John H. Laragh, MD: Clinician-Scientist

Jean E. Sealey[1]

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*[4–9] 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.[13–16]

Using this laborious method, they found that aldosterone is not abnormally high in most hypertensive patients.[13]

Correspondence: Jean E. Sealey (jsealey@med.cornell.edu).

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[1]Department of Medicine, Weill Cornell Medical College, New York.

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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.[14] 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.[15] 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.[16] 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.[17,18] As the data slowly accumulated from normal subjects studied under controlled conditions,[19] 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%.[20] 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[21] or depleting the body of salt with a diuretic.[22] 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.[23,24]

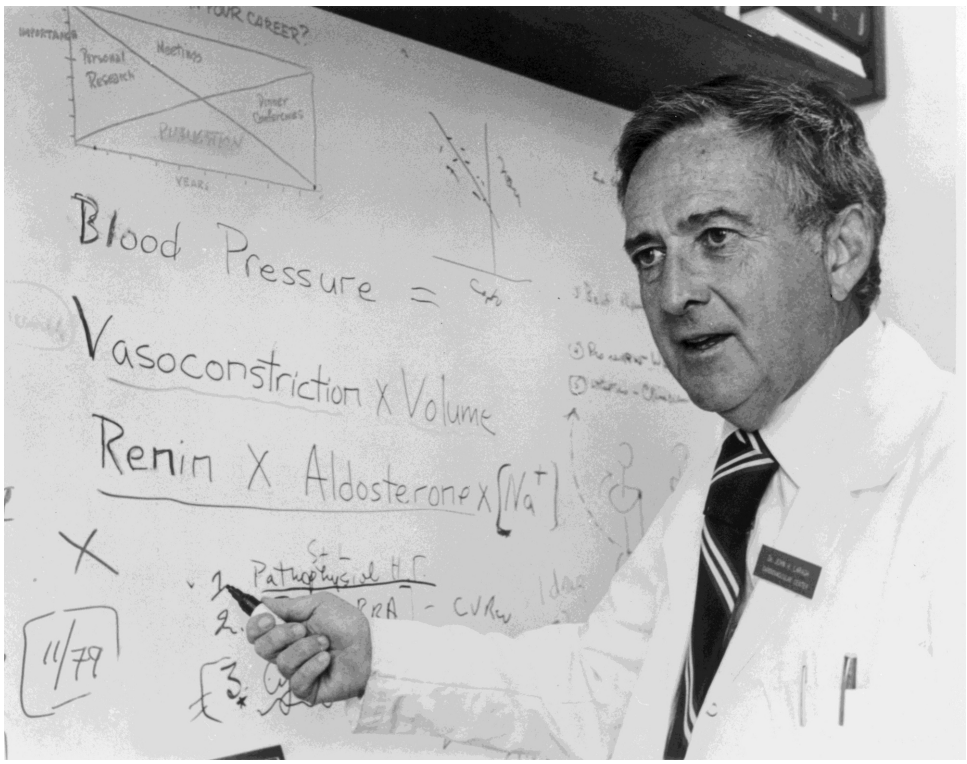

Figure 1. John Laragh explaining his volume-vasoconstriction hypothesis of blood pressure control (1972).

This led Laragh to his volume-vasoconstriction hypothesis[25] (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)[25] 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.[26] 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.[13,16] This led his group to compare outcomes in low, medium, and high renin essential hypertensive patients. They found that the high

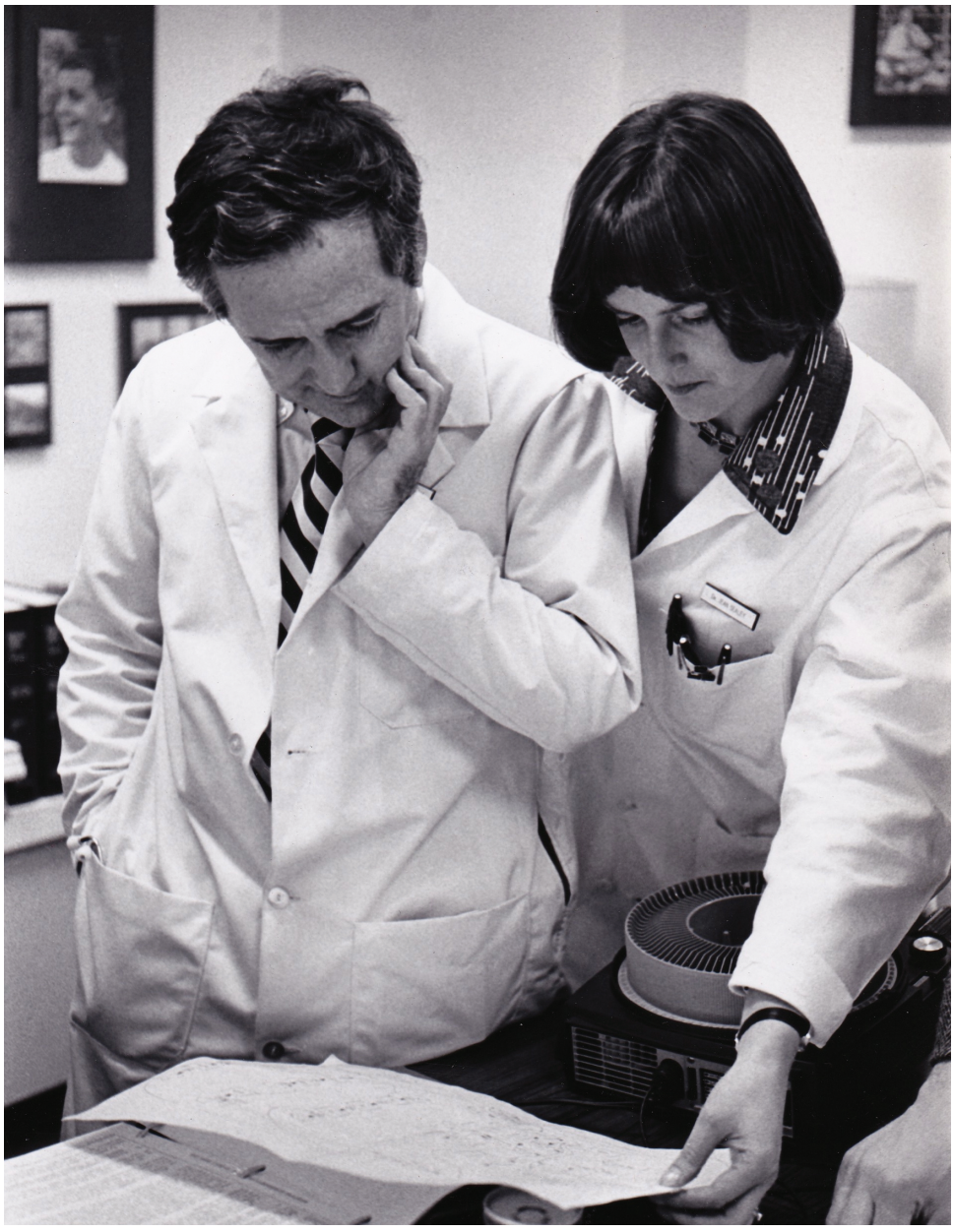

Figure 2. John Laragh and Jean Sealey reviewing data (1974).

renin hypertensives die sooner of heart attacks and strokes than those who have low renin and equivalent or even higher elevations in blood pressure.[3,27–29] 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.[30] 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.[31,32] This approach was successfully tested in a clinical trial[32] and is described step-by-step in a software-based application "PRA and HTN" tailored to the individual patient (http://laraghmethod.org).

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.

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