research cooperative agreement was signed by both governments; the agreement was extended for five years in 1977. A second agreement for cooperation on artificial heart research and development was signed in Moscow in 1974, and was also extended for five years in 1977. In addition to research and exchange of information in cardiovascular diseases, the cooperative agreements cover malignant neoplasia, environmental health, arthritis, and influenza and other acute respiratory diseases.

The latest agreement calls for mutual planning and execution of joint research activities in both countries according to organized work plans and common protocols, and provides for mutual direct cooperation between

Drs. Gorbunova, Fletcher and Donskov during a tour of one of the laboratories at the medical school
specific health institutions in both countries. The National Heart, Lung and Blood Institute of the NIH collaborates with the All-Union Cardiology Research Center of the Soviet Academy of Medical Sciences in Moscow. There are seven program areas for collaboration in cardiovascular diseases: Pathogenesis of Arteriosclerosis, Management of Ischemic Heart Disease, Myocardial Metabolism, Congenital Heart Disease, Sudden Death, Blood Transfusion and related topics, and Hypertension. The Soviet scientists who visited Washington University are all involved in program area six—Blood Transfusion, Blood Components and Prevention of Hepatitis, with particular reference to cardiovascular surgery. High quality blood management is of obvious importance in all forms of surgery and in the prevention of hepatitis.

In a publication discussing program area six, the National Heart, Lung and Blood Institute states: "Meeting (the) increased need for blood and blood products is complex. It requires effective donor recruitment, sterile collecting techniques, optimal blood component separation, detection and elimination of disease-causing agents, matching for compatibility of blood type, and the administration to the patient of the required blood or blood components in a fail-safe and effective manner. It is now abundantly clear that many patients who need blood replacement therapy do not need whole blood. Rather, such patients usually lack a specific component of blood, such as red cells or platelets or a clotting factor such as Factor VIII, which, if replaced, accomplishes the therapeutic objective. Indeed, the indiscriminate use of whole blood where a specific component is indicated, is not only wasteful, it constitutes less than optimal medical practice. Many patients, including patients undergoing cardiovascular surgery, would benefit from the widespread availability and optimal use of blood components and blood derivatives. Moreover, much of this valuable human resource could be conserved if there were available more effective substitutes for the important oncotic properties of plasma and the oxygen-carrying capacity of red cells."

The bilateral approach to blood transfusion problems began with a US delegation's visit to the USSR in 1973, and a reciprocal visit by a Russian delegation in 1974. Soviet and American scientists exchanged information about the US blood transfusion system, blood service in the USSR, blood preservation methods used in each country, the use of blood components, transfusion technology, hepatitis, the effects of massive transfusions, the use of blood in cardiovascular surgery and in heart bypass. Following these exchange visits in the early 1970's, the two countries established two major themes for collaborative work—preventing hepatitis, and the use of whole blood, blood components and derivatives, blood and plasma substitutes, especially in cardiovascular surgery. A series of symposia and joint working meetings have continued through 1979.

Hosts for the four visiting scientists during their stay in St. Louis were Anthony Fletcher, M.D., Associate Professor of Medicine, and Norma Alkjaersig Fletcher, Ph.D., Research Associate Professor of Medicine, husband-and-wife collaborators whose laboratory headquarters are at the Veterans Administration Medical Center in Jefferson Barracks. "We were hosts because the Russians had asked to visit four laboratories in the country, and ours was one of them," said Anthony Fletcher. The Fletchers have developed a technique called plasma fibrinogen chromatography, a non-invasive technique for studying fibrin formation which can be applied to a number of disease states.

Dean M. Kenton King, M.D., gave a dinner party for the entourage at Whittemore House to welcome the visiting scientists. During their eight-day stay at Washington University, they visited seven Medical School laboratories in addition to the Fletchers', and were given tours of the Barnes Hospital Blood Bank and the regional American Red Cross Blood Bank, the Gateway Arch and museum, and a shopping center.

Laurence A. Sherman, M.D., Professor of Pathology and Medicine, and head of the Barnes Hospital blood bank was one faculty member with whom the visitors spent considerable time, discussing thrombosis research and blood bank operations and technology. In conjunction with Barry A. Siegel, M.D., Professor of Radiology, and Michael J. Welch, Ph.D., Professor of Radiation Chemistry in Radiology, Sherman is working on thrombus imaging techniques with radioactive isotopes and a gamma camera. Sherman and Glenn E. Rodey, M.D., Associate Professor of Medicine and Pathology, discussed histocompatibility and participated in the tour of the regional American Red Cross Blood Bank, which is directed by William Miller, M.D. "The state-of-the-art seems to be comparable between the two countries," Sherman said, "and although we seem to use more blood components, they have some interesting aspects of preparing certain kinds of components. It was an interesting visit. It was illuminating to talk to them, and I hope that they benefited, too."
Nigella A. Gorbunova, M.D., of the Laboratory of Pathophysiology, Central Institute of Hematology and Blood Transfusion in Moscow. She graduated from the Stalinabad State Medical Institute in 1955, defended her candidate's dissertation, "The Recovery of the Liquid Part of the Blood and Protein Following Acute Hemorrhage," in 1958, and defended her doctoral dissertation, "Post-hemorrhagic Erythrodieresis, Mechanism and Significance for Blood Regeneration," in 1971. She is a doctor of medical sciences and has published 76 works on problems in hematology, transfusiology and blood coagulation. "My lab participates in research on problem area six of this exchange program. Our principal topic is the role of platelets in thrombosis and in transfusion, and the use of blood components in experimental conditions," Dr. Gorbunova said. She said that some of the work is in conjunction with clinic patients, but that most of it is experimental rather than clinical in nature.

Galina Vorobyova was born in 1934 in Smolensk; she completed her course of study at the Sechenov First Moscow Medical Institute in 1959 and began working at the Central Scientific Research Institute of Hematology and Blood Transfusion of the USSR Ministry of Health. "I am interested in scientific problems of blood preservation, obtaining blood components and separating platelets, white cells and red cells in liquid form and in frozen form," Dr. Vorobyova said. "I was very interested in the Red Cross blood bank here." She defended her graduate dissertation in 1959 on the topic "Production, Preservation and Clinical Use of Washed Erythrocytes for Prophylaxis of Post-transfusion Reactions and Complications." She is the author of 42 scientific works.

Sergei Donskov was born in Makhachkala in 1941, and completed his studies at the Pirogov Second Moscow Institute in 1964. He began work at the Central Scientific Research Institute of Hematology and Blood Transfusion of the USSR Ministry of Health. Since 1978 he has been Chief of the Laboratory of Automated Serologic Techniques of Investigation and the All-Union Center of Hematology and Blood Transfusion at the ministry. His graduate dissertation, in 1969, was on specific methods of determining the Rhesus factor. He is the author of 50 scientific papers. His current scientific interests are linked to the study of T and B lymphocytes in normal and pathologic conditions, and to problems of organizing tissue identification in transplantation. "I am also interested in immune-hemolytic anemia," he said, "and the method of softening the effects of this disease." He also told of his interest in the human lymphocyte action system. "We believe that lately we have found a new antigen system, and it was quite interesting to discuss the new HLA system with American scientists. Of special interest was our discussion with Dr. Anderson at Washington University and his work using a principle formulated in the improvement of kidney transplants. I believe that these discussions in the exchange program are of mutual benefit."

Nina Lagutina, M.D., was born in 1925 in Moscow and completed her studies at the Pirogov Second Moscow Medical Institute in 1948. She worked as a pediatrician in a regional hospital, and then finished her graduate work and internship at the Second Moscow Medical Institute. Since 1956, she has been at the Central Scientific Research Institute of Hematology and Blood Transfusion of the USSR Ministry of Health, and is currently a senior researcher in the Laboratory of Hemostasis. She defended her doctoral dissertation, "Pathology of the Vessels and Impairment of the Hemostasis System in Hypoplastic Anemia," in 1978. She has studied the mechanism of the development of hemophilia and thromboses in various pathological states, and the development of corrective methods. She is the author of 100 scientific papers. At the present time, she said, "I am studying transformation mechanisms and thrombolytic therapy under various pathological conditions which can occur in clinical conditions."
Controlling Hypertension Increases Cholesterol Levels

by Casey Croy

"...my blood speaks to you in my veins..." Shakespeare wrote in The Merchant of Venice. Physicians and researchers, from long before The Bard to the present, have been listening to and looking at blood, trying to determine why composition, texture and pressure sometimes go awry and what to do about it. From primitive herbal teas or the laying-on of leeches to the most modern pharmacology, doctors have tried to alleviate problems laymen sometimes summarize as "high blood pressure" and "thick blood."

"I'm taking some blood thinner now," a person might say, following a transient ischemic attack or an episode of arrhythmia, "and some blood pressure pills." Or a young woman, perhaps in the mid-30's, might routinely — with the morning orange juice, now-decaffeinated coffee and daily vitamin — take a "blood pressure pill" to combat recently discovered mild hypertension and prevent a future heart attack or other related problem. But will it? Old proverb: many medicines, few cures.
A recent study indicates that some medications commonly prescribed to control moderate hypertension increase cholesterol blood levels in the blood. Cholesterol is, of course, related to coronary heart disease and atherosclerosis.

"Total cholesterol is a good indicator of risk. In general, the more lipid, the greater the risk," said H. Mitchell Perry, Jr., M.D., Professor of Medicine and Director of the Hypertension Division. Perry was chairman of a group of scientists which conducted a double-blind, placebo-controlled study of cholesterol levels and drug therapy for mild hypertension. The study was jointly supported by the Cooperative Studies Program of the Medical Research Service of the Veterans Administration, and by the National Heart, Lung and Blood Institute of the National Institutes of Health.

Effective antihypertensive drugs became available in the early 1950s, and it was quickly evident that they were life-saving for people with the most severe kinds of hypertension. For the next 20 years, these drugs and new ones were given to patients with less and less severe hypertension. In August of 1970, a Veterans Administration Cooperative Study, involving 17 VA hospitals including St. Louis, conclusively demonstrated that treatment was beneficial for those with moderate hypertension, i.e. that treatment markedly decreased the number of patients who got sick and died from this disease. This landmark VA study had a major effect in popularizing antihypertensive treatment. It stimulated Elliot Richardson, the then Secretary of H.E.W. to assemble a group of 12 experts to compile guidelines on how to treat hypertension and who should be treated. Perry, who was chairman of that first expert group, noted that in providing guidelines there was only one unanimous decision, and that was to use a diuretic as the first step in the treatment of hypertension.

After the 1970 VA Study, the major unanswered question was whether treatment helped mild hypertension. Perry chaired a Feasibility Trial to determine whether the benefits of treating mild hypertension could be practically studied.

The study which Perry chaired involved more than a thousand patients who were followed for an average of 18 months through a three-step drug therapy program or a placebo program. The patients were seen at one of four participating clinical centers located in Alabama, Iowa, Oklahoma or Missouri. To select the subjects for the study, 118,158 men and women from 21 to 50 years of age were screened. Those selected had consistent mild elevations of diastolic pressures in the 90 to 105 mm Hg range on four consecutive visits and no other demonstrable cardiovascular or renal disease. They also had two separate measurements of total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol levels. Thereafter they were randomly allocated to active or placebo groups. Antihypertensive or placebo drugs were administered once daily according to a three-step regimen. Step 1 consisted of 50 mg of chlorthalidone (or its placebo). Step 3 consisted of 100 mg of chlorthalidone plus 0.25 mg of reserpine (or their placebos). Each subject began step 1 of the regimen at randomization and continued it at each visit when his AvDP was below 85 mm Hg. Step 2 was instituted at any visit when the AvDP equalled or exceeded 85 mm Hg. Similarly, for any patient at step 2, step 3 was substituted whenever the AvDP equalled or exceeded 85 mm Hg. For subjects at step 3, however, treatment continued unchanged not only for AvDP below 85 mm Hg but also for AvDP of 85 to 110 mm Hg.

After 11 to 13 months on the program, the subjects receiving chlorthalidone showed mean increases in plasma concentrations of 9.9 mg/dl for total cholesterol; 4.5 mg/dl for triglycerides; and 12.6 mg/dl for low-density cholesterol. High-density cholesterol levels changed only 1.1 mg/dl. In the placebo group, however, there were no changes in any of the four lipid levels. The trends found in the study did not vary by age, race, sex or clinical center. The increase in cholesterol was not affected by the use of reserpine in the third step of the three-step drug therapy program.

Chlorthalidone was associated with increased levels of cholesterol, but the degree of increase was related only to age and the baseline level of cholesterol. People younger than 30 showed twice the increase found in older people, but people in their 40s had higher baseline levels to begin with, and had less than half the increase in cholesterol concentration. The patients on the active drug regimen experienced changes in average diastolic pressure, body weight, fasting plasma glucose, serum uric acid levels and serum potassium levels. In the placebo group, only the average diastolic pressure changed significantly. It decreased, but the decrease was less than in the placebo group, and the researchers found no consistent pattern of relationships which would lead to an hypothesis of the mechanism of the changes.

"Cholesterol levels increased by approximately five percent," Perry summarized, "but rigid dietary restriction can affect cholesterol levels by ten percent." The increase in cholesterol associated with chlorthalidone could presumably be controlled by following a stringent diet. There is no question that an individual's un manipulated cholesterol level is a risk factor for heart attack and stroke — the higher the level the higher the risk. However, several studies in which the cholesterol level has been lowered by various means have failed to change this risk. Perry continued: "It is, therefore, possible that raising the cholesterol also does not change the risk, but on the other hand an increase in cholesterol is something that physicians do not like to see. It seems to be in the wrong direction, and, of course, we cannot be sure that it does not increase the risk particularly after very long-term exposure, which is what we are talking about in mild hypertension. The average length of treatment might be as long as 40 years; none of our studies provide us with data on this kind of exposure."

Perry said that treating every American with a casual diastolic pressure of 90 or more would involve treating nearly 50 million people. "There are about 1.5 million heart attacks in the United States per year, and most of these occur in the 50 million hypertensives," Perry said. Because of the number involved, even a slight induced increase in risk would pose a major problem. There is no indication that the risk is being increased.

Perry believes that physicians should continue prescribing chlorthalidone "because untreated hypertension raises the risk of stroke or myocardial infarction much more than elevated cholesterol levels raise the risk. Any drug strong enough to be effective will have some other effects. This is true of every drug we use," Perry said. "Untreated hypertension is far more dangerous than a five percent increase in cholesterol levels."
The Alumni Report

Washington University Medical Center
Alumni Association

The alumni office is located in room 107 of Wohl Hospital
Class Notes

'40s

Mary M. Bishop, '40, is in private practice in Walnut Creek, Calif. She also is a council member of the Northern California Psychiatric Society and a faculty member of the California School for Professional Psychologists.

Charles P. McGinty, '49, recently received a Citation of Merit from Southeast Missouri State University. Dr. McGinty is a partner in the Cape Girardeau Surgical Clinic. He and his wife, Martha, have five children.

'50s

Jean Chapman, '53, was presented a Citation of Merit by Southeast Missouri State University recently when the University held a reunion for all its alumni who are doctors or dentists. Dr. Chapman is in private practice in Cape Girardeau, Mo.

Theodore C. Dickinson, '57, was elected president of the Colorado Chapter of the American College of Surgeons. He is in practice in Montrose, Colorado.

'70s

Sydney T. Wright, Jr., '72, has been selected chief resident in psychiatry for the Department of Psychiatry and Behavioral Sciences at Northwestern University Medical School and the Institute of Psychiatry at Northwestern Memorial Hospital in Chicago, beginning in January, 1981.

Thomas C. Namey, '73, joined the faculty of the Medical College of Ohio, Toledo, as an associate professor of medicine and radiology. He completed his residency at the McGill University Hospitals, Montreal, and his postdoctoral studies in rheumatology and nuclear medicine at the Medical University of South Carolina, and the University of Alabama Medical Center, where he served as a research fellow for the National Arthritis Foundation. Dr. Namey is the author of more than 18 scientific papers and of three chapters in medical textbooks, the most recent being a chapter in the Textbook of Rheumatology.

Roslyn Ann K. Yontovian, '74, is a pathologist at Saint Cloud Hospital, St. Cloud, Minnesota. She delivered a paper entitled, "Transfusion Problems in ABO-Incompatible Bone Marrow Transplant Patients," at the Mayo Clinic's Minnesota Association of Blood Bank meeting in October.

Dennis B. Cooke, '76, is the chief resident in medicine at Emory University in Atlanta.
Mail to the following alumni and alumnae has been returned to us, marked not deliverable. Forwarding addresses were not available. If you know the present locations of any of these alums, please write the alumni office or call collect area code 314, 454-2879. Thanks.

Class of 1921
Samuel Indeman

Class of 1923
Elias H. Schiromovitz

Class of 1925
Samuel C. Roth, M.D. 25

Class of 1929
Estella E. Defreitas
Haig H. Mitchell

Class of 1930
William E. Alsup

Class of 1931
Abbott C. Scott

Class of 1933
H. Ewing Wachter

Class of 1934
Ralph Greenberg

Class of 1941
Nelson W. Johnson

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Dorothy M. Case
Ernest S. Rogers

Class of 1944
Warren H. Kempinsky

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Marshall Gollub
Robert D. Hutton

Class of 1967
Alan J. Reich

Class of 1972
Eva Jedlickova

Class of 1975
Michael V. Taylor

Class of 1976
Evelyn S. Weiner

Class of 1977
Alan Philip Newman

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In Memoriam

Paul B. Champlin, '20 ............
September 17, 1980
Leo J. Geppert, '39 ............
November 7, 1980
Robert F. Lamar, '39 ............
October 3, 1980
Paul Max, '32 ............
November 8, 1980
Paul D. Pettigrew ............
December 8, 1979
Oscar J. Raeder, '08 ............
October 20, 1980
Henry P. Thym, '26 ............
October 28, 1980
Julius W. Vieaux, '35 ............
May 19, 1980
Estranged from Beauty — none
   can be —
For Beauty is Infinity —
And power to be finite ceased
Before Identity was leased.
—Emily Dickinson* 

The photo of an orb-weaver spider was taken in Trinidad by Paul Phillip Sher, M.D., '66. OUTLOOK magazine invites students and alumni to submit photos on any subject for use in this space. Color slides are acceptable although the printed picture will be black and white. Please write or call the editor if you need more information.
