John Laragh is an outstanding clinician-scientist who discovered that renin, a mostly forgotten kidney hormone, causes essential hypertension\(^1\,2\) and its complications.\(^3\) This discovery led to two new classes of drugs, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which revolutionized the treatment of hypertension, cardiovascular disease, diabetes, and kidney disease and improved innumerable lives.

**CAREER MILESTONES**

John Laragh’s long career in clinical research began in the 1950s as a resident in medicine at Columbia University College of Physicians and Surgeons where Robert Loeb was chief of medicine. Loeb loved the practice of medicine, the search for evidence, the identification of the disease, the exploration of the physiologic background, and the selection of the most specific treatment. Loeb taught John to investigate fundamental questions in medicine, to find answers by listening to his patients, and to use the most precise laboratory methods in his search. He sparked John's curiosity about the mechanisms that control sodium and potassium metabolism. From that base, John progressed to a lifetime of clinical research and discovery, described in a series of reports in the *American Journal of Hypertension*\(^4\,\ldots\,9\) and in his 2002 book, *Laragh’s Lessons in Renin System Pathophysiology for Treating Hypertension and its Fatal Cardiovascular Consequences*.\(^10\)

His discoveries and career are breathtaking in their scope.

Always questioning dogma, John crossed the traditional boundaries of medicine. Although he trained as a cardiologist, his studies were often endocrine in nature but based in nephrology. He became chief of nephrology at Columbia College of Physicians & Surgeons, and then chief of cardiology at Weill Cornell Medical College where he founded the Cardiovascular Center. He established the first Hypertension Center supported by the Heart, Lung and Blood Institute of the National Institutes of Health. He was a founding president of the American Society of Hypertension and a founding editor-in-chief of the *American Journal of Hypertension*. His research program was a source of bright and creative clinician-scientists who became world leaders.

John's active clinical practice set the stage for his research. His patients became his friends, advisors, and supporters of his research, from whom he learned about the worlds of finance, insurance, real estate, and the arts. Through them he played the nation’s best golf courses where he met his other hero, Ben Hogan.

**RESEARCH MILESTONES**

Laragh’s discoveries of the relationships between plasma renin, body salt, blood pressure, and cardiovascular disease have origins in the work of Harry Goldblatt, who demonstrated that renal artery constriction raises blood pressure by increasing the renal secretion of renin.\(^11\) However, Goldblatt was unable to prove that renin is a cause of clinical hypertension.

Laragh’s research career began soon after Conn’s discovery of primary aldosteronism, a form of hypertension cured by removal of a sodium-retaining, aldosterone-secreting, adrenal tumor.\(^12\) John decided to investigate whether abnormally high aldosterone levels are a common cause of hypertension. He set out to measure aldosterone in a range of hypertensive patients by collaborating with Stanley Ulick. Stanley had developed a double isotope dilution method for measuring aldosterone in which synthetic aldosterone was tritiated, purified, and injected into the patient; a 24-hour urine was collected; a urinary metabolite was purified, acetylated with carbon 14, and repurified; and after 3–5 weeks of intensive work, aldosterone secretion was calculated from the tritium/carbon 14 ratio.\(^13\,\ldots\,16\)

Using this laborious method, they found that aldosterone is not abnormally high in most hypertensive patients.\(^13\)
However, aldosterone levels were very high in John’s very sick patients with malignant hypertension. He persuaded 6 of them to have one of their adrenals removed, expecting a tumor. However, the adrenals were hyperplastic, and the patients’ blood pressure remained high. John then persuaded them that their only hope was to remove their second adrenal gland. However, the other adrenal was also hyperplastic, their blood pressure remained high, and they died on schedule.

He was devastated. He had failed his patients. He had spectacularly failed his first attempt at a rational approach to treatment.

Laragh was ready to become a doctor in his home town of Yonkers, New York, and play golf. But Loeb stood by him and continued to encourage him. So John persevered. He began to explore the idea that a hormone was stimulating both adrenals of the patients with malignant hypertension and that the same substance might also be causing his patients’ hypertension. The fact that malignant hypertensive patients all had severe kidney disease led him to Harry Goldblatt’s work. He decided to test the effect of renin, as well as other vasoactive substances, on aldosterone secretion. The timing was perfect; Ciba had just synthesized angiotensin II (Ang II), the vasoactive product of renin. He asked for a sample. He infused it, as well as several other vasoactive substances, into normal volunteers. Only Ang II stimulated aldosterone secretion. Was there a eureka moment? Not really! It took months to carry out all of the infusions and the aldosterone measurements. I remember it well; I extracted aldosterone from liters of urine and ran paper chromatographs for weeks on end.

With his discovery that Ang II stimulates aldosterone secretion, John revived interest in the renin-angiotensin system. He received the Stouffer Award from the Council for High Blood Pressure Research of the American Heart Association.

John’s research and clinical careers continued in parallel. He decided to explore the effect of dietary sodium on plasma renin activity (PRA) and aldosterone secretion. He dedicated years to developing sensitive and accurate methods. As the data slowly accumulated from normal subjects studied under controlled conditions, he observed that renin-angiotensin system activity becomes increasingly important for sustaining blood pressure and renal function as the body becomes progressively more sodium depleted.

He also investigated PRA levels in hypertensive patients in relation to salt intake; it was abnormally high in only 10%. Nonetheless, he thought it possible that renin might govern blood pressure homeostasis in the rest. So, he divided the patients into low, medium, or high PRA subgroups and tested the blood pressure effect of either suppressing renin secretion with beta-blockers or depleting the body of salt with a diuretic. He and his growing group of young investigators found that renin system activity sustains the high blood pressure of both the medium and the high PRA patients (two-thirds of them), whereas the hypertension of low renin patients is entirely dependent on an excess of body sodium. Parallel studies in two types of Goldblatt hypertensive rats revealed that their hypertension is also sustained by either excess renin or excess sodium.
This led Laragh to his volume-vasoconstriction hypothesis (Figure 1), in which he proposed that dual mechanisms are responsible for the pathophysiology of hypertension: (i) an excess of body sodium-volume in low renin patients and (ii) plasma renin levels that are too high for the current body sodium-volume content in medium to high renin patients. His observation that all effective antihypertensive drugs are either natriuretic (anti-V) or block or suppress the activity of the renin-angiotensin system (anti-R) supported this hypothesis.

John’s discovery that hypertension could be controlled by blocking the renin-angiotensin system with an intravenous extract of snake venom that stopped the conversion of Ang I to Ang II was a major breakthrough. It led the pharmaceutical industry to develop orally active angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, thereby revolutionizing the treatment of hypertension and its complications. In 1975, Time Magazine put John H. Laragh on its cover for this pioneering work (Figure 2).

Early in his research career, Laragh was struck by the dichotomy in outcomes of patients with high or low PRA levels. His patients with malignant hypertension had very high PRA and aldosterone levels and died within a year, whereas his patients with primary aldosteronism had similarly high aldosterone levels but suppressed PRA levels and they had a relatively benign disease. This led his group to compare outcomes in low, medium, and high renin essential hypertensive patients. They found that the high

Figure 2. John Laragh and Jean Sealey reviewing data (1974).
that supports all normotension or hypertension. *Am J Hypertens* 2001; 14:397–404.
8. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. Lesson XVI: how to choose the correct drug treatment for each hypertensive patient using a plasma renin-based method with volume-vasoconstriction analysis. *Am J Hypertens* 2001; 14:491–503.
9. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. *Am J Hypertens* 2001; 14:603–609.
10. Laragh JH. Laragh's Lessons in Renin System Pathophysiology for Treating Hypertension and Its Fatal Cardiovascular Consequences. Elsevier Science: New York, 2002.
11. Goldblatt H, Lynch J, Hanzal RE, Summervile WW. Studies on experimental hypertension: I. the production of persistent elevation of systemic blood pressure by means of renal ischemia. *J Exp Med* 1934; 59:347–379.
12. Conn JW, Louis LH. Primary aldosteronism, a new clinical entity. *Ann Intern Med* 1956; 44:1–15.
13. Laragh JH, Ulick S, Januszewicz V, Deming QB, Kelly WG, Lieberman S. Aldosterone secretion and primary and malignant hypertension. *J Clin Invest* 1969; 46:1901–1106.
14. Laragh JH, Ulick S, Januszewicz V, Kelly WG, Lieberman S. Electrolyte metabolism and aldosterone secretion in benign and malignant hypertension. *Ann Intern Med* 1969; 53:259–272.
15. Laragh JH, Angers M, Kelly WG, Lieberman S. Hypotensive agents and pressor substances. The effect of epinephrine, norepinephrine, angiotensin II, and others on the secretory rate of aldosterone in man. *JAMA* 1968; 174:234–240.
16. Laragh JH. The role of aldosterone in man. Evidence for regulation of electrolyte balance and arterial pressure by a renal-adenal system which may be involved in malignant hypertension. *JAMA* 1968; 174:293–295.
17. Sealey JE, Buhler FR, Laragh JH, Manning EL, Brunner HR. Aldosterone excretion. Physiological variations in man measured by radioimmunoassay or double-isotope dilution. *Circ Res* 1972; 31:367–378.
18. Sealey JE, Gerten-Banes J, Laragh JH. The renin system: variations in man measured by radioimmunoassay or bioassay. *Kidney Int* 1972; 1:240–253.
19. Laragh JH, Sealey JE, Sommers SC. Patterns of adrenal secretion and urinary excretion of aldosterone and plasma renin activity in normal and hypertensive subjects. *Circ Res* 1966; 18:15–17.
20. Laragh JH, Baer L, Brunner HR, Buhler FR, Sealey JE, Vaughan ED Jr. Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease. *Am J Med* 1972; 32:633–652.
21. Buhler FR, Laragh JH, Vaughan ED Jr, Brunner HR, Gavras H, Baer L. Antihypertensive action of propranolol. Specific antirenin responses in high and normal renin forms of essential, renal, renovascular and malignant hypertension. *Am J Cardiol* 1973; 32:511–522.
22. Vaughan ED Jr, Laragh JH, Gavras I, Buhler FR, Gavras H, Brunner HR, Baer L. Volume factor in low and normal renin essential hypertension. Treatment with either spironolactone or chlordiazepoxide. *Am J Cardiol* 1973; 32:523–532.
23. Brunner HR, Kirshman JD, Sealey JE, Laragh JH. Hypertension of renal origin: evidence for two different mechanisms. *Science* 1971; 174:1344–1346.
24. Gavras H, Brunner HB, Vaughan ED, Laragh JH. Angiotensin-sodium interaction in blood pressure maintenance of renal hypertensive and normotensive rats. *Science* 1973; 180:1369–1371.
25. Laragh JH. Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. *Am J Med* 1973; 55:261–274.
26. Case D, Wallace J, Keim H, Weber M, Sealey J, Laragh J. Possible role of renin in hypertension as suggested by renin-sodium profile and inhibition of converting enzyme. *New Engl J Med* 1977; 296:641–646.
27. Alderman MH, Madhavan S, Ooi WL, Cohen H, Sealey JE, Laragh JH. The association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med* 1991; 324:1098–1104.
28. Blumenfeld JD, Sealey JE, Alderman MH, Cohen H, Lappin R, Canatanzo DF, Laragh JH. Plasma renin activity in the emergency department and its independent association with acute myocardial infarction. *Am J Hypertens* 2000; 13:855–863.

REFERENCES

1. Buhler FR, Laragh JH, Baer L, Vaughan ED Jr, Brunner HR. Propranolol inhibition of renin secretion. A specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. *N Engl J Med* 1972; 287:1209–1214.
2. Case DB, Atlas SA, Laragh JH, Sealey JE, Sullivan PA, McKinstry DN. Clinical experience with blockade of the renin-angiotensin-aldosterone system by an oral converting-enzyme inhibitor (SQ 14,225, captopril) in hypertensive patients. *Prog Cardiovasc Dis* 1978; 21:195–206.
3. Brunner HR, Laragh JH, Baer L, Newton MA, Goodwin FT, Krakoff LR, Bard RH, Buhler FR. Essential hypertension: renin and aldosterone, heart attack and stroke. *N Engl J Med* 1972; 286:441–449.
4. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. Clinical Pearl #1: the miracle of spironolactone. *Am J Hypertens* 2001; 14:84–89.
5. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension: three pharmacologic ways to block the circulating renin-angiotensin-aldosterone system and lower pressure in hypertensive patients. *Am J Hypertens* 2001; 14:296–304.
6. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension: lesson X. The inappropriately high plasma renin levels that sustain medium and high renin essential hypertension are also associated with later heart attacks or strokes not observed in low renin essential hypertension. *Am J Hypertens* 2001; 14:307–310.
7. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. Lesson XV: Volume-vasoconstriction equation

John Laragh is now 89 years old. He has led an incredible life. He set a course to study salt and water metabolism by learning from his patients, by asking the big questions, by setting up the best methods, and by teaching, encouraging, and inspiring his collaborators as well as generations of physician-scientists. In the course of his research he brought the treatment of hypertension and cardiovascular disease into the 21st century and thereby improved innumerable lives.

renin hypertensives die sooner of heart attacks and strokes than those who have low renin and equivalent or even higher elevations in blood pressure. More recently, they observed that even patients whose high PRA levels are induced by successful treatment die sooner than those whose PRA levels remain low. Altogether Laragh came to the view that cardiovascular health is better sustained when there is adequate body salt and circulatory volume and hence little demand for renin-angiotensin system–mediated vasoconstriction.

Laragh's goal in treating hypertension has always been monotherapy, targeted to either excess renin or excess body salt. This is reflected in his favorite saying, "There is no drug like no drug." He abhors "stepped care" in which drugs are added one after another without stopping those that are ineffective. His other motto is "Salt is the essence of life." He disdains JNC7, in which treatment is always initiated with a diuretic that is never stopped. With the goal of monotherapy in mind, his group developed a PRA-guided treatment strategy tailored to the individual hypertensive patient. Patients with medium to high PRA levels are given drugs that block or suppress renin-angiotensin system activity, whereas natriuretic drugs are reserved for those with either suppressed or blocked PRA levels. This approach was successfully tested in a clinical trial and is described step-by-step in a software-based application "PRA and HTN" tailored to the individual patient (http://laraghmethod.org).

Sealey
29. Gonzalez MC, Cohen HW, Sealey JE, Laragh JH, Alderman MH. Enduring direct association of baseline plasma renin activity with all-cause and cardiovascular mortality in hypertensive patients. *Am J Hypertens* 2011; 24:1181–1186.

30. Sealey JE, Alderman MH, Furberg CD, Laragh JH. Renin-angiotensin system blockers may create more risk than reward for sodium-depleted cardiovascular patients with high plasma renin levels. *Am J Hypertens* 2013; 26:727–738.

31. Laragh JH, Sealey JE. The plasma renin test reveals the contribution of body sodium-volume content (V) and renin-angiotensin (R) vasoconstriction to long-term blood pressure. *Am J Hypertens* 2011; 24:1164–1180.

32. Egan BM, Basile JN, Rehman SU, Davis PB, Grob CH 3rd, Riehle JF, Walters CA, Lackland DT, Merali C, Sealey JE, Laragh JH. Plasma renin test-guided drug treatment algorithm for correcting patients with treated but uncontrolled hypertension: a randomized controlled trial. *Am J Hypertens* 2009; 22:792–801.