Pathophysiology and Clinical Application of the Renin System: Early Steps Toward Personalized Medicine

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John H. Laragh was a visionary translational scientist, from bench to bedside. During his entire life, he worked on fitting together the complex cybernetic system of renin-angiotensin vasoconstriction and the commensurate angiotensin-aldosterone sodium-volume homeostasis and renal potassium control. It was John Laragh who infused subpressor doses of angiotensin into man and demonstrated the attendant rise of aldosterone secretion.[1] (By the way, both angiotensin peptides and aldosterone had been synthetized at CIBA (now fused with Sandoz to Novartis) where Franz Gross played a pivotal role and interacted frequently with John Laragh.) The question always was—still is?—whether, functionally, the renin system is an archaic bystander (e.g., for severe blood volume or salt loss) or is pathophysiologically involved in fine-tuning cardiovascular control and the regulation of normal and elevated blood pressure? John Laragh devoted his professional and scientific life to this question. His laboratory power and his many clinical fellows, mostly from Europe, were put behind it with the support of major National Institutes of Health grants. I had the great pleasure of being a member of that elitist, competitive yet collegial Laragh Family team during John Laragh's most productive years (1970–1974) (see authors of ref. 3–5).

GENESIS OF THE RENIN-SODIUM INDEX

In the early 1970s, great care was spent measuring with great precision and characterizing the hormonal factors involved in the renin system: renin, plasma renin activity (PRA), the different angiotensin peptides, particularly angiotensin II (octapeptide), the most powerful vasoconstrictor, as well as aldosterone in urine and plasma; the latter was one of my own lab tasks.[2] Behind all bench work in John Laragh's lab was a woman, as behind every strong man, Jean Sealey, with her strong and critical scientific mind and her technical talents. We all learned a great deal from John Laragh, as well as each other, but Jean Sealey was the master of quality and scientific rigor.

One of the questions was how to relate PRA (with a 100-fold gain from 0.2 ng/ml/hour (if you can measure it at all) to 20 ng/ml/hour to normal and hypertensive people? There was relentless work. Hans R. Brunner carried the ball (a colleague from Basel; both our fathers had worked in the pharmaceutical industry!) in carrying out metabolic studies of normal and hypertensive subjects who ingested a wide range of sodium intakes and in whom PRA was related to 24-hour urinary sodium excretion rates. We found a roughly semiparabolic relationship but, despite the help of a mathematics professor, were unable to define the relationship in mathematical terms. We therefore arbitrarily identified the "waterfall-like" boundaries of this renin–sodium relationship in normotensive individuals and then defined the renin–sodium index in patients with so-called essential hypertension. PRA measurements were performed before treatment—possible at that time!—or after a 3-week washout period. Approximately 30% of hypertensive patients had low renin, 55% were "normal" (in fact too high for their elevated blood pressure), and 15% had high PRA. In a landmark article, the 3 renin subtypes of hypertension were defined, as was increased cardiovascular mortality in the high-renin compared with the low-renin patients.[3] This all happened under the merciless analytical scrutiny of John H. Laragh.

RENIN-SUPPRESSIVE POWER OF BETA-ADRENOCEPTOR BLOCKERS

At that time (Figure 1), a paper was published showing that beta-blockers suppress renin secretion in dogs. John Laragh wanted to test whether propranolol (the only beta-blocker available in the United States) had antihypertensive effects in the 3 renin subgroups. Because I had experience with oxprenolol (from CIBA) at the University of Basel, I was put in charge of treating the first patients without knowing the renin type. Many more patients followed. In all, I analyzed the responses of 48 of them. Propranolol lowered blood pressure in the high-renin patients and did so to a lesser degree in the normal-renin patients, whereas patients with low renin did not benefit much; indeed some had increased blood pressure.[4]

Later we found a direct relationship between the fall in renin and the fall in blood pressure.[5] This was shown with

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Initially submitted April 18, 2014; accepted for publication May 6, 2014.

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doi:10.1093/ajh/hpu114

Figure 1. John H. Laragh (left) and Fritz R. Bühler in one of many ardent debates during a 1980 visit to New York.

Figure 2. John H. Laragh (left) and Fritz R. Bühler continuing ardent, although somewhat more relaxed, debates in the Village of Golf, Florida, Fall 2010.

other beta-blockers alone or in combination with diuretics.[6] In the early 1970s, the use of a beta-blocker for antihypertensive monotherapy was heretic because beta-blockers weaken the heart because of their negative inotropic effect; to play it safe, beta-blockers were almost always combined with a diuretic. This report[4] revolutionized antihypertensive treatment and for a number of years was the most cited clinical research article in the International Citation Index. But, by that time I had moved on to testing saralasin, the first angiotensin receptor blocker, and teprotide, the prototype angiotensin-converting enzyme inhibitor. These drugs had to be given intravenously because they were not orally active. They confirmed the propranolol story. John Laragh's renin–sodium index and the differential use of antihypertensive drugs based on PRA levels opened the way to pathophysiological therapy in essential hypertension, practically anticipating personalized medicine.

RENIN–ENDOCRINE ARM OF THE SYMPATHETIC NERVOUS SYSTEM

When I left John Laragh's group as a fellow in 1974 I knew that I had a good friend. To this day, we still talk about our mutual interests. Meanwhile the next generation of Laragh's

trainees continued to work in New York, whereas the rest of us returned to our own institutions to continue further work on the antihypertensive mode of action of renin-angiotensin system inhibition: after beta-blockers, there were orally active angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and lately the renin inhibitors.[7] John said that it's almost impossible to "cheat" the renin axis completely, and research showed that there are always compensatory mechanisms following each site of inhibition.

Back at the University of Basel, we explored how the beta-adrenoceptors–mediated renin system activation interplayed with the sympathetic nervous system, adrenergic receptors, and ionic channels–mediated control of vasoconstriction. (We applied a forearm perfusion model in man.[8]) Because of John Laragh's concepts—and Arthur Guyton's work in Jackson, Mississippi—we viewed cardiovascular regulation as a cybernetic interaction of different systems for blood pressure control, ultimately mediated by intracellular calcium.[9] Over many years, John Laragh—often together with Jean Sealey—became a unique and most critical sounding board for our own research concepts in Basel.

REGULATION OF PLATELET CALCIUM, ANALOGIES TO VASCULAR SMOOTH MUSCLE CELLS

Human platelets have many subcellular mechanisms in common with vascular smooth muscle cells: they have surface angiotensin receptors and a number of other control mechanisms that can be readily studied *ex vivo*.[10] They have actin and myosin interaction that causes them to contract and change their shape.[9,11] In the late 1970s, single cell measurement of ionic fluxes became available,[12] enabling measurement of intercellular Ca^{++} concentrations.[9] We considered the platelets to be "swimming smooth muscle cells." We studied the angiotensin effect on vascular composition and vascular matrix[13] and the role of endothelium.[14]

CALCIUM ANTAGONIST FOR TREATMENT OF LOW-RENIN HYPERTENSION

Based on my work with Laragh's group and the volume-vasoconstriction paradigm,[15] we sought to find an antihypertensive tool to attack the volume-factor—other than with the well-known diuretics,[16] which were reported to increase heart attacks in high doses.[17]

In the forearm perfusion model, we found that the degree of vasodilation during infusion of the calcium-antagonist verapamil was inversely related to baseline PRA.[18] This led to the demonstration that, like diuretics, calcium antagonists—all 3 types—lower blood pressure most effectively in low-renin patients[19] and are complementary as well as additive in combination with renin-angiotensin system blockers.[20] Thus we showed that the renin–sodium index forecasts the antihypertensive response to calcium antagonists. Based on this work, John Laragh designated calcium antagonists as antivolume (anti-V) drugs.[7]

JOHN H. LARAGH: A CHARISMATIC ROLE MODEL

I worked with John Laragh for 4 years, and this influenced my life and my entire career. When I arrived in the lab in 1970, it was difficult to gain access to his thinking, but he liked the European work attitude, even if he ignored those unable to speak English proficiently. I was pretty much a novice in both clinical and bench research but had solid bedside training in internal medicine. Unfortunately, the English language was not my forte, and in the early weeks John almost refused to talk to me. But, he came around when he saw my expertise with patients.

John Laragh was a creative thinker and excellent writer (and editor) with a warm-hearted and sometimes boyish charm. It was fun to see him swaying through hospital corridors, singing or whistling, and we copied him for a while. During these days, it became clear to us that John would marry Jean Sealey, DSc, his laboratory head, an elegant way to assure quality of scientific lab work. As Stanley Peart once said, "Most of us think that the renin test is important, John Laragh married it!" It is a pleasure and privilege to continue friendship with John (Figure 2) and Jean. John Laragh and his disciples triggered an avalanche of research in hypertension and particularly antihypertensive treatment, thereby reducing cardiovascular risk and improving health care. In my later capacity as the global head of clinical research and development at a major pharmaceutical company, the economical impact of Laragh's fermentative role became very obvious. John Laragh has impacted my personal life and my professional career more than anybody else. Thank you, John and Jean, *ad multos annos. Ultima latet.*

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