In this review, I chronicle some of my research on small and large blood vessels in vivo. This research was a direct outgrowth of research conducted by my advisor, Maurice B. Visscher, and his research was in turn greatly influenced by one of his advisors, Ernest H. Starling. My research was also stimulated and influenced by the tremendous activity in cardiac surgery and, to a lesser extent, poliomyelitis research while I was in training at the University of Minnesota. The contributions of Starling and Visscher and the environment at the University of Minnesota during the development of cardiac surgery set the stage for my small and large blood vessel research.

Why Cardiovascular Physiology?

My interest in the physiology of in vivo small and large blood vessels developed accidentally. During medical school at the University of Minnesota, a rotating internship at Minneapolis General Hospital, and service in the United States Army Air Force in Panama, my intent was to pursue a residency in internal medicine as soon as feasible. However, there was a period of rapid military demobilization after World War II, and I was suddenly and unexpectedly released from the Army Air Force in 1948 before I had secured a position in one of the two desirable residency programs in my home state of Minnesota, either at the University of Minnesota or the Mayo Clinic. When I inquired, I was told that the positions would not be available for a year. What should I do with this time?

I knew that a year in research could be applied toward the formal training requirements of the American Board of Internal Medicine and therefore spoke to Elexious T. Bell in the Department of Pathology at the University of Minnesota. Dr. Bell was an internationally known pathologist, admired by students and colleagues, and I liked and had done well in his course in medical school. However, he too said all research and teaching assistant positions were filled. As a last resort I walked directly from the Department of Pathology to the Department of Physiology, where the chairman was Maurice B. Visscher, also internationally known, mainly for work on cardiac energetics, some of it with Ernest H. Starling.

Dr. Visscher had a research assistant position open, and since my overall medical school grade point average was good, he offered it to me, suggesting that I also work toward a masters’ degree. Physiology did not particularly interest me; I had not excelled in it in medical school. However, I thought the position would give me the opportunity to test an idea I had that pulmonary insufficiency could be treated with intravenous oxygen, and Dr. Visscher assured me that the year would in fact be applicable to the formal training requirements of the American Board of Internal Medicine. I therefore accepted the position.

Maurice B. Visscher and Ernest H. Starling

Maurice Visscher was an unusually broad and versatile person. He made important contributions to a variety of areas in both science and society and these many activities, accomplished so well, impressed and motivated me. His graduate and medical education had been at the University of Minnesota. His graduate advisor, Frederick Hughes Scott, encouraged him to use the field of physical chemistry as a minor field for his PhD program. This background in physical chemistry permitted him to approach the problems of material transport and other basic problems in ways that would have been impossible without it. An “honors program” for specially selected students eliminated entirely the lock step curriculum choices for medical students and allowed him, with considerable independent study, to satisfy the requirements for both the PhD and MD in 4 calendar years at the university. In 1969, while reviewing his half century in science and society, he commented that he regretted the fact that the students in the then newly integrated, streamlined, and shortened so-called core curricula actually had less freedom of action than he himself had had some 50 years earlier. Major factors in his own education as a scientist were his experiences as a postdoctoral National Research Council Fellow in two great centers of physiological research, University College, London, and the University of Chicago.

In London, Dr. Visscher worked with Ernest H. Starling and had intimate contact with A.V. Hill, E.B.
Verney, and others. Starling was internationally known for studies in endocrinology (secretin), fluid flux across the capillary membrane (Starling-Landis Hypothesis), and cardiac function (Starling’s Law of the Heart). It was in the latter area that Visscher interacted with Starling, and it was during this period that he started the studies for which he is perhaps best known, energetics of the failing heart. Visscher showed that in spontaneous failure, without disturbances in myocardial perfusion, failure is always associated with a declining efficiency and that the cardiac glycosides increase the efficiency of the failing heart.

Starling was nearing the end of a brilliant career in medicine and physiology when Visscher joined him. Yet the impact on Visscher was great. This is not hard to understand. According to Carlton B. Chapman,

In circulatory physiology, the Starling legacy is conceptionally one of the most influential in the twentieth century. The “Starling sequence,” embracing both central circulatory function and fluid exchange at the capillary level was and remains the unifying theme of contemporary circulatory theory.”

Starling was influenced by two visits in Germany, one to Kühne’s laboratory in Heidelberg and the other to Heidenhain’s laboratory in Breslau, the latter leading to the “Starling equilibrium” of fluid exchange across the capillary membrane. He was also influenced by a lifetime association with William Maddock Bayliss, who was known, among other things, for the “Bayliss response.” “It was a highly productive and complimentary union. Bayliss was the learned, methodical and cautious partner, Starling the aggressive, impatient, and sometimes uncautious visionary.” Together they opened the door to the vast field of hormonal action, and Starling coined the word “hormone” in 1905. Immediately preceding World War I, two of Starling’s important papers on the control of the heart appeared, and these were followed by many others on heart function. The two papers were written with S.W. Patterson who later became Starling’s son-in-law.

Starling succeeded to a remarkable degree in replacing empiricism with scientific understanding as a basis for practice at the bedside. He and his colleagues, notably Bayliss, changed the face of classical physiology more, probably than any other group since Harvey’s time.

This must have left a lasting impression on the young Visscher, just as Visscher left a lasting impact on me.

In Chicago, Visscher worked with A.J. Carlson, A.B. Luckhardt, Baird Hastings, and George Burget. Hastings taught him practical micromethods for measuring hydrogen ion concentration in blood, which allowed him and George Burget to discover the pH dependence of epinephrine in its actions on blood vessels, a phenomenon that has been found to be a general one for most catecholamine actions.

Visscher demonstrated his versatility in research quite early. In the 1930s, he became interested in the transport of materials, particularly the transport of urea and other crystalloids across the intestinal mucosa at various levels of the gut. He consulted his friends in physics and obtained isotopes of chloride and sodium. These isotopes allowed the first direct study of the bidirectional movement of these ions. He considered this to be one of his most creative works. In his 1969 review, he recalled the splendid cooperation he received from physicists and other colleagues during this study. Some of his comments are reprinted below, because although they were written 21 years ago, they are even more appropriate today. The comments demonstrate his foresight as well as his mastery of the English language.

After saying he owes colleagues and students the greatest of debts, Visscher goes on to say:

A university—a community of scholars—from the beginner in search of knowledge to the most sophisticated scholar—is an environment in which creativity can and does flourish. Our society has not produced any other mechanism which is as generally successful in the advancement of basic knowledge. It is certainly true that many basic discoveries have been made in research institutes, divorced from educational activities, but historically until the present, most basic discoveries have come from the universities and other teaching institutions.

There are voices today suggesting that this era is passing, because teaching must be the primary function of educational institutions and for them additions to knowledge are secondary goals. However, I would point out that graduate education is impossible except in the context of creative scholarship. Insofar as an educational institution even pretends to carry on graduate instruction, it must of necessity support research as a major function. Unless it does, its graduate programs are a fraud, both upon its students and upon society at large. The proportionate emphasis upon teaching and research activities that may be optimal may be arguable but again, let it be noted well that graduate schools are training grounds for almost all investigators. An environment in which mediocre research is done is not optimal for the training of superior investigators. Thus, if only to have superior investigators to work in industrial and other non teaching research institutes, one must support universities liberally enough to provide them adequate quotas of the most competent researchers. To do otherwise would be to kill the goose that lays the golden egg.

Another evidence of his broad interests, versatility, and deeply felt civic and humanitarian obligations include scientific publications on endotoxin shock, pulmonary edema, peripheral veins, calcium flux in heart muscle, chronobiology, aging, and cancer, and his involvement in scientific communications. He was instrumental in the development of biological abstracts, annual reviews, and the handbooks of physiology. He published two books on medical ethics. He was a leader in animal welfare (he organized the National Society for Medical Research, one of two predecessors of the National Association for Bio-
Maurice Visscher, M.D., Ph.D. joined Modern Medicine shortly after it was founded in 1932. For nearly 50 years he served as a primary medical resource and confidante to the Journal's editorial staff until his death earlier this year. When we say it takes character to do something, we mean it takes courage, integrity, diligence, patience, and many other admirable qualities. Another synonym for "character" is Maurice Visscher, our fellow editor of Modern Medicine.

That he was born (Holland, Michigan, 1901) and died (Minneapolis, Minnesota, 1983) and was a member of almost every reputable scientific society that could honor him is all a matter of public record. As a physiologist and physician, he was a widely and deeply appreciated role model, representing the best of both disciplines. His life and activities speak for themselves and need no repetition.

What is harder to convey is the quality of the man. There were so many aspects of his life that took character. He headed the National Society for Medical Research and thereby engendered the wrath of antivivisectionists, such as the dancer-celebrity, Irene Castle. He fought the Congressional Committee on Un-American Activities and chaired the AAAS Committee on Civil Liberties for Scientists. He was deeply involved in the antiwar movement. He remained a Democrat from beginning to end, which tells us something.

Maurice was nearly, but not quite, as deeply involved in the ethics and morals of scientists and physicians. Two books, Humanistic Perspectives in Medical Ethics and Constraints and Imperatives in Medical Ethics, testify to this. Supporting the need for animal experimentation was only one facet that occupied much of his attention and for which he was seldom thanked by those who should have been most grateful.

It took less courage, but far more time, to conduct other aspects of his busy life—active participation in the American Physiological Society, the American Heart Association, International Union of Physiological Sciences, Group Health Plan, Society for Experimental Biology and Medicine, and Modern Medicine.

With all of this, Visscher maintained one of the principal teaching and research departments of physiology in the world. Studies of the circulation and exchange of electrolytes in the gastrointestinal tract were the recurrent themes. Each paper fulfilled the high quality of workmanship that he demanded. Time has proved this virtue applicable to his multifaceted research.

But what kind of person was this paragon? With his busy and often contentious life, he maintained a calm and equanimity that was remarkable. One could differ—heatedly—with his opinions, but anger never ensued. I have had frequent occasions to test this observation, and the result was always the same. This warm, intelligent, and decent man set standards of behavior that his students and many friends would like to emulate. We all recognized that here was a person who dared to do those things it takes character to do. He has bequeathed us not only his many scientific accomplishments, but also a lasting memory of a rare human being.

Senator Hubert H. Humphrey had this to say about the man:

Maurice Visscher is a man respected for his professional excellence, an outstanding teacher, a long-time friend who is deeply concerned with the social, economic and political conditions of our society. He is a political activist who is able to blend the excellence of his professional ability with his outrage against any form of injustice. Those of us in political life know him as fiercely independent and always persevering.

Visscher had an unusually cordial relationship with Owen H. Wangensteen, Professor and Chairman of the Department of Surgery at the University of Minnesota, who said that the University of Minnesota's leadership and involvement in intracardiac surgery evolved as a direct result of his friendship with Visscher. "It simply wouldn't have transpired without him." Early in his chairmanship, Wangensteen began sending a succession of brilliant young surgeons to Visscher for 1 to 3 years of study of the physiological problems involved in heart surgery. Clarence Dennis, Richard Varco, C. Walton Lillehei, K. Alvin Merendino, Herbert Warden, Ivan Barofsky, Morley Cohen, Lloyd MacLean, Vincent Gott, Gilbert Campbell, Norman Shumway, Christiaan Barnard, and others benefitted from this program. Visscher and Wangensteen held weekly interdepartmental physiology-surgery conferences throughout the years they chaired their respective departments. The conferences were invariably interesting and informative. One of the sessions led to the work of Fletcher Miller and Richard Varco on the mass spectrophotograph to assess the concentrations of inhaled anesthetic gases. Alfred Nier of the Department of Physics contributed one of his early models for the studies.

It was into this environment of scholarly activity in the medical sciences and of social and civic consciousness that I was thrust in 1948 by accepting the position offered me by Visscher, at a time when cardiac surgery was awakening and poliomyelitis was rampant.

Left Heart Catheterization

I told Dr. Visscher about my interest in intravenous oxygen. He promptly ignored it and asked me to try to confirm a report that hemorrhage causes pulmonary edema in dogs. I failed to confirm the report but Dr. Visscher's interest in pulmonary edema led to an attempt to catheterize the left heart and pulmonary veins in dogs. Courand et al had
earlier catheterized the right heart, and Visscher felt that the mechanism of pulmonary edema would not be clarified until we were able to measure pulmonary venous pressure in the intact closed chest state. Could this be accomplished with the "flexible catheter technique" of Courmand et al? He teamed me with Gilbert S. Campbell, one of Owen Wangensteen's surgical residents who was rotating through the Department of Physiology, and Wayne Adams, his resourceful and experienced technician, and gave us a large (no. 10) whistle-tipped, radiopaque ureteral catheter. We inserted it retrogradely into the carotid artery of an anesthetized dog and, under fluoroscopic control, manipulated it down the ascending aorta, past the aortic valves, into the left ventricle, past the mitral valves, into the left atrium, and then into the pulmonary vein (Figure 1)—at that time an astounding feat! Hellemes et al did the same using more standard cardiac catheters and beat us into print.

We used the technique to show that cardiac output in fact increases with left atrial pressure in the intact anesthetized animal as predicted by Starling from studies in the heart–lung preparation. We estimated cardiac output by the direct Fick method, laboriously measuring arterial and venous oxygen contents by the Van Slyke manometric method and oxygen consumption with a spirometer. Left atrial pressure was recorded on photographic paper using the newly introduced resistance wire pressure "transmitter" (Statham strain gauge), Heiland mirrored oscillograph galvanometers, and a Waters-Conley camera cart; we didn't initially trust this new pressure recording system so we verified the pressures with Hamilton and mercury manometers. We also used the flexible catheter technique to show that the pulmonary edema due to increased intracranial pressure or airway resistance correlates positively with pulmonary venous pressure (some of the airway resistance experiments lasted through the night, requiring sleep on laboratory desks; this quickly taught me to design research protocols not lasting past lunch time). During this period, the pulmonary edema associated with increased intracranial pressure was thought to result from a neurogenically induced increase in capillary membrane permeability to plasma proteins. It was also the time of the great poliomyelitis epidemics, and airway obstruction and pulmonary edema (mechanism unknown) were sometimes seen in the bulbar form. I used some of the data we generated for my masters' thesis, which I defended in 1949. Earl Wood, an earlier student of Visscher's, was a member of my committee.

After a year and a half in Visscher's department, I spent the next 2 years as a Fellow in Internal Medicine at the Mayo Clinic in Rochester, Minn., thus satisfying the formal training requirements mandated by the American Board of Internal Medicine (I was certified 4 years later). While in Rochester, I missed research and therefore arranged with Dr. Visscher to return, supported by a Research Fellowship of the American Heart Association, to the Department of Physiology in Minneapolis in 1951.

In Situ Peripheral Small and Large Blood Vessels

Dr. Visscher had two suggestions this time. One was to again enroll in graduate school but this time work toward a PhD in physiology. I had no interest in another doctorate but he argued that it would someday stand me in good stead, increasing my options, so I acquiesced. The other was to extend the flexible catheter technique to the periphery. We did and thus began a long interest in situ small blood vessels in relation to fluid flux across the capillary membrane, local blood flow regulation, and arterial hypertension, particularly with respect to the roles of the blood vessel Na⁺-K⁺ pump, ouabain-like substance, and vascular smooth muscle cell membrane permeability to sodium.

The war had stimulated great technological advances, and some of them were finding their way into physiological research. Pressure transducers or strain gauges replaced the mirrors and shim brass of the Hamilton manometer. I can still see Earl Wood and Lyle Petersen demonstrating and discussing these newer pressure-measuring devices at the first fall meeting of the American Physiological Society meeting in Minneapolis. Polyethylene tubing became available in a variety of sizes, rotometers and later electromagnetic flowmeters gave visual readout of blood flow, and finger pumps propelled blood without touching it (independently of pressure if desired).

I met with Dr. Visscher on the first day of my return to the Department of Physiology, and he pulled from his desk the first PE-10 polyethylene tubing I had ever seen. He asked me to manipulate it retrogradely in a peripheral vein, past valves to a peripheral position, and measure the pressure with a low volume displacement strain gauge. I tried this in
the dorsal foot vein in the forelimb of the anesthetized dog but could not manipulate the tip past the venous valves (why I selected the forelimb I'm not sure but I learned its vascular anatomy well and therefore stuck with it for most subsequent animal studies). I therefore fitted a 7-cm long 0.2–0.5-mm diameter, thin-walled glass tube with a polished tip to the end of the PE-10 polyethylene tubing. The rigidity of this "catheter" allowed me to bypass or fracture the valves as I manipulated it distally in a forepaw vein and placed it in a wedged position in or near the web between the toes; the vein then acted as an extension of the catheter and the pressure measured was that in the first collateral, usually one about 0.2–0.5 mm in diameter. We subsequently adapted the technique to unanesthetized dogs and humans using very small stiff plastic catheters, and we soon found that it was even easier to wedge it distally in a small artery in the forepaw.

We pointed out that pressures in small veins are important because capillary pressure in open beds cannot be lower than those pressures; therefore, small vein pressures represent minimal values for the venous capillary pressures. We found that there need be no fixed correlation between small vein pressures and those in more central veins. In normal waking dogs, the small subcutaneous vein pressure in the foot ranged from 8 to 25 mm Hg with 13.1 mm Hg as the mean value, not greatly different from the value under pentobarbital anesthesia. Large spontaneous fluctuations in small vein pressure occurred in the waking state (Figure 2) that were not associated with significant changes in large vein pressure, suggesting that the venous system is subject to nervous and humoral control and, further, that the pressures in capillary beds are not static over time. Exercise produced a large elevation in small vein pressure. Hind limb edema due to femoral arteriovenous anastomoses was associated with hind limb small vein pressures approaching the value of plasma colloid osmotic pressure (Figure 3). Norepinephrine, serotonin (Figure 4), and histamine increased small vein pressure, the first two by constricting veins and the latter by increasing flow. The mean value for small footpad artery pressure was 65 mm Hg. These data formed the basis of my PhD thesis, which was examined by Visscher, Howard Burchell, Edgar V. Allen, and others in 1953.

Models of Cardiac Valvular Disease

I didn't abandon left heart catheterization while working on my PhD in physiology. This was the period during which cardiac surgery was developed at the University of Minnesota, and Owen Wangensteen and Dr. Visscher encouraged collaboration between surgical residents and physiology graduate students and fellows. During my period in the Department of Physiology, many surgical residents, including Walt and Richard Lillehei, worked in the physiology laboratories on the second floor of Millard Hall, and many physiology fellows, including myself, worked in the Department of Surgery "dog labora-
Haddy

In Situ Blood Vessels

SMALL VEIN PRESSURE

IO» SEROTONIN, BRACHIAL ARTERY

SMALL ARTERY PRESSURE

BRACHIAL ARTERY PRESSURE

BRACHIAL ARTERY BLOOD FLOW

TIME

FIGURE 4. Effect of intrabrachially injected serotonin on pressures and flow in the forelimb of the anesthetized dog. Large vein pressure (not shown here) did not change. Reprinted from PhD thesis (1953) and from Reference 9, with permission, ©1985, Minnesota Medical Association.

We used this approach to show that most of the peripheral resistance is in the small vessel segment and that, under most circumstances, this segment is also the main variable resistance but that under some circumstances, large veins and large arteries may also offer substantial variable resistance to blood flow (e.g., during infusion of serotonin into the brachial artery) (Figure 5). It soon became apparent from our studies and from the neural studies of Abboud and colleagues using our technique that veins are not simply passive conduits returning blood from the periphery to the heart but that spontaneous or evoked venomotor activity can have great influence on venous capacitance, venous return, and fluid flux across the capillary membrane.

In 1953, fearful that I would not finish school before my children started kindergarten, I took my first job and moved with my family from Minneapolis. I moved to Chicago with Richard Ebert, Craig Borden, and Ben Heller to help open the Veterans Administration Research Hospital associated with the Northwestern University Medical School. Here I found that combining the small vessel pressures with pressure measurements in the brachial artery and cephalic and brachial veins and measurements of blood flow or constant flow allowed us to divide the vascular bed in skin or muscle in the dog forelimb into three serial segments by calculating segmental vascular resistances to blood flow. The three serial segments were large artery, small vessel, and large vein. This allowed us to quantitate vasomotion in large and small vessels.
We found that, in essential and renal hypertension, the pressure gradient from small artery to small vein was elevated. The pressure gradient from brachial artery to small artery and from small vein to antecubital vein were normal. These findings suggest that the elevated peripheral resistance results from constriction of the smaller vessels.

We showed that congestive heart failure decreased the rate of blood flow by increasing the resistance to blood flow. Venous resistance was normal, indicating that the vascular constriction is upstream to the small vein. Antecubital and small vein pressures, and by inference, capillary hydrostatic pressure, were elevated. Antecubital vein pressure was elevated more than the small vein pressure. Normal venous resistance in the face of elevated transmural pressures indicates decreased venous compliance.

Other studies in the human upper extremity showed that exercise increased small vein pressure in normal subjects and in patients with compensated heart disease, suggesting that the loss of plasma volume during exercise results from elevation of a capillary hydrostatic pressure. Norepinephrine and angiotensin also increased small vein pressure, probably because of venous constriction, as did local cold exposure, and here the change in small vein pressure was large (Figure 7). As observed earlier in unanesthetized dogs (Figure 2), small vein pressure was spontaneously more variable than antecubital vein pressure in resting subjects.

It was in Chicago in 1953 that I first employed Booker T. Swindall as a surgical technician. He is with me today, functioning as chief animal surgery technician with no cardiovascular surgical procedure in the dog beyond his expertise. In the mid-1950s, I was recalled into the service and, with the help of Dr. Visscher, was assigned to the Army Medical Research Laboratory at Fort Knox, Ky., where Ray G. Daggs was the director. It was here that I met Jerry B. Scott, who became my closest collaborator and friend until his untimely death in 1982. Jerry was a
great scientist with a gift for creating an atmosphere in which people worked together harmoniously.

Local Blood Flow Regulation in Canine Vascular Beds

In the mid-1950s, the mechanism of autoregulation of blood flow was of great interest, and one hypothesis attributed the phenomenon to changes in blood viscosity. While at Fort Knox, we showed that this is not the case in the canine kidney because autoregulation still occurs during perfusion with cell-free fluids. This led to other studies in local blood flow regulation that together formed the basis for the lecture I presented before the circulation group of the American Physiological Society in 1966 at the time of the first Wiggers Award.

Histamine Edema

In a companion study at Fort Knox, we developed a method for cannulating lymph vessels in the hilus of the kidney and Mr. Swindall later, after our moves from Illinois to Oklahoma and then to Michigan, adapted the technique to the forelimb of the dog, thus allowing us to measure flow and protein concentration of lymph from skin and skeletal muscle. We also developed techniques for measuring net fluid flux across the microvascular membrane. In a study published in 1960, I observed that brachial arterial infusion of histamine raises small vein pressure in the dog forelimb and suggested that elevated capillary hydrostatic pressure is an adequate explanation for histamine edema. However, when we saw lymph protein concentrations approaching those in plasma on infusion of histamine, but not on raising capillary pressure by venous compression, we quickly changed our minds and attributed the edema to both an increase in capillary hydrostatic pressure and an increase in microvascular permeability to plasma proteins.

Ionic Action on Blood Vessels

We reported in 1959 and 1960 that potassium, sodium, and magnesium, infused intrabrachially at rates that raise local plasma concentrations over physiological ranges, produce small vessel dilation in the dog forelimb; conversely, calcium produces small vessel constriction (after presenting these data to the Council for High Blood Pressure Research in Cleveland, I was seated beside Carl Wiggers at lunch who in a very fatherly way encouraged me to continue this line of investigation). The sodium effect results from increase in osmolality; we and others later showed sodium has no effect independent of that due to hypertonicity. We also later showed that hypertonicity causes vasoconstriction. We examined the local effects of many anions in the dog forelimb and found only one with substantial activity: acetate produces vasodilation. All of these ionic effects were essentially limited to the small vessel segment, presumably mainly at the arteriolar level.

Visscher was right. My dual training increased my options, opened doors for me, and influenced the types of research I did and the reviews I wrote. My research has always had applied (i.e., clinical) goals including edema, shock, myocardial ischemia, and hypertension, and the reviews I wrote were often clinically oriented because I found that my training was ideally suited for bridging any communication gap between basic scientists and clinicians. It also created a problem or two, namely a second tour of duty in the United States Army at Fort Knox, Ky. and an offer of chairmanship of a Department of Physiology, which forced me to declare what I was. After much reflection I finally decided that I was, in fact, predominantly a physiologist and accepted the chair at the University of Oklahoma. I did not, however, give up my connection with internal medicine and continued to hold a secondary appointment in that discipline for another 15 years.

In Oklahoma, in 1963, using a dilutional method, and in Michigan, in 1972, using a miniature hemodialyzer interposed in the arterial supply, we showed that local hypokalemia produces vasoconstriction in peripheral vascular beds, just the opposite of the vasodilation we observed in the dog forelimb with local hyperkalemia in 1959. In 1966, Overbeck reported that this potassium vasodilation in the dog forelimb appears to be reduced in dogs with one-kidney, one wrapped hypertension, a form of low renin hypertension. We then observed that potassium vasodilation and hypokalemic vasoconstriction are blocked by ouabain (Figure 8), a Na⁺,K⁺-ATPase inhibitor. We therefore postulated that potassium vasodilation results from stimulation of Na⁺,K⁺-ATPase and the electrogenic Na⁺-K⁺ pump, membrane hyperpolarization and thus reduced calcium influx into vascular smooth muscle, and that hypokalemic vasoconstriction results from the reverse.
therefore decided to study the vascular Na⁺-K⁺ pump in one-kidney, one wrapped hypertension.

**Mechanism of Low Renin Hypertension**

In Michigan, Pamnani adapted the rubidium-86 uptake technique for measuring Na⁺-K⁺ pump activity to blood vessels, and we measured ouabain-sensitive and ouabain-insensitive ⁸⁶Rb uptakes in mesenteric arteries and veins of dogs with one-kidney, one wrapped hypertension of 5 weeks' duration. We found that ouabain-sensitive ⁸⁶Rb uptake, an index of Na⁺-K⁺ pump activity, is suppressed in both arteries and veins. We also found Na⁺,K⁺-ATPase activity suppressed in left ventricular myocardial microsomes of rats with one-kidney, one clip hypertension, another model of low renin hypertension. These and all subsequent studies were promoted by the excellent chemical and administrative expertise of Josephine Johnston, who joined the group in Michigan and is still with us.

On the basis of this evidence and findings in the literature, we hypothesized in 1976 that "some humoral agent or agents, operating throughout the Na⁺-K⁺ pump in cardiovascular muscle, participates in the genesis of volume expanded hypertension," and we suggested that the Na⁺-K⁺ pump inhibitor was the natriuretic hormone of deWardener. Blaustein published a similar hypothesis a year later.

These studies were continued after a move to Bethesda in 1976, and the findings supported the view that the changes resulted from a circulating Na⁺-K⁺ pump inhibitor. Our Bethesda studies showed reduced Na⁺,K⁺-ATPase activity in right ventricular myocardium of rats with one-kidney, one clip hypertension, reduced Na⁺-K⁺ pump activity in arteries from other models of low renin hypertension, and decreased Na⁺-K⁺ pump inhibitory activity in plasma from rats following acute volume expansion. The term "ouabain-like" started appearing in the literature. I can't recall who first started using the term "ouabain-like"; we first started using it in 1978 because the changes in ⁸⁶Rb uptake seen in hypertensive arteries and produced by hypertensive plasma were like those produced by ouabain. We continued to use the term for several years but stopped when journal editors and referees objected because "its use implied structure." The abstract of that review summarized our thinking in 1978.

Decreased arterial Na⁺-K⁺ pump and cardiac Na⁺,K⁺-ATPase activities have now been demonstrated in several types of experimental volume expanded hypertension. The changes are not secondary to elevated pressure since they also occur in veins and right ventricle where pressure is not elevated. Decreased arterial Na⁺-K⁺ pump activity can be reproduced by acute volume expansion of the normal rat and plasma extracts from this rat suppress pump activity when applied to arteries from another rat. Suppression of Na⁺-K⁺ pump activity in arteries, veins and heart, with ouabain, for example, leads to increased contractile activity. Thus the volume expansion, reduced pump activity, and hypertension appear to be causally related through an ouabain-like humoral agent. Certain other evidence suggests that the pump defect extends to the sympathetic nerve endings, thereby reducing the efficiency of neural compensatory mechanisms.

**Plasma Bioassay for Circulating Na⁺-K⁺ Pump Inhibitor in Hypertension**

The case for a circulating Na⁺-K⁺ pump inhibitor was greatly strengthened when Pamnani extended the plasma bioassay he used for acute volume expansion to animals with hypertension (Figure 9). He found that
Na⁺-K⁺ pump activity in arteries from normal animals was reduced when incubated in plasma supernates from dogs with one-kidney, one clip and reduced renal mass-saline hypertension, all models of low renin hypertension. Plasma supernates from dogs with one-kidney, one clipped hypertension also reduced short circuit current in toad bladder, and plasma supernates from rats with one-kidney, one clip hypertension depolarized vascular smooth muscle cells in tail arteries from normal rats to the same extent as ouabain and to the same degree as found in arteries from one-kidney, one clip hypertensive rats.

Time course studies showed that arterial blood pressure and artery Na⁺-K⁺ pump activity correlate during the onset of reduced renal mass-saline hypertension and that the changes in arterial Na⁺-K⁺ pump activity, myocardial Na⁺,K⁺-ATPase activity, plasma Na⁺-ATPase pump inhibitor level, and arterial smooth muscle cell membrane potential disappear when reduced renal mass-saline and one-kidney, one clip hypertension are reversed by, respectively, substituting water for saline as the drinking fluid and removing the clip. Reduced artery pump activity also disappears when reduced renal mass-saline hypertension is reversed with canrenone, a competitive inhibitor of ouabain binding to Na⁺,K⁺-ATPase.

In 1978, we showed that locally applied ouabain, like local hypokalemia, does in fact constrict small vessels in skin and muscle of the dog forelimb but that the effect is sustained only in skin (Figure 10). We later showed that ouabain also increased forelimb blood vessel response to norepinephrine and that, administered into the renal artery, ouabain produces natriuresis and diuresis.

Our attempts to localize the source of the inhibitor included inducing a lesion of the anteroventral third ventricle area. This abolished the decrease in arterial Na⁺-K⁺ pump activity and the increase in plasma Na⁺-K⁺ pump inhibitory activity seen in rats during acute volume expansion and prevented the increase in blood pressure and plasma inhibitory activity and decrease in arterial Na⁺-K⁺ pump activity seen in rats with reduced renal mass-saline hypertension, suggesting that the hypothalamus produces or influences the production of the agent from another region, the adrenal for example. By 1987, the hypothalamus...
pressure in the central circulation stimulates the release of a Na+-K+ pump inhibitor that, through actions on cardiovascular muscle, leads to increased contractile activity and hence arterial pressure. This, along with its action on the renal tubule, tends to normalize volume via diuresis. The rise in pressure in the central circulation also increases the release of atrial natriuretic peptide, which also tends to reverse the sequence by increasing the ability of the kidney to excrete sodium and water. Thus, according to this view, the elevated pressure is in part generated by a Na+-K+ pump inhibitor acting on heart and blood vessels and is in part compensated by pressure, sodium pump inhibitor, and atrial natriuretic peptide acting on kidney. (+), stimulation of contraction or Na+ excretion; (−), suppression of contraction. Reprinted with permission.39

FIGURE 11. Schematic diagram showing hypothesized roles of the Na+-K+ pump inhibitor (ouabain-like factor) and atrial natriuretic peptide in low renin hypertension. An increase in pressure in the central circulation stimulates the release of a Na+-K+ pump inhibitor that, through actions on cardiovascular muscle, leads to increased contractile activity and hence arterial pressure. This, along with its action on the renal tubule, tends to normalize volume via diuresis. The rise in pressure in the central circulation also increases the release of atrial natriuretic peptide, which also tends to reverse the sequence by increasing the ability of the kidney to excrete sodium and water. Thus, according to this view, the elevated pressure is in part generated by a Na+-K+ pump inhibitor acting on heart and blood vessels and is in part compensated by pressure, sodium pump inhibitor, and atrial natriuretic peptide acting on kidney. (+), stimulation of contraction or Na+ excretion; (−), suppression of contraction. Reprinted with permission.39

Pharmacological Probes for Detecting Sodium Transport Defects in Hypertension

More recently we have turned our attention to in vivo diagnosis and treatment of those types of hypertension characterized by increased vascular smooth muscle cell permeability to sodium (e.g., the Okamoto strain of spontaneously hypertensive rat [SHR]). Noteworthy is our observation that 6-iodo-amiloride, an analogue of amiloride with potent sodium channel blocking and vasodilator activities, lowers blood pressure in two genetic types of hypertension, SHR and the Dahl salt-sensitive rat, but has no sustained effect on blood pressure in two investigator-induced models of low renin hypertension characterized by normal vascular smooth muscle cell permeability to sodium, namely one-kidney, one clip and reduced renal mass—saline hypertension.45 The latter model responds to canrenone46 whereas SHR does not.35,45

These studies suggest that pharmacological probes may eventually be used in vivo in the intact unanesthetized animal or patient to subdivide hypertensive subjects into those with genetic permeability defects and those with acquired Na+-K+ pump defects.

The Future

I continue to study in situ blood vessels, particularly in relation to hypertension. A new interest stems from my life sciences advisory committee activities and sabbatical leave with the National Aeronautics and Space Administration (NASA). Cardiovascular deconditioning is a complication of space flight and one manifestation is postural hypotension on return to the gravity environment. It is possible that this results in part from changes in veins and small vessels. For example, atrophy of the muscle in the wall of the veins would make them more compliant and thus able to hold more blood on standing. Skeletal muscle atrophy is a well-known phenomenon during prolonged space flight but venous smooth muscle has not been adequately studied in relation to living at reduced gravity.

In conclusion, I have spent 43 years studying small and large pulmonary and systemic blood vessels in situ because only here can the investigator observe the net vascular effects of all environmental forces—local, humoral, and neural. It is, of course, important to also study them in isolation when the aim is to dissect this net effect into its component parts, and this can be done in various ways (e.g., by bathing them in artificial fluid to study local forces or in plasma to better understand the humoral forces). However, only in situ are blood vessels operating in the presence of the myriad of factors that determine their function. If one starts in vitro one must eventually study the vessels in situ to determine the proportionate contribution of the parts to the whole and to fully appreciate their function in health and disease.
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My forty-three years with in situ small and large blood vessels.

F J Haddy

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