The Plasma And Direct Renin Assays

PJR: The key to your treatment method appears to be the ability to measure plasma renin or angiotensin activity accurately. The difficulty that most physicians had was that these were quite complicated and sensitive procedures that were not widely available and were also expensive, since in those days insurance companies did not cover them. Paul Brown, who had founded Metpath Laboratories, was a good friend and I recall taking you over to New Jersey around 25 years ago to meet him. Metpath was well on its way to becoming the largest clinical laboratory in the U.S. and since I served as a consultant at the time, I wanted to explore the possibility of providing renin testing as part of a hypertension profile. Nothing apparently came of that but Corning later acquired Metpath, which subsequently became Quest Laboratories. Quest now offers an automated ambulatory direct Renin immunoassay. Is this procedure as accurate as the Sealey-Laragh plasma renin activity assay? JHL: I remember our visit with Paul Brown quite well. You were on the right track then, but as usual, a little ahead of the curve. Jean Sealey joined our laboratory in 1960 as a biochemist with excellent credentials and she soon showed us how our aldosterone assay could be improved. Over the next ten years Jean worked with us to perfect the world's most sensitive and accurate plasma renin activity assay (PRA). She also worked in Harry Goldblatt's lab for several months to learn his 12 step human renin purification procedure, which gave us a very valuable reagent to use.

All of the previous renin assays were very inaccurate because they didn't reference the level of renin activity to the current state of sodium balance, poor angiotensinase inhibition, poor pH control and were unaware of the effect of cryoactivated prorenin. Jean showed that a previously unappreciated large amount of prorenin occurs in human plasma and is converted to active renin in vitro when plasma or blood is exposed to cold temperatures. This was why most labs that routinely chilled their plasma samples had very high false results. As a result, they were unable to measure low renin accurately, which is critical for identifying low renin hypertension patients.

During this period, although there were constant criticisms and objections to my renin hypothesis, nobody ever questioned the superior accuracy of our testing procedure. Our renin assay remains the only method that can accurately measure the low values, and this is absolutely crucial since it is the only way to positively identify and separate the salt-volume "V" patients whose hypertension is caused by salt and have no renin in their plasma.

Quest has been using our Sealey-Laragh method for the past 7-8 years in their New Jersey laboratory since we are close by to help with any problems. They confirmed our results but unfortunately, our method proved too skilled-labor intensive for them to put into a mass production mode. Recently, we have helped them to switch to their automated Direct Renin test. While the current Quest-Nichols chemiluminescence Direct Renin assay is much better than all of its predecessors, it is still not as sensitive as our PRA procedure for defining and discriminating the low renin salt-volume caused hypertensive patients.

However, we are hopeful, since recent comparisons with our assay show that the Quest Direct Renin assay is improving. Most people don't appreciate that plasma renin activity (PRA) levels can be significant and high enough to produce a fatal stroke at 12 molar concentrations of renin or one ten billionth of the molar concentrations of plasma glucose or cholesterol! This is why very sophisticated detection technology amenable to mass production is required. The pivotal values for these two procedures are shown below.

(V) Volume Hypertension  (R) Renin Hypertension
PRA levels < 0.65 ng/ml/hr  PRA levels > 0.65 ng/ml/hr
Direct Renin < 5 mU/ml  Direct Renin > 5 mU/ml
This is predominantly sodium-volume caused hypertension  This is predominantly due to renin-angiotensin caused vasoconstriction

Measuring renin allows you to identify which type of antihypertensive medication is most likely to be effective and possibly safer in any given patient. The advantage here is that once this is established it is possible for patients to have their blood pressure controlled with one drug permanently. Monotherapy for life is our nirvana for hypertension treatment.