How The Renin Story Began And Evolved

PJR: What led to your interest in renin?

JHL: At Columbia, as an intern and resident in medicine and then in cardiology I was surrounded by frontier clinical science, the direct product of Bob Loeb’s passion for new knowledge and its basic link to clinical excellence. Loeb spawned many professors of medicine, but what is generally not known is that his department also produced 6 Nobel Laureates including Dickinson Richards, André Courmand, Barry Blumberg, Dan Nathan and Carleton Gajdusek, an incredible record. For about 10 years I used to meet with Loeb almost daily at 8 AM in his office along with other house staff and young faculty members. With his help and advice I was working on congestive heart failure, and on the roles of sodium and potassium balance on edema formation and especially on aldosterone secretion, soon after its discovery in 1953. After he became interested in my work he couldn’t get enough of it, and sometimes would come back to my lab in the afternoons for a second round! I also worked a bit and talked a lot with Marcel Goldenberg, a marvelous neighboring scientist, who discovered noradrenalin in the adrenal medulla and defined its differences from adrenalin. To block its biosynthesis, he also introduced alpha methyl DOPA (Aldomet) to Merck. Marcel fits into my story too, because I was also his physician. He died of renin caused malignant hypertension due to scleroderma. We could have easily saved him today but all this occurred before we had figured out what causes malignant hypertension and had introduced the antirenin R drugs to correct it.

What led to my interest in renin was a 57-year-old CEO of a large company that Loeb had referred to me in 1957. He had malignant hypertension with grade III retinopathy and generalized muscle weakness from very low serum potassium. His aldosterone secretion was over 800 mgm/day while our normal values were less than 50. I should say that we were very proud of our aldosterone assay even though it could take up to 6 weeks to complete a test since it required labeling aldosterone with radioactive H3 and then injecting a tracer I.V. into our patients and ourselves.

The degree to which the radioactivity was diluted by aldosterone in the patient’s blood in 24 hours gave us the daily secretory rate. Unlike most everybody else, we found aldosterone to be quite normal in essential hypertension. But, to our amazement, it was massively increased in fatal hypokalemic malignant hypertension. We removed the adrenals in 4 such patients to eliminate aldosterone without any benefit, since they all died on schedule.

Thus, we showed that malignant hypertension and its diffuse vasculitis was not caused by high aldosterone since this fatal condition progressed in the absence of the adrenals and there was no aldosterone. There had to be something else circulating in these patients that (1) raised blood pressure, but most importantly, this substance should also (2) produce prompt and progressive injury to blood vessels in the heart, brain and kidneys resulting in the rapidly fatal heart attack, stroke, heart or kidney failure typical of malignant hypertension. Because adrenalectomy did not help, it was obviously not anything manufactured in the adrenal so the most likely cause appeared to be excess renin from the severely damaged kidneys of these patients.

In 1898, Tigerstedt and Bergman published an article in a Scandinavian journal describing an amazing and powerful blood pressure raising substance they had isolated from rabbit kidney extracts. They called this substance renin. But subsequent scientists failed to confirm Tigerstedt and Bergman’s findings and there was little interest in renin until 1934 when Harry Goldblatt published the landmark results of his dog experiments. Harry had induced what appeared to be the equivalent of essential hypertension in humans by constricting either one or both renal arteries with a silver clamp. In addition, more severe renal ischemia produced in this fashion resulted in a syndrome that closely simulated malignant hypertension that was also assumed to be due to increased renin release.

It was therefore very disappointing that numerous attempts showed absolutely no evidence that plasma renin levels were increased in essential hypertension or even that renin had important physiologic actions of its own.