David S. Warner, M.D., Editor

Snakes and Hypertension

Edward D. Miller, Jr., M.D.

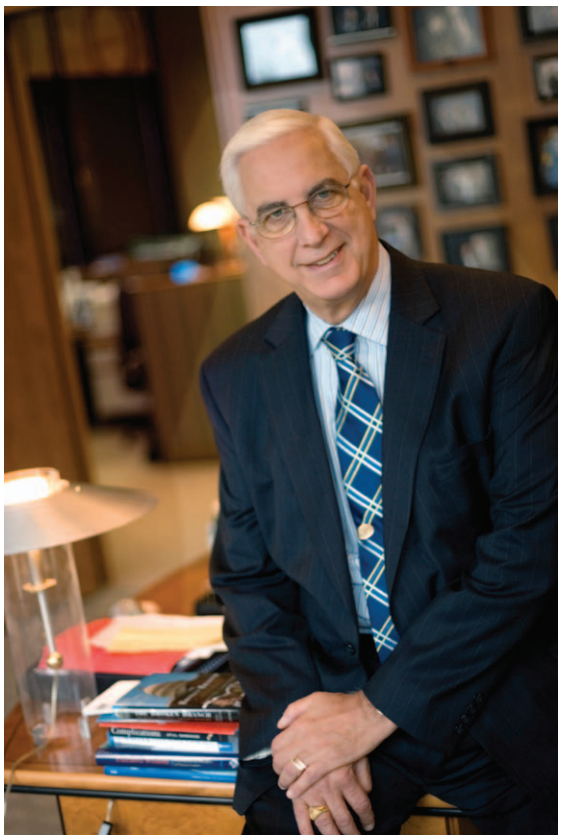
Inhibition of Angiotensin Conversion in Experimental Renovascular Hypertension. By Miller ED Jr, Samuels A, Haber E, and Barger AC. Science 1972; 177:1108–9. Reprinted with permission from AAAS.

Abstract: Constriction of the renal artery and controlled reduction of renal perfusion pressure is followed by a prompt increase in systemic renin activity and a concomitant rise in blood pressure in trained, unanesthetized dogs. The elevated blood pressure induced by the renal artery stenosis can be prevented by prior treatment with the nonapeptide Pyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro, which blocks conversion of angiotensin I to angiotensin II. Further, the nonapeptide can restore systemic pressure to normal in the early phase of renovascular hypertension. These results offer strong evidence that the renin–-angiotensin system is responsible for the initiation of hypertension in the unilaterally nephrectomized dog with renal artery constriction.

THE measurement of blood pressure during surgical procedures has been one of the foundations upon which the patient's welfare is measured by the anesthesiologist. Classic work by Cedric Prys-Roberts, D.M., Ph.D., in the 1970s showed detrimental effects of severe hypertension when these patients underwent surgical procedures.[1] However, treatment of hypertension at that time was difficult because so few drugs were available and those that were available had significant negative side effects. In our article entitled "Inhibition of Angiotensin Conversion in Experimental Renovascular Hypertension," we were one of the first to explore the use of a new category of drugs that could have a significant effect on blood pressure.[2]

After finishing my residency at the Peter Bent Brigham Hospital, Boston, Massachusetts, my chief, Leroy D. Vandam, M.D. (Supplemental Figure 1, http://links.lww.com/ALN/B338), instructed me to do a fellowship. I decided to go to the laboratory of A. Clifford Barger, M.D., the head of physiology at Harvard Medical School, Boston, Massachusetts (Supplemental Figure 2, http://links.lww.com/ALN/B338). Dr. Barger's laboratory had developed techniques to measure distribution of blood flow within the kidney in an instrumented, awake dog model. The purpose was to better understand fluid retention in congestive heart failure.

Shortly after my arrival in the laboratory, the focus of investigation changed. The laboratory had developed a technique to constrict the renal artery and measure blood pressure distal to the constriction, again in an awake dog model. The mechanism of renovascular hypertension was unknown.



Edward D. Miller, Jr., M.D.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication September 13, 2016. Accepted for publication September 14, 2016. From the Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Medicine Emeritus, Baltimore, Maryland.

 Anesthesiology 2017; 126:321-4

<zdoi;10.1097/ALN.0000000000001441>

In 1897, Robert A. A. Tigerstedt, M.D., Karolinska Institutet, Stockholm, Sweden, found a substance in the kidney, which elevated blood pressure, and he named it renin since it came from the kidney. His findings were largely ignored until 1934 when Goldblatt *et al.*[3] produced a model for renovascular hypertension by constricting the renal artery. Goldblatt *et al.*[3] theorized that blood pressure elevation might be due to renin release in patients with normal renal function. However, until the biochemical nature of renin could be elucidated and inhibitors found, the role of renin in blood pressure control could not be ascertained.

Two independent laboratories, one in Argentina and one in Indiana, discovered that renin acted upon a precursor, angiotensinogen, that was made in the liver and circulated in the blood. Renin cleaves off a 10-amino acid chain called angiotensin I. Angiotensin I has no vasopressor properties. Angiotensin I is converted to the potent vasopressor angiotensin II by an enzyme in the lung called angiotensin-converting enzyme (ACE), which cleaves off two-end terminal amino acids. Angiotensin II is also a potent stimulus to aldosterone secretion.

Then, serendipity came into play. Banana plantation workers in Brazil were known to collapse suddenly after being bitten by a pit viper (Bothrops jararaca). A biochemist (Mauricio Rocha e Silva, M.D.) working at the Brazilian Instituto Biologico (Campinas, Brazil) made extracts of venom from the snake and began to study its effects in experimental animals. One of Rocha e Silva's postdoctoral students wanted to work in the laboratory of Sir John Vane, Professor of Experimental Pharmacology, University of London, London, United Kingdom, and carried with him a full vial of the venom from this snake. Vane was already interested in the conversion of angiotensin I to angiotensin II and wondered if the snake venom could give him a key to better understand this conversion.

Vane was a consultant to the Squibb Institute for Medical Research (New Brunswick, New Jersey) and convinced leadership that pursuing studies related to this snake venom might lead to drugs that could control blood pressure. David W. Cushman, Ph.D., and Miquel A. Ondetti, Ph.D., at Squibb purified the snake venom, a nonapeptide called teprotide, and made a synthetic version called SQ 20,881.[4] Others were also working on other ways to inhibit the system. Norwich Pharmaceutical (Norwich, New York) had developed P113 (saralasin), a synthetic inhibitor of angiotensin II. Our laboratory was one of the first to have access to these two compounds.

I initially used P113 in our control experiments (an awake, unrestrained dog) where I could measure systolic/diastolic blood pressure and heart rate (100/60 mmHg and 40 beats/min average values, respectively) and draw blood samples. When I infused P113, there was a dramatic increase in the blood pressure. I thought we had a dirty drug, but in retrospect, we were dealing with the initial agonist properties of this antagonist.

We then began our experiments with SQ 20,881. We initially infused the drug in our normotensive dog and saw no effect in heart rate or blood pressure. On the following day, we constricted the renal artery to produce a distal mean pressure of 50 mmHg for 60 min and saw the systemic mean arterial blood pressure rise from 85 to 120 mmHg (fig. 1). Plasma renin activity also rose. The following day, we infused SQ 20,881 and then constricted the renal artery to a distal mean pressure of 50 mmHg. Despite this low pressure, blood pressure did not rise. Plasma renin activity rose significantly. The following day, in the same dog, we lowered distal renal artery pressure to 50 mmHg and observed the blood pressure rise and at 60 min infused SQ 20,881. There was a dramatic fall in blood pressure to preconstruction levels (fig. 2). Plasma renin activity rose dramatically.

These initial studies in dogs showed that the renin–angiotensin played a significant role in blood pressure control in at least in one form of experimental hypertension. Subsequent studies in our laboratory showed that blood pressure was dramatically influenced by the renin–angiotensin system in sodium-depleted animals and in dogs with surgically induced congestive heart failure.

Subsequent work in many laboratories throughout the world investigated the use of SQ 20,881 and P113 in humans. Hollenberg *et al.*[5] infused P113 in a normal man and found agonist properties when infused. Williams and Hollenberg[6] infused SQ 20,881 in patients with essential hypertension and found, surprisingly, a significant fall in blood pressure even though plasma renin activity was considered normal.

But the story would not be complete until an oral medication became available. Cushman and Ondetti[7] worked for years on developing a substance that would block ACE but would not be destroyed by gut enzymes. In 1975, they produced the first ACE inhibitor captopril.[7] There are now many other agents that block either ACE or direct antagonists to either angiotensin II or renin.

What has been intriguing about this story is that experiments in one uncommon form of hypertension opened the door to explore how the renin–angiotensin system functioned in a variety of physiologic and pathologic states. While thousands of studies have been done examining the renin–angiotensin system, a few deserve special mention.

As previously noted, angiotensin II plays a pivotal role in secretion of aldosterone from the adrenal gland. Increased aldosterone production results in the retention of sodium and therefore water retention and loss of potassium. Early on in space exploration, a couple of astronauts developed cardiac arrhythmias while in space, and subsequent studies showed that they had low serum potassium. It was hypothesized that the renin–angiotensin system was the cause of this potassium loss, and thus, astronauts were given Tang to drink.

Inhibitors of the renin–angiotensin system now play a major role in treating patients with essential hypertension. This is truly a remarkable finding because most patients with essential hypertension have normal plasma renin activity. Early clinical studies with essential hypertension attempted to categorize patients into low, normal, or high renin activity, hoping to predict which patients would benefit most from renin–angiotensin inhibitors. Contrary to popular thought, almost all patients responded to these inhibitors regardless of their plasma renin activity. Since blood pressure is affected by compliance, vascular reactivity, and volume status, it is not surprising that the

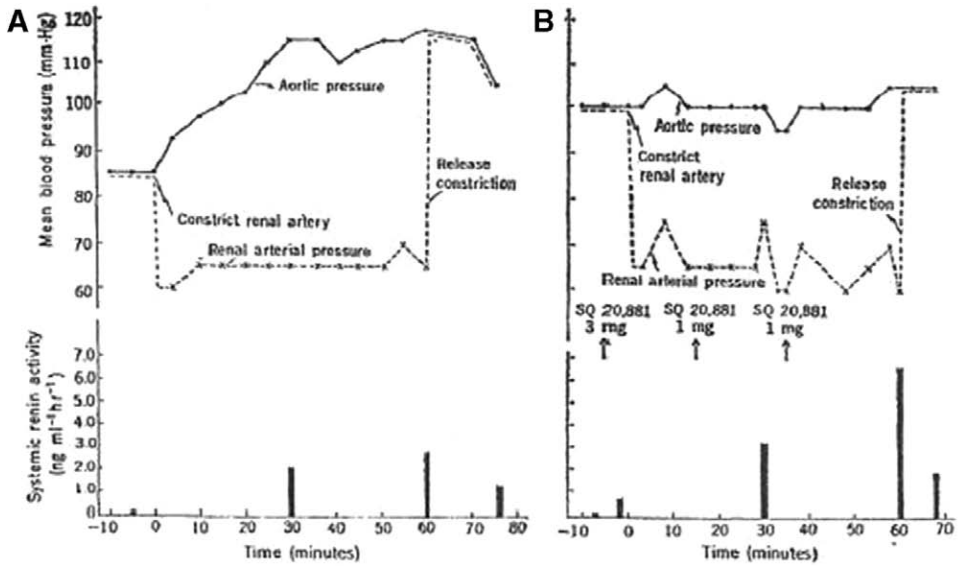


Fig. 1. Prevention of rise in systemic blood pressure after renal artery constriction by blockade of conversion of angiotensin I to angiotensin II by the nonapeptide. Data are for an untreated dog (*A*) and for the same dog (*B*) after intravenous administration of the drug. Reprinted with permission from Miller ED Jr, Samuels A, Haber E, Barger AC: Inhibition of angiotensin conversion in experimental renovascular hypertension. Science 1972; 177:1108–9. AAAS.

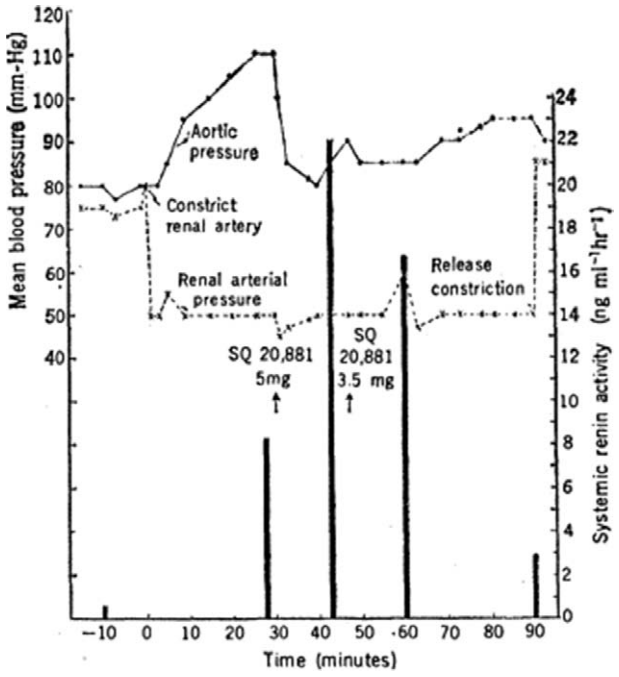


Fig. 2. Restoration of normal blood pressure by blockade of conversion of angiotensin I to angiotensin II 30 min after renal artery occlusion. From Miller ED Jr, Samuels A, Haber E, Barger AC: Inhibition of angiotensin conversion in experimental renovascular hypertension. Science 1972; 177:1108–9. AAAS.

combination of ACE inhibitors with a low-dose diuretic has a positive response to blood pressure control.[8]

Of equal importance is the use of ACE inhibitors after acute myocardial infarction. Several studies have shown that treatment with captopril immediately after an acute myocardial infarction reduced the recurrence of a myocardial infarction by 25% and decreased the risk of death after recurrent myocardial infarction by 32%.[9] The reason that captopril has these positive effects is related, in part, to peripheral vasodilation, ventricular unloading, attenuation of ventricular dilation, and ablation of the neurohormonal responses that occur at the time of a myocardial infarction.

I was given an opportunity at a very young age to add to my medical training by working in a basic science laboratory for 2 yr while still practicing anesthesia. Forty-five years later, it has been rewarding to see how some initial findings in a dog model have developed into a whole field of study that has benefited mankind.

Research Support

Support was provided solely from institutional and/or departmental sources.

Correspondence

Address for correspondence to Edward D. Miller, Jr., M.D., Dean/CEO, Johns Hopkins Medicine Emeritus, John Hopkins University, Professor of Anesthesiology and Critical Care Medicine, 132 SE Rio Casarano, Port St. Lucie, Florida 34984. emiller@jhmi.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

REFERENCES

1. Prys-Roberts C, Meloche R, Foëx P: Studies of anaesthesia in relation to hypertension. I. Cardiovascular responses of treated and untreated patients. Br J Anaesth 1971; 43:122–37
2. Miller ED Jr, Samuels A, Haber E, Barger AC: Inhibition of angiotensin conversion in experimental renovascular hypertension. Science 1972; 177:1108–9
3. Goldblatt H, Lynch J, Hanzal RF, Summerville WW: Studies on experimental hypertension: I. The production of persistent

elevation of systolic blood pressure by means of renal ischemia. J Exp Med 1934; 59:347–79
4. Vane JR: The history of inhibitors of angiotensin converting enzyme. J Physiol Pharmacol 1999; 50:489–98
5. Hollenberg NK, Williams GH, Burger B, Ishikawa I, Adams DF: Blockade and stimulation of renal, adrenal, and vascular angiotensin II receptors with 1-Sar, 8-Ala angiotensin II in normal man. J Clin Invest 1976; 57:39–46
6. Williams GH, Hollenberg NK: Accentuated vascular and endocrine response to SQ 20881 in hypertension. N Engl J Med 1977; 297:184–8
7. Cushman DW, Ondetti MA: History of the design of captopril and related inhibitors of angiotensin converting enzyme. Hypertension 1991; 17:589–92
8. Rabinad Estrada E, Ingelmo Morin M, Martinez Amenos A, Alsina J, Balcells Gorina A: Captopril in essential hypertension. Br J Clin Pharmacol 1982; 14(Suppl 2):103S–5S
9. Rutherford JD, Pfeffer MA, Moyé LA, Davis BR, Flaker GC, Kowey PR, Lamas GA, Miller HS, Packer M, Rouleau JL: Effects of captopril on ischemic events after myocardial infarction. Results of the Survival and Ventricular Enlargement trial. SAVE investigators. Circulation 1994; 90:1731–8

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Drs. Marcus and Gledhill: Short-lived Partners Using Long-lived Laughing Gas

Two pheasants grace the obverse (*right*) of this dental trade card from Drs. Marcus and Gledhill of Philadelphia, Pennsylvania. Sadly, both of these dentists and even their dental partnership were all short lived. The Marcus–Gledhill partnership was only advertised for a single year, in the 1889 directory for Philadelphia, Pennsylvania. Born in England, the senior dental partner, Dr. Thomas C. Gledhill (1866 to 1900), earned his D.D.S. in 1886 at the Philadelphia Dental College, Philadelphia, Pennsylvania. Unfortunately, he would succumb to tuberculosis by the age of 34 years. Born in Paris, France, to an Austrian father and Romanian mother, Dr. Herman D. Marcus (1870 to 1910) immigrated to the United States in 1884 before advertising himself in 1889 as the dental partner fluent in French, German, English, "and several other languages." After abandoning his senior dental partner, Dr. Marcus earned his M.D. in 1891 from the Medico-Chirurgical College of Philadelphia, Philadelphia, Pennsylvania. By June 1910, after moving to Atlantic City, New Jersey, the 40-year-old Dr. Marcus committed suicide with cyanide. Although both dentists were short lived personally, their brief Marcus–Gledhill dental partnership administered laughing "gas" (*left*), a general anesthetic in use from 1844 to this day. This trade card is part of the Ben Z. Swanson Collection of the Wood Library-Museum. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.