John Laragh and the Renin Thesis: Creating a Paradigm

Michael A. Weber

I first heard from John Laragh when I was a research fellow with Gordon Stokes at Sydney Hospital. My main area of interest was the regulation of renin release from the kidney, and Dr. Laragh had noticed some of my published reports describing the effects on renin of beta blockade and other interventions.

Of course I was already aware of John Laragh’s two dramatic observations published in the New England Journal of Medicine. The first of these was to forever change the landscape of cardiovascular medicine, for John and his group provided evidence that inappropriately high plasma levels of renin in patients with hypertension were associated with an increased risk of myocardial infarction and other outcomes. This critical observation was later confirmed by a larger prospective study conducted by Michael Alderman. Over time, this discovery became progressively broadened and led to the recognition that excess activity of the renin-angiotensin system is an adverse factor in several forms of cardiovascular and renal disease.

The second major finding by the Laragh group was that the efficacy of antihypertensive treatment with a beta-blocker was largely dependent on the drug’s ability to reduce plasma renin activity. This sentinel observation demonstrated that the renin-angiotensin system plays a causative role in blood pressure elevations in a large proportion of patients with hypertension. Based on this discovery, drugs that block the renin-angiotensin system have now become one of the mainstays of hypertension therapy.

**A RELUCTANT RESPONSE**

This research became the basis of major controversy. I was privileged to be working in John’s department during those exciting days. The ideas put forward by the Laragh group created a great deal of reaction and became the subject of debate at several national and international scientific meetings. I was fortunate enough to participate in some of these events, which—thanks to John painstakingly giving me his insights into the details and nuances of this new science—became a wonderful learning experience.

Many experts at the time had great difficulty believing that renin, which previously had been limited to a role in the particular condition of renovascular hypertension, could actually underlie and explain a large part of all forms of hypertension. Those of us in the Laragh camp encountered some angry moments, although I still recall the humor of one of our critics, the highly respected hypertension authority, Ray Gifford, who made the memorable comment, “Far more people are making a living off renin than ever died from it!”

Inexorably, John’s “renin thesis” gained ground and soon terms such as “high renin” and “low renin” became part of the standard vocabulary of hypertension. These concepts were developed by John Laragh and his colleagues into what became known as the vasoconstriction-volume model of hypertension, in essence defining hypertension as renin-dependent, volume-dependent, or a combination of both. A key lesson of this creative thinking was that hypertension could no longer be regarded as a monolithic concept, but rather that heterogeneous mechanisms must be taken into account when describing this condition and selecting appropriate therapies.

**MAKING FURTHER PROGRESS**

In working with John Laragh, we noted that reactive changes in renin during treatment could determine the effectiveness of therapy. We also found that reactive changes in aldosterone, a product regulated by the renin-angiotensin system, also played a key role. In our internal discussions at Cornell, Jean Sealey and others advanced the idea that aldosterone, quite apart from its mineralocorticoid salt-retaining properties, might have direct vasoconstrictor actions. A few years later, studying isolated arterial preparations with Ralph Purdy at the University of California, Irvine, we confirmed the ideas that began with the conjectures of Jean, John, and the group at Cornell. I suspect that most contemporary hypertension experts who advocate using aldosterone antagonists for patients with treatment-resistant hypertension have no inkling how this concept was developed more than 3 decades ago.

**GETTING THINGS DONE**

Working with John Laragh was not just about hands-on science. John is a meticulous writer, and I became very

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fond of our manuscript writing sessions in which our whole group would participate in round-table fashion. Every word had to do its job, every sentence had to make a decisive statement. And, most important, the manuscript’s title had to tell the essence of the story, much like a good newspaper headline. John Laragh exhibited an uncompromising attitude to research: it was a calling, all day, every day.

John Laragh’s willingness to take the extra step was exemplified by his belief that developing drugs to block the renin-angiotensin system would have clinical benefits across cardiovascular disease. He was aware that the pharmaceutical company Squibb (later Bristol Myers Squibb) was working on drugs that would become the angiotensin-converting inhibitors. But despite their breakthroughs in this pharmacologic science, there was uncertainty within the company as to the potential clinical value of these agents. John went directly to the leaders at Squibb and forcibly argued for the continuation of their program. His efforts contributed substantially to the release of the agent captopril. I believe that his assertiveness played a major part in making this lifesaving agent, as well as others that followed it, available to tens of millions of patients around the world in need of this therapy. John Laragh had masterminded this whole incredible strategy from basic clinical research all the way into the patient’s hand.

LATER YEARS

When I left Cornell for my new position in California, I decided that my laboratory would measure renin using the method developed by Jean Sealey. When I asked Jean if she would be willing to provide me with some of the essential materials for the assay, she was extraordinarily generous and personally invited my laboratory technician to New York to be trained in her renin method.

My interactions with John Laragh continued. I recall how we collaborated in writing a strong editorial in 1993 that accompanied the new JNC 5 Report, strongly questioning the report’s insistence on recommending diuretics as first-line hypertension treatment even though copious research had clearly demonstrated the need to match appropriate drugs to different forms of hypertension. I was also delighted to be part of the group working with John that established the American Society of Hypertension and later the American Journal of Hypertension.

To this day, I remember many things I learned from John and Jean about the complex process of science and academic medicine. I am delighted to be part of this Festschrift honoring a good friend and mentor, truly one of the innovative leaders of American medicine.

REFERENCES