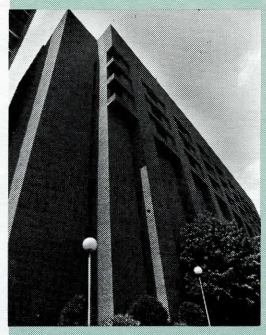
1987

Evans Medicine: Summer 1987 v. 3, no. 2

BOSTON UNIVERSITY MEDICAL CENTER

EVANS MEDICINE

Evans Memorial Department of Clinical Research and Preventive Medicine



VOLUME 3, NUMBER 2
SUMMER 1987

75th anniversary issue

The vision of its founding benefactor still animates the work of the Evans

By Norman G. Levinsky, M.D.
Director, Evans Department of Medicine

The Robert Dawson Evans Memorial Department of Clinical Research and Preventive Medicine—to give the Evans its full, official name—was dedicated on March 6, 1912. The department was established with a gift from Mrs. Maria Antoinette Evans as a memorial to her husband. Above the entrance to the Evans Building was inscribed the personal credo of the donor: "Truth Above Everything."

She set forth, as goals of the department, the following:

- To seek improved methods for the prevention of disease and for its alleviation and cure: Clinical Research.
- To aid those who may prove worthy in their efforts to secure advanced education in the medical sciences: Training.
- To furnish instruction to the public in the preservation of health: Public Education.

Robert Dawson Evans, a colorful and vigorous businessman, had risen from poverty to riches. Son of a Canadian seaman who had been lost at sea, young Evans and his family moved to Boston. He fought in the Civil War and, having been wounded twice in the Battle of Bull Run, returned to his first job, at a local rubber store, for $10 per week.

Building an art collection

Within a few years Evans had risen from employee to president of his own rubber company, and he ultimately became one of the leaders of the rubber industry in the United States. In the 1890s, however, Evans gave up his interests in rubber and turned his energies to the creation of an even more lucrative career in gold mining, in the state of California. By the turn of the century, he was an established "captain of industry," living in splendor in his mansion at the corner of Commonwealth Avenue and Gloucester Street in Boston. There, he pursued his interest in fine art, developing a notable collection of paintings. On July 1, 1909, Evans was thrown from his horse while preparing his North Shore summer estate for a visit by President William Howard Taft. By July 4, it was evident that he had suffered a ruptured viscus. He was taken to the Massachusetts Homeopathic Hospital, forerunner to the present University Hospital. After a rapid downhill course, he died on July 6, 1909.

The *Boston Evening Transcript*, the leading Boston newspaper of its time, headlined his obituary, "Robert D. Evans dead—He came to Boston a poor boy and amassed a fortune of $12,000,000."

A memorial tribute

As a tribute to Evans, his widow, Maria Antoinette, donated to the Massachusetts Homeopathic Hospital a medical research building and an endowment of $100,000 to maintain the research department.

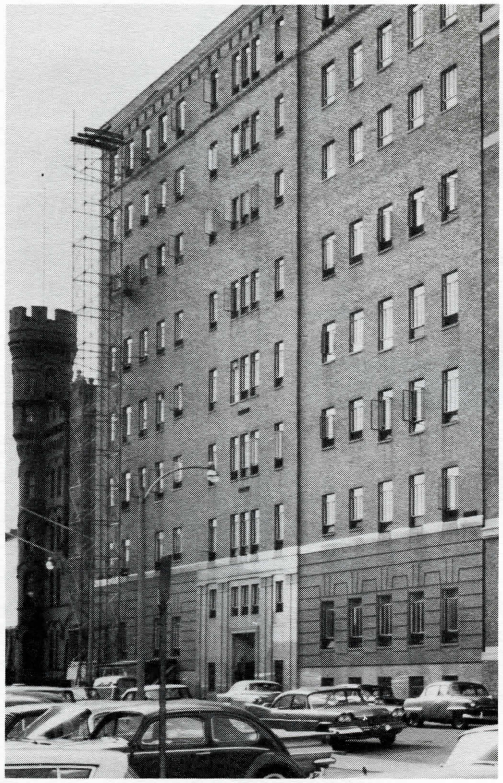
Over the next several years she made additional gifts, and at her death, her estate was divided equally between the Evans Department of Clinical Research and the Boston Museum of Fine Arts.

When the Evans Department was established in 1912 it was one of the few institutions of its kind in the world. Clinical

Continued on page 2

The 75th anniversary celebration will feature an extensive scientific program and varied social events. Page 5.

The University Hospital



View from early 1960s shows 1942 Evans Building. Visible at left is East Newton Street Armory, then being used as athletic building by Boston-area students. Part of armory's site was later used for new Evans Building, which was completed in 1972.

investigation was carried on in a number of hospitals and research facilities, but separate departments of research were rare. At the time of the department's founding, the modern scientific revolution and the advance of American research-oriented medicine were just beginning. Perhaps with the advice of Dr. Frank C. Richardson, personal physician to the Evans family and first director of the Evans, the purposes of the department were formulated by Mrs. Evans in a remarkably enlightened manner that was much ahead of its time.

A strong emphasis on research

Mrs. Evans indicated that the "laboratories are to be maintained for research work and restricted to such purposes. Two floors of the building are to be devoted exclusively to the care of patients under the treatment and observation of research workers. One additional floor is to be used as an auditorium for purposes pertaining to research, preventive medicine and public education in the preservation of health. The Evans Department is not a hospital and must not be considered from that standpoint as are those institutions whose sole function is the healing of the sick."

Thus, from its beginnings the Evans was designed to foster clinical research by providing facilities and support for clinician-investigators who would conduct laboratory research directed toward the solution of clinical problems presented by patients under their care.

The department was also intended from its origin to educate the lay public about health and disease. Within a few days of the opening of the Evans, a series of health talks was initiated for the general public. From the start, the Evans also functioned as a training facility for clinical investigators and students, the latter through its connection (physical as well as administrative) with Boston University School of Medicine.

Contributions by the Evans

Over the past 75 years, the department has been home to hundreds of staff, who have carried out its prime mission of clinical investigation. A number of its physician-scientists achieved international recognition for their research advances. Examples which come readily to mind are Chester Keefer and Louis Weinstein in infectious diseases; Robert Wilkins in hypertension; Franz Ingelfinger in gastroenterology; and Arnold Relman in nephrology. Thousands of fellows, residents and medical students, moreover, have trained at the Evans.

The original Evans Building, which now houses administrative offices of the School of Medicine and its School of Public Health, was succeeded in 1942 by a "new Evans." In 1972, the "new Evans," located on East Newton Street near Harrison Avenue, was succeeded by the current Evans Building. This facility today houses a staff of about 80 M.D. and Ph.D. investigators; more than half the patients under the care of the University Hospital Department of Medicine; and the 50 medical residents and 50-to-60 fellows who are in training at the Evans.

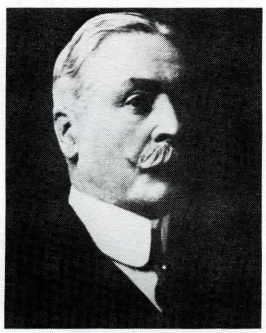
Over the past 75 years, the size of the staff has increased severalfold. The pace and volume of medical research at the Evans have reached levels undreamt of in 1912. Still, the original goals of the Evans—to discover "Truth Above Everything" from scientific research into the causes, treatment and prevention of human disease; to train the next generation of medical investigators and scientific clinicians; and to educate the public about the fruits of medical research—these purposes are as valid in 1987 as they were in 1912.

No better formulation of the *modus operandi* of the Evans can be offered than that which Dr. Wilkins, previous director of the Evans, wrote on the occasion of the department's 50th anniversary:

Dr. Wilkins's statement

"All of these developments denote a broadening of the interests and activities of the Evans Memorial beyond the strict limits of the Hospital or of the Department of Medicine, to other parts of the Medical Center. While due precautions will be taken not to spread the Evans's resources too thin, nor to expand its activities beyond closely manageable proportions, further broadening of its scope may be expected. This is possible only because of strict adherence to two cardinal principles of Evans Policy:

Continued on page 6



Robert Dawson Evans

When the Evans Department was established in 1912, it was one of the few institutions of its kind in the world.

Hypertension research, long an Evans tradition, today focuses on how vessels are damaged

The history of hypertension research and treatment is intimately bound up with that of the Evans, especially over the department's past four decades.

To cite selected examples of key developments in this area that have emerged from the Evans:

Robert W. Wilkins, M.D., director of the Evans and the UH Department of Medicine from 1960 to 1972, along with his associates, was responsible for introducing in the United States the drug reserpine, the first effective anti-hypertensive medication. Dr. Wilkins, now retired and living in Newburyport, Mass., also devised the step-care approach to hypertension treatment, in which agents with different mechanisms of action are combined sequentially, as needed, in order to control hypertension.

In 1957, Dr. Wilkins, William Hollander, M.D., and Aram V. Chobanian, M.D., developed diuretic therapy for hypertension. This approach represented a major breakthrough, making possible the management of severe as well as mild hypertension.

The advances in antihypertensive therapy have continued in the past decade. Harambolos Gavras and his wife, Irene, both M.D.s and both members of the Evans Section of Hypertension and Atherosclerosis, collaborated with Dr. Chobanian on the development of captopril, and subsequently enalapril. Both are angiotensin-inhibiting enzymes, and they represent an exciting direction in therapy, providing what is now the most useful approach available for managing refractory hypertensives as well as patients affected by congestive heart failure.

Changing attitude toward treatment

As these investigators and their counterparts at other institutions have been introducing an array of new treatments, medicine as a whole has undergone a marked change in attitude toward hypertension therapy.

"When I first came here as a fellow in the late '50s, there was a very strong feeling in some circles that lowering blood pressure would be injurious," recalls Dr. Chobanian, who heads the Evans Section of Hypertension and Atherosclerosis.

Numerous studies, however, have since demonstrated that treating hypertension can be highly effective.

The earliest studies, says Dr. Chobanian, showed that lowering pressure is very beneficial for individuals with severe or malignant hypertension. "Ninety percent or more of those individuals would die within a year without treatment," says the investigator, "but most of those who are treated medically survive."

Subsequent studies showed that therapy also offered important benefits for patients with milder forms of hypertension, producing a marked reduction in the incidence of strokes, and heart and kidney failure.

Such findings have helped fuel widespread acceptance of the need for treatment. Yet while acceptance has grown, there is controversy about some of the benefits of therapy for the mildest forms of hypertension, where the diastolic pressure is roughly between 90 and 100.

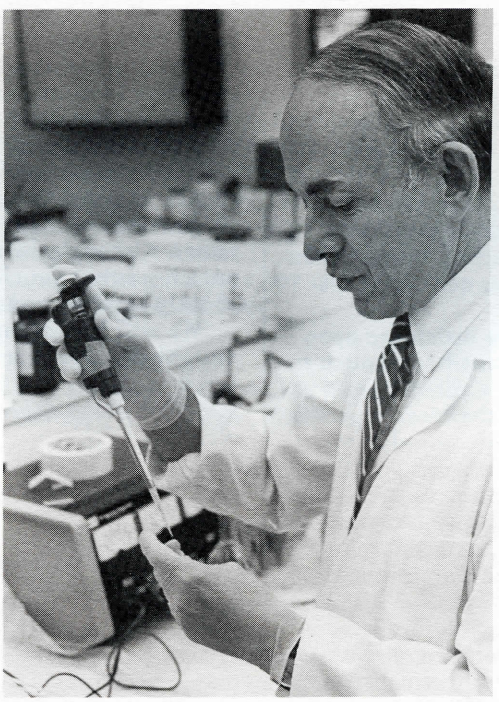
Coronary disease at issue

"The big clinical question right now is, Why are we not getting a better reduction in the incidence of coronary disease from lower blood pressure?" says Dr. Chobanian. "We're preventing strokes and we're preventing heart failure, but most of the studies involving mild hypertensives indicate that we have only had a slight impact on coronary disease or overall mortality."

That concern has given new impetus to the basic research being pursued by Dr. Chobanian and his colleagues. Their inquiries may help explain why treatment apparently is not prolonging life or reducing rates of myocardial infarction in individuals with mild hypertension, and also may suggest new types of therapies.

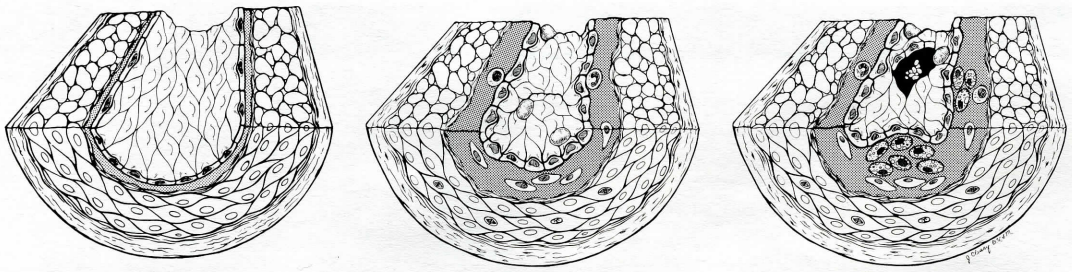
A consistent thread running through Dr. Chobanian's research interests is the mechanisms by which the vessel wall is damaged.

In the 1950s and 1960s, he, along with Dr. Hollander—now a BUSM professor of medicine, biochemistry and physiology—and others helped illuminate the factors that produce atherosclerotic plaques. The group showed that the key factors are the extent of penetration of cholesterol into the arterial intima, metabolic activities within arteries, and the effectiveness of the body's mecha-



Dr. Chobanian in his Cardiovascular Institute laboratory.

"When I first came here in the late '50s, there was a very strong feeling in some circles that lowering blood pressure would be injurious."



Diagrams illustrate response to different types of insults. From left, they depict: 1., normal rat aorta; 2., aorta after six weeks exposure to elevated blood pressures, with thickened media, adherence of blood cells to intimal surface, and increased mitotic activity among smooth-muscle cells; and, 3., artery affected by both hypercholesterolemia and hypertension, with cell loss and platelet aggregation of endothelium, and accumulation of smooth-muscle and circulating blood cells in subendothelium.

nisms for clearing the cholesterol once it has entered the vessel wall.

Studying arterial responses

Among Dr. Chobanian's chief current interests is how the artery wall responds to hypertension. He and Peter I. Brecher, Ph.D., a professor of biochemistry at BUSM as well as a member of the Evans, have helped shed light on one of the mechanisms by which blood pressure produces thickening of the arterial wall and hypertrophy of its smooth-muscle cells.

"From work that we and others have done in the rat model, it's clear that the amount of DNA in many of the arterial smooth-muscle cells can double in response to hypertension," says Dr. Chobanian.

This phenomenon, called polyploidy, can occur within a month of the time that the animals' pressures are raised, and a quarter or more of the smooth-muscle cells may be affected. "The cells seem to go into the growth cycle," says the investigator, "but for some reason they don't divide, so DNA builds up within individual cells."

The extent to which polyploidy is responsible for the smooth-muscle hypertrophy that occurs in arteries exposed to high blood pressures is unclear, because smooth-muscle cells also become hypertrophic or hyperplastic in the absence of DNA abnormalities. The findings about the DNA buildup, however, raise the possibility that genetic malfunctioning may be implicated in damage to arteries.

A group working under Dr. Chobanian is exploring this possibility. Their specific focus is whether growth factors are somehow stimulated by hypertension, and thus are partly to blame for the abnormal growth of cells in artery walls affected by high blood pressure.

Probing age-related damage

Dr. Chobanian's investigations have implications not only for the types of arterial hypertrophy widely recognized as abnormal, but also for the arterial changes long regarded as a normal part of aging.

The investigator says his studies related to the aging of vessels were stimulated in part by some intriguing observations in animals. "If you look at the blood vessels from young, hypertensive rats," he says, "you'll see that they often look virtually the same as vessels from older, normotensive animals."

To test whether lowering pressures might prevent the hypertrophy and hyperplasia that underlies these changes, Dr. Chobanian and his associate Christian Haudenschild, M.D., a professor of pathology at BUSM, experimentally reduced the pressures in rats to the low normal range. The result was that arteries from the treated animals exhibited almost none of the changes normally associated with aging.

Does this mean that it might be appropriate to consider treating individuals with presumably normal blood pressures? Not yet, says Dr. Chobanian. "At this point, we're really concerned with the basic process that is going on," he notes. "It would be a tremendous step from where we are now to begin talking about clinical applications."

Protecting the endothelium

While the investigators' laboratory work is

Continued on page 6

"If you look at the blood vessels from young, hypertensive rats, you'll see that they often look virtually the same as vessels from older, normotensive animals."

Cardiovascular Institute: Focal point for hypertension studies

Since 1974, much of the hypertension research at Boston University Medical Center has been carried out under the auspices of the Cardiovascular Institute (CVI), which was founded that year by Dr. Aram Chobanian.

Not long after its founding, the Institute was designated a Specialized Center for Research in Hypertension by the National Institutes of Health. It is one of five such centers in the country.

Last year, the National Institutes of Health named the CVI the first—and so far the only—National Research and Demonstration Center for Hypertension. As such, it has responsibilities that include not only carrying out basic and clinical research, but also developing new systems for the control of hypertension in the community and exploring national health-policy issues related to hypertension. □

The 75th anniversary program: Come one, come all!

The Evans will mark its 75th anniversary with a scientific program and gala celebration on Thursday and Friday, Oct. 29 and 30.

All former Evans staff, fellows, residents and students are invited to participate. The scientific program will include 12 satellite symposia on recent advances in internal medicine on Thursday, a series of "state-of-the-art" lectures on Friday, and the Distinguished Basic Science Lecture by Nobel laureate Walter Gilbert, M.D., professor of molecular biology at Harvard Medical School, also on Friday. The program is certified for continuing medical education credit and is open to Evans graduates and former fellows without charge.

There will be a reception at Boston's Park Plaza Hotel, site of the satellite symposia, on Thursday after the symposia have concluded.

On Friday, there will be a combined luncheon and "poster session" in the BUSM's Hiebert Lounge. That day's plenary lectures will be given in the Evans Building's Keefer Auditorium. There also will be opportunities to visit the Hospital's new Atrium Pavilion, a 233-bed core clinical facility that will have its grand opening in November.

For further information on the satellite symposia, please contact:

Office of Continuing Medical Education
Boston University School of Medicine
80 East Concord Street
Boston, MA 02118
(617) 638-4605

Following are the faculty and topics for the symposia and the plenary lectures:

Satellite Symposia, Oct. 29, 1987

(Park Plaza Hotel)

Title	*Sponsoring Evans Section*	*Faculty Director*
Current Views in Cardiology	Cardiology	Thomas J. Ryan, M.D.
Advances in Hematology/ Oncology	Hematology/Oncology	Lewis R. Weintraub, M.D. Ronald P. McCaffrey, M.D.
Gastroenterology at the Evans	Gastroenterology	J. Thomas LaMont, M.D.
Fungal Infections and Antifungal Therapy	Infectious Diseases	Richard Diamond, M.D.
A 30-Year Perspective on Cardiovascular Epidemiology from the Framingham Study	Epidemiology	Joseph Stokes III, M.D.
Update in Nephrology	Renal	Norman G. Levinsky, M.D.
Progress in Hypertension	Hypertension	Aram V. Chobanian, M.D.
Recent Progress in Selective Targeting of Cancer Cells	Medical Oncology/ Biomolecular Medicine	Ronald McCaffrey, M.D. John R. Murphy, Ph.D.
Recent Advances in Endocrinology	Endocrinology	James C. Melby, M.D.
Mechanisms of Cell Activation	Pulmonary/Immunology	David Center, M.D. David I. Beller, Ph.D.
Special Topics for the Practicing Internist	General Medicine	Robert Friedman, M.D.

State-of-the-Art Lectures, Oct. 30, 1987

(Evans Building, The University Hospital)

- Plagues of the Twentieth Century—Louis Weinstein, M.D., formerly chief of the Evans Section of Infectious Diseases; professor of medicine, emeritus, Harvard Medical School.
- Contributions of the Framingham Heart Study to the Conquest of Cardiovascular Plagues—William Kannel, M.D., chief, Evans Section of Preventive Medicine and Epidemiology; professor of medicine, Boston University School of Medicine.
- Gallstones: Observe, Obliterate or Operate—Martin C. Carey, M.D., D.Sc.; formerly Evans fellow in gastroenterology; Lawrence J. Henderson Associate Professor of Health Sciences and Technology, Harvard-M.I.T. Division of Health Sciences and Technology.

Current Research at the Evans, poster session (Hiebert Lounge, BUSM)

- Redesigning the Diphtheria Toxin Structural Gene: Targeted Cytotoxins for Potential Therpeutic Use—John R. Murphy, Ph.D., chief, Evans Section of Biomolecular Medicine; research professor of medicine, Boston University School of Medicine.

Distinguished Basic Science Lecture. Walter Gilbert, Ph.D., professor of molecular biology, Harvard University.

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Benefactor...

Continued from page 2

1. The insistence on excellence in Evans personnel.

2. The delegation of authority and responsibility to these highly qualified persons for the development and financing (mainly through outside grants) of their own programs.

"In this way, Evans funds can be used to get new programs under way and to back them up in times of emergency, but can then be released to support other new activities that need development.

"As always, there will be insistence upon the principles that have contributed much to the success of the Evans: Excellence and Freedom. Other than this, the location, form and program of the Evans Memorial of the future will be flexible and adaptable to the circumstances and needs of the future. Thus, the Evans Department of Clinical Research will continue to honor its name and to fulfill its mission of service to the Community and Mankind."

The staff has grown, the buildings have been replaced by successively larger structures, but the *raison d'etre* of the department begun by a woman of foresight 75 years ago persists intact. □

Hypertension...

Continued from page 4

still focused on basic questions, it is nonetheless taking directions that may eventually have important clinical implications. Some recent research, for example, has made use of propanolol, the beta blocker that is widely used to treat arrhythmias, angina and related conditions.

"In animal studies," says Dr. Chobanian, "we've found that when you use a beta blocker like propanolol, it prevents the buildup of excess DNA in response to hypertension." Other studies, meanwhile, have shown that propanolol also prevents the formation of atherosclerotic plaques in rabbits on high-cholesterol diets.

The studies support the hypothesis that the sympathetic nervous system's adrenergic pathways play a critical role in the arterial wall's response to injury. They also suggest, however, that other mechanisms are at work as well. One of the forms of propanolol administered to the rabbits has little effect on the beta adrenergic receptors at the relatively low doses employed. Yet it, too, helped retard plaque formation.

Dr. Chobanian says the effect may be related to the drug's stabilizing effects on cell membranes. "We think the propanolol is changing the permeability of the endothelial cells by a local membrane effect," he explains, "so you don't get as much cholesterol coming into the cell."

Dr. Chobanian says that in time, new therapeutic approaches are likely to emerge from studies such as those under way in his laboratory. Although the nature of these approaches is not yet clear, he has some ideas about what directions they may take.

"We will be looking for approaches that do more than just lower blood pressure," he suggests. "That will probably mean lowering serum cholesterol levels as well, for example." □

Suggested further reading

1. Chobanian, A.V.: Hypertension, antihypertensive drugs, and atherogenesis: Mechanisms and clinical implications. J Clin Hypert *2*: 148s-157s, 1986.

2. Chobanian, A.V., Brecher, P.I., Haudenschild, C.C.: Effects of hypertension and antihypertensive therapy on atherosclerosis. Hypertension *8*; I-l5-I-21, 1986.

Evans Medicine is published by the Evans Memorial Department of Clinical Research and Preventive Medicine of The University Hospital, a member of Boston University Medical Center. Editor is Jay D. Coffman, M.D., associate director of the Department; associate editor is Richard P. Anthony; designer is Kredlow & Gonzalez. *Evans Medicine* is produced by Boston University Medical Center's Office of Publication Services, Owen J. McNamara, director. Send any correspondence to the Evans Memorial Department of Clinical Research, 75 East Newton St., Boston, MA 02118. Norman G. Levinsky, M.D., is director of the Department.

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