Abstract, Closing Summary, and Table of Contents for Laragh’s 25 Lessons in Pathophysiology and 12 Clinical Pearls for Treating Hypertension*

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These 25 lessons 1) review the roles of plasma renin levels for causing malignant and most essential hypertension and their related vascular injuries (heart attack, heart failure, kidney failure and stroke); 2) review how antihypertensive anti-R drugs that block renin activity (beta blockers, the first converting enzyme inhibitor from venom, and the first angiotensin receptor blocker) were used to reveal plasma renin involvement in the hypertension of medium and high renin patients and to show; 3) that the 30% with low renin essential hypertension do not respond to R drugs, are not prone to heart attack or stroke, and BP is corrected instead by the natriuretic anti-V drugs (diuretics, spironolactone, CCB, alpha blockers); 4) thus, all hypertensives can be divided into R patients who have too much renin vasoconstriction or V patients who instead have predominant sodium-volume mediation. Furthermore, all antihypertensive drug classes can be divided into R drugs that block the renin factor, or V drugs that reduce body sodium volume; 5) these findings document our conception of two biochemically and physiologically different final factors that sustain all BP in which the sodium-volume factor continuously sustains cardiac output and flow while plasma renin-angiotensin sets total peripheral resistance (TPR), which, within the Poiseuille Equation (BP = cardiac output [CO] × TPR) describes our [Na⁺-volume × renin-angiotensin vasoconstriction] model that supports all normotension or hypertension; 6) in this light, we designed a visit-by-visit method for treating untreated hypertensives using the ambient plasma renin level and BP responses to guide primary drug therapy against either the V or R factor; and 7) for also correcting nonresponders receiving multiple drugs where renin testing correctly guides addition or subtraction of drugs depending on whether the test indicates unresponsiveness due to a reactive sodium-volume excess, or to lack of effectiveness of an R drug in a V patient or of a V drug in an R patient, or from large reactive increases in renin that override the R drug, calling for strengthening the R and/or removing V drugs. This objective, biochemically based method results in effective longterm BP control of nearly all patients using fewer, but the correct drug(s) for each individual. Am J Hypertens 2001;14:84–89, 186–194, 296–304, 307–310, 397–404, 491–503, 603–609, 733–742, 837–854, 1173–1177 © 2001 American Journal of Hypertension, Ltd.

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Closing Summary

An important achievement of the 20th century for hypertension and cardiovascular medicine emerged from original human and laboratory research begun in 1955, in which we discovered and characterized a major new endocrine servocontrol, the renin angiotensin aldosterone system for normal regulation of blood pressure (BP) and body sodium and potassium content in all of us. At the same time we showed that overactivity of the system, with very high plasma renin-angiotensin and aldosterone levels, causes malignant hypertension and its rapidly fatal consequences (heart attack, heart failure, stroke, kidney failure) and, in a milder expression, also...
causes or sustains 70% of essential hypertension (plasma renin activity [PRA] >0.65 ng/mL/h) and their more gradually occurring but similar cardiovascular consequences. Conversely, the 30% of essential hypertension who have low-renin values (PRA <0.65 ng/mL/h) have salt-mediated hypertension and they are not prone to premature heart attack or stroke. They do not respond to antirenin system R drugs and their high BP is corrected instead by sodium volume depletion or by a natriuretic V type drug.

Two basic prerequisites for success of this research were: 1) our development of a uniquely sensitive plasma renin assay to readily define the low point below which plasma renin is no longer pressor, and to also discriminate among lower normal values to consistently separate out salt-mediated from renin-mediated hypertension. 2) The second essential resource was our introduction and definition of the concept of R-type antirenin system drugs to assess the BP support of the renin level by blocking it in vivo and relating induced decrements in renin activity to decrements in BP. Thus, we introduced β-blockers to persistently reduce plasma renin levels, the original intravenous nonapeptide from venom, converting enzyme inhibitor (CEI) to block angiotensin II (Ang II) formation, and the first angiotensin receptor blocker (ARB) the intravenous octapeptide, sarasalin, to block the Ang II receptor. The impressive and congruent antirenin system depressor effects of these three differently acting antirenin system agents to lower BP according to the height of their antecedent ambient plasma renin levels (PRA >0.65 ng/mL/h) inspired industry to design orally active analog CEI with exactly the same actions (e.g., captopril, enalapril, and lisinopril [and then many analogs of the latter two], and later the saralasin-like ARB (losartan, valsartan, candesartan, irbesartan) that, together with the already available β-blockers provided the means for broad clinical use of antirenin system R drugs, the effectiveness of which verified our original conceptions of the causal roles of excess plasma renin angiotensin not only in hypertension but also in related heart, brain, and kidney vessel diseases, thereby concurrently revolutionizing treatment of both hypertension and of its renin-mediated fatal consequences (heart attack, heart failure and stroke, and kidney failure).

In this research we also documented our conception (the volume-vasoconstriction model) in which there are of only two different final biochemical and pathophysiologic pathways for sustaining all normotension or hypertension. One form is salt-mediated V hypertension (PRA <0.65 ng/mL/h) and the other is renin or R-mediated (PRA >0.65 ng/mL/h). In this volume vasoconstriction model, our differentiation of those two final pathways is supported by 1) the above biochemical differences in their renin levels, 2) the corresponding but reciprocal differences in depressor responses to either V or R antihypertensive drugs in V or R patients, 3) the much greater occurrence of later cardiovascular sequelae (heart attack, stroke, heart failure, kidney failure) in R patients, as described in our two 8-year human trials, and 4) the fact that the above three differences are also consistently demonstrable in the animal models of classic salt- or renin-mediated hypertensions.

With these tenets in hand, the centerpiece of our method for treating each patient is how we use ambient plasma renin levels together with the initial and follow-up BP readings and our volume vasoconstriction analytical model to administer the correct and the fewest number of drugs for long-term correction of hypertension and for prevention or arrest of its fatal cardiovascular consequences. Thus, within this volume-vasoconstriction model all antihypertensive drugs can be rationally divided into V drugs, which reduce the sodium-volume V factor, and R drugs, which block the renin R factor. Correspondingly, all hypertensive patients can be divided into primarily V (PRA <0.65 ng/mL/h) or R categories (PRA progressively >0.65 ng/mL/h).

Our volume-vasoconstriction analytical model passes a most severe test of its utility and relevance because it is especially useful for rapid analysis and treatment of hypertensive crises to thereby hasten delivery of the correct life-saving R or V drug treatment. This is accomplished by entry renin testing followed immediately by an R drug trial to correct, or rule out, the more common and fatal renin mediated hypertensive crises (see Lession XXV). Our research shows that renin involvement in these crises is more common than generally recognized and is the likely cause of their fatal vascular injury, resembling in this way our template of malignant hypertension, with its rapidly fatal plasma renin-angiotensin mediated vasculotoxic injury to heart, brain and kidney vessels, expressed as heart attack, heart failure, stroke, or kidney failure.

In these contexts, in these lessons I have therefore described a visit-by-visit method for treating untreated patients based on ambient plasma renin testing to target primary therapy against either the V or R factor. I also describe how plasma renin testing is especially useful for finding the correct therapy for nonresponding patients on multiple drugs. Here the renin level correctly guides the addition or subtraction of drugs, depending on whether the test indicates unresponsiveness due to a reactive sodium volume excess (low PRA) or a lack of response to a CEI or ARB (low PRA) or to a large reactive increase in renin induced by a diuretic or by a CEI that overcomes the drug action (PRA >6.5 ng/mL/h). The latter calls for withdrawal of the V drug and a strengthening of the R drug. In our Lessons we define seven different situations where either intuition, guessing, or logic, without the renin test result will almost certainly fail to sort out the predicament and will often make it worse by adding or subtracting the wrong drug types.

I believe you will find that the enormous satisfactions from using our method are worthwhile for the physician, the paraprofessional, and especially for the patient. The daily correction of hypertension will be more fun because it will have a rational and objective basis.