The Pivotal Role Of Angiotensin

PJR: Why is renin so important if it is inactive?
JHL: What we and others proved was that renin acted enzymatically on a circulating plasma protein (angiotensinogen) to release an inactive decapetide (angiotensin I). This was rapidly hydrolyzed by converting enzymes to the most powerful pressor octapeptide known, angiotensin II. It was this vasoconstrictor angiotensin II, released only by renin, that played the crucial role in causing human hypertension. When you give angiotensin II to humans it produces a rapid rise in blood pressure by promoting vasoconstriction and also via a slower effect by stimulating aldosterone secretion to promote sodium retention by the kidney. However, it was many years before either the normal roles of plasma renin or angiotensin would finally be acknowledged and longer still before the establishment began to accept renin as a major cause of human essential hypertension.

But in 1958, when we discovered very high aldosterone levels in fatal malignant hypertension, the octapeptide angiotensin II had just been synthesized by CIBA. They provided samples to us for human research and we cautiously administered tiny subpressor amounts of it intravenously to six normal volunteers. In over 40 such infusion studies, only angiotensin II (but not adrenalin, noradrenalin, serotonin or vasopressin) consistently and strikingly stimulated adrenal aldosterone secretion. Thus, we had discovered the missing biologic role for renin. It was to maintain normal blood pressure not only via direct angiotensin II arteriolar vasoconstriction but also by angiotensin induced adrenal aldosterone release. Aldosterone expands blood volume by causing the kidneys to retain sodium and thus water.

PJR: How did this information help you target treatment to a specific hypertensive patient?
JHL: The new data led us to propose and later prove that the malignant hypertension syndrome is caused by an unchecked runaway release of renin leading to very high plasma angiotensin levels. This raises blood pressure and also injures coronary, cerebral and renal vessels, rapidly leading to fatal complications.

We were able to correct all of this not only by removing both kidneys, but also by treating each patient with any one of the 3 antirenin (R) types of drugs that we characterized and introduced: first propranolol, a beta blocker, to block the kidney beta receptor activated renin release, then, the snake venom peptide (teprotide), the original intravenous angiotensin converting enzyme (ACE) inhibitor, and finally, intravenous octapeptide saralasin, the first angiotensin II receptor blocker (ARB). Our findings soon persuaded industry to synthesize many orally active analogs of the venom peptide teprotide (e.g. captopril, enalapril, lisinopril) and later on, many orally active ARB's resembling saralasin (losartan, valsartan, candesartan, olmesartan, irbesartan, telmisartan, eprosartan).

As you know, these explicit antirenin system drugs, together with the beta blockers, another R drug class, have revolutionized the treatment of human hypertension. They have had an even greater impact for preventing or arresting eliminating plasma renin-caused fatal consequences, i.e. heart attack, heart failure, stroke and kidney failure similar to the correction of all these by total nephrectomy in patients with malignant hypertension. Collectively, these numerous commercially available antirenin drugs produce similar truly dramatic and lasting correction for patients with renin mediated hypertension lasting for 15 years or more!

Marcel Goldenberg was one of my malignant hypertension patients whose rapidly fatal outcome proved this entire story for us. I cry whenever I think about him because five years later we could have saved him. We also showed that milder excesses of renin angiotensin activity were responsible for about 2 out of 3 cases of essential hypertension. In these patients we could also prevent the same but more gradually developed fatal sequelae of heart attacks, stroke, heart failure and kidney failure with one of our three antirenin (R) drug types. However, these (R) drugs did not benefit patients with low renin hypertension who, on the other hand, responded incredibly well to (V) drugs that reduced blood volume.