Laragh’s Lessons in Pathophysiology and Clinical Pearls for Treating Hypertension


In preceding lessons we reviewed the high points of a great explosion in our knowledge during the past 40 years in which the circulating renin-angiotensin aldosterone system has been put on the biological map and shown to play a central role for regulating, from minute to minute arterial blood pressure (BP) levels, while also regulating the amounts of dietary sodium and potassium that we keep in our bodies.

Our research also indicates that this plasma renin launched system plays a backup role to support normal BP because available dietary salt, by determining the size of extracellular and plasma volumes, provides the primary defense of BP. Accordingly, if you and I happen to eat salt in abundance the renin system will work at a very minimal level or not at all in the body. But, whenever salt is in short supply from sweating, exercise, alimentary loss, hemorrhage, or trauma, or even just from a low salt diet, the renin system kicks in promptly, in just the right amount, just as it does every morning when you stand up, to keep your BP level normal. However, there is a long-term cost for this renin bailout because, when renin-angiotensin vasoconstriction takes over, there is a persistent and demonstrable reduction in tissue flow for as long as these higher renin levels are sustained. Thus, in this new steady state, as indicated by the Morganti experiment (Lesson XIV), blockade of plasma renin by a CEI or by a β-blocker in the absence of dietary salt will produce a prompt collapse of the BP, in either normal or hypertensive people, and in animal models.

Thus, the state of hypertension is a parallel model of our normal control system, in which the Poiseuille equation applies to both. This means that all hypertension must be sustained by too much arteriolar vasoconstriction (usually the plasma renin-angiotensin level) relative to the sodium-created volume status, or by vice versa. At present, with the guidance given in these lessons, we can readily measure plasma renin levels to access either the renin or sodium volume status so that by recognizing and using the modern antirenin R drugs or antisodium V drugs we have the basic tools to mechanistically correct and systematically control practically all the hypertension of (PRA <0.65).

We can do this because we know from our research that the plasma renin levels (PRA >0.65) operate to sustain part or all of the BP of about 70% of essential hypertension (“R” patients), whereas a relative or absolute excess in the sodium volume (“V” patients) factor primarily sustains the rest of (PRA <0.65) (Lessons IX and XI). Thus, there are two basic types of hypertensive patients, renin-mediated R patients (PRA >0.65) and sodium volume-mediated V patients (PRA <0.65) (see Lessons XVI, XVII, XVIII).

Furthermore, we know that inappropriately high plasma levels of renin are associated with and likely to cause potentially fatal vascular disease in heart, brain, and kidney vessels, in a range of situations in either hypertensive human or animal models. Such vascular injury (Lesson X) is uniquely preventable or arrestable by the specific antirenin system R drugs. All of this means that, from now on, the promise of applying drug therapy that will protect from potentially fatal cardiovascular sequelae should be a main goal for designing antihypertensive drug therapy.

The challenge is here. How do we take advantage of this information to treat individual patients by using plasma renin activity (PRA) testing in our new, fully objective plasma renin-based treatment method. Then, for those patients not fully corrected, further renin testing guides us to efficiently correct the remainder of the patients, using fewer but again, the most appropriate, renin test targeted drugs.

This is why we have great hopes and expectations for our method using our cutoff PRA value of 0.65 ng/mL/h to separate patients into V or R types. This method, abetted by our parallel classification of drugs into basic V and R types enables this first objective biochemically based treatment method to deliver the correct drug type or types to all patients according to how the renin sodium seesaw is involved.

In these lessons, if I have convinced you that all essential hypertension is not alike mechanistically and therefore, that all hypertension cannot be treated the same way or with the same drug type, then I will be very happy, because you will realize that you can build rational V or R or V+R programs to correct all forms of human hypertension.

In the light of this framework in this Lesson, I propose to respond to a number of questions raised from the preceding lessons by our students, colleagues, and practicing physicians. Let’s begin with some simple questions about patients with high BP and their renin levels.
Questions and Answers

1. Q: WHAT ARE THE PRIMARY GOALS OF ANTIHYPERTENSIVE DRUG THERAPY?
   
   A: Traditionally, the main goal of antihypertensive therapy has been to correct the high BP per se. According to this view restoring the pressure to lower and normal levels corrects all of the problems and eliminates the added risk of premature fatal cardiovascular sequelae, for example, heart attack, congestive heart failure, kidney failure, or stroke. Of course, in fact we know that many of these major cardiovascular sequelae are not solely pressure related. Thus, in toto, more heart attacks and strokes occur in normotensive than in hypertensive individuals. However, statistically, hypertensives are significantly more likely to develop these sequelae. Congestive heart failure and dissecting aortic aneurysms are even more highly associated statistically and mechanically with antecedent hypertension and both can be most dramatically corrected or arrested by lowering BP, even pressures already within the normal range. A higher BP level, even if it is not the primary cause, often operates to amplify or hasten the progression of these potentially fatal cardiovascular disorders. In this context, the modern goal of long-term antihypertensive drug therapy is finding a drug treatment regimen that not only reduces BP but also prevents or arrests the progression of the major fatal cardiovascular sequelae that shorten useful life.

When the modern treatment era of drug treatment for hypertension began in the 1970s it was assumed that the means by which BP was reduced was irrelevant. If the pressure came down the job would be done, barring of course unacceptable side effects. But now that we have many different types of effective antihypertensive drugs and that we know that all hypertensive patients are not alike mechanistically (patients are readily definable as either R-renin-mediated or V-sodium-mediated hypertensives) we have an opportunity to apply objective biochemically indicated drug treatments to all patients.

The available evidence from major clinical trials support this approach. The anti-R drugs used in trials of more than 100,000 patients are the only drug types proven to improve survival and prevent or arrest progression of coronary events in patients after a myocardial infarction (MI) or with congestive heart failure (CHF) (see Lesson XII) (HOPE trial, N Engl J Med 2000;342:145–153). These drugs can provide a benefit even if the BP is not reduced by the drug. Similar benefits accrue to patients with renal failure given R drugs (Lesson XII). Moreover, selective benefit for aldosterone blockade compared with the usual diuretic therapy (Rales Trial, see Clinical Pearl I) again implicates an overactive renin system in the progression of coronary artery disease (see also Garg R and Yusuf S, JAMA 1995; 273:1450–1456).

Compared with the R drugs, it has been more difficult to demonstrate similar survival and cardioprotective benefits for traditional V drug diuretic therapy alone or for the use of dihydropyridine calcium channel blockers (CCB). In fact, short-acting versions of the latter appear to accelerate the progression of coronary disease when given to patients after MI. Much of the confusion about all of these drugs is based on the fact that, in the absence of doing renin testing, CCB and diuretics are often given unwittingly to R hypertensive patients and the R drugs too are often given, again unwittingly, to V patients where antihypertensive responses are lacking. No wonder its been hard tofigure out the true value of some of these drugs and no wonder so few patients are staying with the treatment plans they have been saddled with.

2. Q: WHY IS RENIN TESTING MORE SUCCESSFUL WITH YOUR NEW METHOD THAN IT WAS IN THE PAST?
   
   A: Here are four reasons:

   1. We have perfected an extremely sensitive and accurate renin test that fully explores and defines the subnormal as well as the low and medium ranges. We have identified a key plasma renin value, a PRA of 0.65 ng/mL/h. This is the cutoff that sets apart sodium volume-mediated hypertension (<0.65 ng/mL/h) from renin-mediated hypertension (>0.65 ng/mL/h). Thus, there are basically two types of hypertensive patients, V hypertensive patients and R hypertensive patients.

   2. Now we just use the plasma renin test. Renin sodium profiling is not necessary, and we still do not require any dietary manipulation of sodium intake. To classify patients, we simply measure the ambulatory plasma renin level and record the BP to evaluate to what extent the renin level or the sodium volume factor is contributing to the high BP in the ambulatory patient.

   3. There are two basic classes of antihypertensive drugs: the V drugs (antisodium volume) and the R (anti-renin system) drugs. Respectively, when they lower BP they oppose the sodium volume factor or the plasma renin angiotensin factor involved in the hypertension.

   4. We can also use the ambulatory plasma renin level in unsuccessfully treated patients already on drugs to identify the correct drug therapy for the V (sodium volume) or the R (renin-angiotensin) biochemical lesions revealed by the renin test. This all-encompassing treatment method is reproducible and highly teachable.

3. Q: IS IT NECESSARY TO MEASURE PLASMA RENIN IN THE SUPINE POSITION OR ON A LOW SALT DIET?
   
   A: This is a key question because many people have the perception that you have to put your patients supine for a half an hour or so before measuring renin, or
put them on a low salt diet for a week or so, or give them a diuretic to activate the system.

Actually, we seek to measure renin on the diet that the patient normally eats because this is the salt intake that determines the renin level and hence the concurrent high BP. We simply want to determine the renin level that is contributing, or not contributing, (low renin values) to the patient’s ambulatory high BP level. Accordingly, we have simplified how to measure renin. We just have the patient seat in the usual clinic setting and draw the blood with no need for any special diet.

4. Q: IS IT NECESSARY TO MEASURE A 24-H URINARY SODIUM WITH A RENIN TEST?
A: Effectively, I just answered that question. We really only need to know what the renin and BP levels are under the conditions of salt intake the person normally eats. We base this judgment on our years of experience measuring thousands of 24-h urine sodium values. This convinced us of the validity and practicality of our present approach. In the presence of hypertension, we have learned that any renin value >0.65 ng/mL/h is progressively more likely to be sustaining some or all of the hypertensive conditions. This is verifiable by their depressor responses to an “R” drug.

However, it is a fact that some clinicians still recommend the “stimulated renin” of salt depletion as being more valuable. We do not agree. At present, this is only advised by those clinicians who have invested in insensitive immunoradiometric assay (IRMA)-type assays, mainly to try to boost the patient’s renin level enough to measure a real number. Unfortunately, using these insensitive “direct” immunoasays you cannot properly investigate the relevance of someone’s renin level, because you need to know its position in the whole renin spectrum, an unachievable goal with either a direct IRMA or with a short incubation time kinetic assay. The derived low “numbers” are not meaningful with these crude tests. These assays can only show with some certainty that the very high numbers are correct. But to know where you are with your patients, you must be able to discriminate among the medium, the low, and the subnormal values that surround the crucial point (0.65 ng/mL/h) above which plasma renin levels begin to become biologically relevant (ie, pressor).

5. Q: WHAT ARE THE MAIN BENEFITS OF RENIN TESTING TO PROVIDE TREATMENT FOR A HYPERTENSIVE PATIENT?
A: There are three factors every physician needs to know: 1) Why the BP is high; 2) which drug type is going to effectively control the BP; and perhaps most important, 3) which patients are at the greatest risk for a hypertensive complication, either a stroke, a heart attack, or kidney failure.

The primary value of the renin test is that, from the very beginning, you know why you are giving a particular drug to your hypertensive patient. You have escaped from the dart board approach that has only one endpoint, BP reduction, and considers the role of other factors in the development of hypertension or end organ damage as irrelevant. The value of renin testing is that, for the individual patient, it leads more quickly to the simplest effective treatment regimen. For the physician, it rationalizes and efficiently enables the correct selection of either a V or a R drug as initial or follow-up therapy.

There are many benefits of PRA testing for both the physician and the patients:

For the Physician
1. The volume vasoconstriction hypothesis, which is based on an understanding of how the renin system interacts with the body sodium volume content for the regulation of BP simplifies drug selection by the primary classification of all hypertensive patients into V patients or R patients and by the classification of all antihypertensive drugs into two basic groups: anti-renin R drugs and anti-sodium volume V drugs. Thus, renin testing to define V and R patients together with the classification of hypertensive drugs into V and R types allows for a simple and rational approach to treatment (Protocol I; Lesson XVI).
2. The correct drug, one targeted at the primary pathophysiologic abnormality, is usually associated with fewer side effects. Fewer side effects results in fewer patient calls and visits.
3. Renin testing at the same time can be used to rule in or out curable forms of hypertension, either renovascular or primary aldosteronism.
4. Renin testing also identifies the patient at greater risk for later cardiovascular disease and, therefore, in need of more aggressive treatment.
5. Renin testing increases the percentage of patients in your practice who will have their BP controlled and reduces the number of office visits needed to achieve successful treatment.

For the Patient
1. For most patients, the use of renin testing reduces the number of drugs that are necessary for successful treatment.
2. A reduction in the number of drugs reduces the likelihood of side effects.
3. A reduction in the number of drugs is also likely to reduce the cost of treatment.
4. Lower cost and fewer side effects increase the likelihood of patient compliance.
5. Renin testing at the same time increases the likelihood of identifying curable hypertension, renovascular or primary aldosteronism.
6. Renin testing assures that those with renin-mediated R hypertension will first receive the correct antirenin R therapy because it can prevent or arrest angiotensin vas-
culotoxic effects resulting in heart attack, stroke, or heart failure.

7. Conversely too, those with sodium-mediated V hypertension will be assured primary therapy with anti-sodium V drugs.

The range of plasma renin levels is wider in hypertensives than in normotensives, and it also expresses a general bias toward lower values because the presence of a higher BP per se is “normally” or correctly perceived by the renal arteriolar baroreceptors as indicating a need to reduce kidney renin secretion. Accordingly, truly lower ambulatory plasma renin values indicate a sodium volume excess hypertension that can be corrected primarily and often solely by a V drug. Conversely, patients with higher renin levels than >0.65 ng/mL/h are correctable primarily and often solely by an R drug. When you put those two groups together you can account for 60% to 80% of all hypertensive patients. Thus, just by knowing the renin level one can make informed decisions not possible using other less relevant or weakly based statistical guidelines. With the plasma renin test you get a risk profile, you get a handle on which drug type should be given first, and you rule in or out the curable forms. You’re in business!

6. Q: DO ANTIHYPERTENSIVE MEDICATIONS PREDICTABLY AFFECT THE PRA LEVEL?

A: Yes, under most circumstances, PRA values increase with antihypertensive medication because a major stimulus for renin secretion is a reduced BP in the renal arteries. Reciprocally, an elevated BP reduces renin secretion, as does excess body salt, both of which occur in patients with sodium volume-mediated forms of hypertension and work to lower their renin levels (PRA <0.65 ng/mL/h). Accordingly, the magnitude of the increase in PRA with antihypertensive drug treatment is inversely related to the induced reduction in BP and to the reduction of body salt content caused by drug treatment.

Drugs that increase PRA levels: the CEIs and ARBs. Angiotensin II levels in the blood normally exerts a negative feedback effect on kidney renin secretion. When angiotensin II levels are decreased during treatment with an angiotensin converting enzyme (ACE) inhibitor, or when angiotensin II binding to blood vessels is blocked by an ARB, this negative feedback signal is lost or blocked and PRA levels reactively increase. This increase can be dramatic in patients who are effectively treated by these drugs. Conversely, it follows that if the patient’s BP is not lowered by either a CEI or ARB drug, there will be little or no reactive increase in renin and the drug should be stopped because it is functioning only as a placebo. This is what occurs when low renin patients are treated with these antirenin drugs.

Diuretics stimulate renin secretion by reducing body sodium content and, therefore, blood volume to thereby lower BP. Loop diuretics stimulate PRA more than thiazide diuretics for two reasons. First, they induce a greater natriuresis. Second, they also block chloride transport at the macula densa sensor, which is normally a signal to suppress renin secretion.

Calcium channel blockers also usually stimulate renin secretion whenever they lower BP, but less than CEIs or ARBs. This seems surprising because they should increase renin secretion by lowering BP and also by blocking the entry of calcium into the cells that secrete renin, and by blocking sodium reabsorption. These actions appear to be offset by their potent vasodilating effect on the renal afferent arterioles. This allows greater transmission of arterial pressure into the juxtaglomerular apparatus (JGA) cells, and this increase in pressure at the renin secretory site dampens the signal for renin release. Alpha blockers, like CCBs, produce only moderate increases in PRA when they lower BP, probably also related to their renal vasodilation.

Other potent, direct, vasodilators, including hydrazine, minoxidil, and nitroprusside more strikingly stimulate renin secretion whenever they lower BP, thereby also promoting overproduction of aldosterone, and, in turn, edema formation. Because these vasodilators activate the entire renin–aldosterone system more than CCB, they are practically always best given together with an antirenin drug (eg, β-blocker, CEI, or ARB) to block the renin response and also the tachycardia and headache.

Drugs that decrease PRA levels: β-Adrenergic neural activity directly stimulates kidney β-receptors to increase renin secretion. Hence, β-blockers suppress kidney renin secretion, thereby lowering PRA and plasma angiotensin II formation by about 75% for as long as they are given. Thus, a β-blocker is the prototype of an antirenin drug that lowers BP by directly lowering PRA rather than by blocking angiotensin I conversion (CEI) or angiotensin II action (ARB). Clonidine and methyl DOPA-type drugs are centrally acting α2-agonists that, like β-blockers, lower BP by lowering PRA, but this time it is by suppressing sympathetic outflow from the brain to the kidney β receptors. Renin secretion again decreases because β-adrenergic signals to the JGA cells are reduced.

7. Q: BASED ON THE PRA TEST CAN I TREAT A PATIENT ALREADY ON A DRUG?

A: Yes, you certainly can. You can learn a lot from the PRA test in treated patients. Our Lessons XVI, XVII, XVIII and Protocol II illustrate treatment strategies based on the PRA level. For example, any patient with a renin level <0.65 ng/mL/h on any drug (other than a β-blocker or clonidine) is a low renin V patient and is likely to be most effectively treated by an antisympathetic V drug: a diuretic, a specific aldosterone receptor antagonist (SARA), a CCB, or an α-blocker.

Another example is the uncontrolled patient on a diuretic with a treatment PRA level of >6.5 ng/mL/h. The elevated PRA level may be attributable to sodium depletion by the diuretic or the patient may have high renin...
hypertension. Irrespective of the reason for the high renin level, the diuretic should be withdrawn and an antirenin system drug started (ACE inhibitor, ARB, β-blocker) because the renin level is too high, and the diuretic may be increasing it even further, so that it has countered the effects of the diuretic treatment on BP.

If a patient with a PRA level >6.5 ng/mL/h is uncontrolled even on a CEI or ARB, it is likely that these drugs are inducing such big reactive increases in renin that they cannot prevent some angiotensin II from breaking through their blockade. Most CEI and ARB are only about 90% blockers of the renin system. Thus, a 10-fold increase in PRA can completely overwhelm their effectiveness. The strategy here is to add an ARB to a CEI or a CEI to an ARB. A β-blocker could be added instead to lower the level of renin secretion. Sometimes, but rarely, all three agents must be given to cope with big reactive renin increases. In such patients, unilateral renovascular disease should be considered, especially if other clinical features are indicative of that disorder.

8. Q: IS THERE ANY CLINICAL VALUE IN A LOW RENIN?
A: You can learn a lot from a low PRA level in a hypertensive patient, provided it has been measured properly using a kinetic assay with an 18-h incubation to generate enough angiotensin for an accurate assay.

1. It rules out curable renovascular hypertension (PRA values <1.5 ng/mL/h).
2. If the PRA is <0.65 ng/mL/h and especially if the patient is hypokalemic, or develops hypokalemia on a diuretic, it strengthens the possibility of primary aldosteronism.
3. For all of these patients a low plasma renin level (<0.65 ng/mL/h) indicates that the patient has a primarily volume-dependent form of hypertension. The nephrons of the kidneys may not be filtering enough salt or reabsorbing too much. Treatment with a natriuretic volume-depleting V drug is indicated and is often all that will be needed.
4. The low renin level also indicates that the patient is not at high risk of cardiovascular complications. The work-up can proceed at a reasonable pace, with several BP readings before treatment, to ensure that the hypertension is fixed and consistently high enough to be treated. There is time to initiate treatment with low doses and allow 3 weeks between visits to ensure that maximum response to each dose has been achieved.

9. Q: WHICH OF MY HIGH BP PATIENTS SHOULD HAVE A RENIN TEST?
A: All of them. However, there are priorities:

1. The difficult to treat, severely hypertensive patient who is on multiple drugs. The treatment PRA serves as a guide as to how to proceed and can be used to determine the next course of action (see Protocol II, Lesson XVI).
2. The hypokalemic patient, on or off antihypertensive treatment. A PRA <0.65 ng/mL/h in a hypokalemic patient not taking a β-blocker suggests the possibility of primary aldosteronism.
3. The severely hypertensive patient and the hypertensive emergency patient because, even if you decide to initiate treatment before getting the result of the test, the baseline PRA value will help to guide or change follow-up treatment. We believe all such patients should first receive an angiotensin drug because these act quickly to give a BP response, or lack of response to an antirenin system drug quickly tells you a lot about the mechanism of the hypertension. Also renin involvement is more likely and more lethal than the sodium volume factor.
4. Any untreated clearly hypertensive patient with BP consistently ≥140/95 mm Hg.

10. Q: WHICH OF MY HYPERTENSIVE PATIENTS SHOULD NOT HAVE A RENIN TEST?
A: 1. Normotensive patients should not have the PRA test because, as we have discussed, normotensive patients generally have higher PRA levels than hypertensive patients because the presence of hypertension per se reduces PRA levels by acting on renal afferent arteriolar baroreceptors.
2. Ideally PRA levels should not be measured in a patient with borderline hypertension or at a time when BP has fallen into the normal range because the effect of the “hypertension” on the renin level is not being expressed.
3. It follows that a captopril test should not be performed in any patient whose BP is not clearly hypertensive because renin secretion is more reactive to its interruption during the normotensive state and false-positive results will be obtained from the captopril test (see Muller FB, Sealey JE, et al, Am J Med 1986;80:633–644).
4. Accordingly, we too recommend plasma renin testing routinely only for patients who clearly have hypertension (ie, BP >140/95 mm Hg). This avoids the need to study uncomplicated borderline hypertension where risks are minimal and drug therapy is neither cost effective nor of certain value. However, in the presence of coronary, renal, or cerebral vascular disease baseline plasma renin testing may indicate a renin factor possibly worthy of renin testing and drug therapy.
5. Notwithstanding these caveats, the fact remains that if renin testing points to a V-type hypertension is always worth knowing. But if an R factor is revealed in the face of little or no hypertension and no cardiovascular risk factors, you might be seeing a “normal” variant who is not truly hypertensive or revealing a hyperadrenergic state reported by some investigators to occur in younger adults.

11. Q: SHOULD I REPEAT THE RENIN TEST AFTER INITIATING THERAPY? WHAT EFFECT DOES THERAPY HAVE ON PRA LEVELS?
A: If therapy is unsuccessful, or only partially
successful, the renin test can help to redirect treatment, especially if BP is uncontrolled or poorly controlled with the combination of full-dose antivolume and antirenin system drugs (Protocol IIc). It is especially useful in conjunction with the baseline PRA level, as any effective antihypertensive agent increases kidney renin release and PRA values. The one exception is β-blockers or centrally acting α-agonists, which reduce β-adrenergic outflow (eg, clonidine). But for all other antihypertensive drug classes if the PRA level does not increase during treatment it means that the patient is not taking the drug or the antihypertensive treatment has not been effective and a different approach is needed (see Protocols). If the PRA level was initially high and did not decrease during β-blockade it means that the patient is noncompliant or the renin secretion in that patient is independent of β-adrenergic tone (very unusual) and that a CEI or ARB is likely to be more effective.

12. Q: IS THERE A ROLE FOR RENIN TESTING IN SCREENING FOR CURABLE FORMS OF HYPERTENSION?

A: Yes. There are two highly curable forms of hypertension (primary aldosteronism and renovascular hypertension), the diagnosis of which can be ruled in or out by a renin test.

Primary aldosteronism may be suspected in any untreated hypertensive patient with hypokalemia or any patient who develops hypokalemia during treatment. The renin test discriminates the patient with primary aldosteronism from those in whom the hyperaldosteronism is due to excessive renin secretion (secondary aldosteronism). A PRA value <0.65 ng/mL/h in a hypokalemic patient suggests the possibility of curable primary aldosteronism due to a removable adrenal cortical tumor (adenoma).

The renin test can be used in several ways to diagnose or rule out patients with renovascular hypertension. First, a PRA level <1.5 ng/mL/h in an untreated or even in a treated (by other than β-blockade) patient rules out the likelihood of unilateral renovascular hypertension. In the nonazotemic patient, the higher the PRA >1.5 ng/mL/h the more likely is the diagnosis of unilateral renovascular hypertension. The presence of hypertension with a PRA level >1.5 ng/mL/h, a mildly elevated creatinine, and a tendency toward pulmonary congestion suggests the possibility of bilateral renovascular hypertension. Renal vein renin measurements, with and without a captopril test, can provide information concerning which kidney is affected or which kidney is more affected. This can be verified by more expensive renogram testing but it is usually more informative to go directly to renal angiography.

13. Q: WHAT DO I DO IF I CANNOT WAIT 2 DAYS TO GET RENIN TEST RESULTS?

A: In this situation, we advocate immediately starting treatment with an antirenin system drug such as a CEI or an ARB 1) because a patient with an elevated renin level is at more risk than one who has a suppressed renin level, and 2) because the response, or lack of response, provides powerful diagnostic information about the presence or absence of a renin factor, and 3) because more than half of patients with essential hypertension do in fact have a significant renin factor supporting their hypertension.

14. Q: HOW SHOULD I TREAT A HYPERTENSIVE PATIENT WHOSE BP WAS NOT LOWERED BY AN ACE INHIBITOR (CEI) OR ANGIOTENSIN RECEPTOR BLOCKER (ARB) AND WHO HAS A TREATMENT PRA VALUE <0.65 ng/mL/h?

A: This is a chance for a HOME RUN, which you could not make without renin testing. CEIs and ARBs always increase plasma renin values when they are effective in lowering BP. Because this patient’s plasma renin level was low and the pressure remained high, the drug was functioning only as a placebo. Any nonresponding patient with a low renin value on a CEI or ARB is a low renin patient and is likely to respond instead to an antiso-dium volume V-type drug such as a diuretic or aldosterone antagonist, or an α-antagonist, or a calcium channel blocker.

15. Q: ARE THERE OTHER HOME RUNS IN CLINICAL PRACTICE THAT ARE MADE POSSIBLE BY RENIN TESTING?

A: Yes, The biggest HOME RUN occurs whenever you test the effects of 25 to 50 mg of oral captopril or a rapidly acting ARB in a new ambulatory patient seated in your office. A dramatic decrease in BP 30 to 60 minutes later strongly indicates that you have discovered a renin factor! You’re on your way. Conversely, a total failure of response means a sodium volume factor is most likely. Another similar HOME RUN occurs in hypertensive emergencies. The responses to oral captopril or intravenous enalapril can immediately prove or rule out a renin factor. This strategy of rapid diagnosing while treating with a specific probe can be lifesaving. This strategy has been called diagnost ex juvantibus, which means the response to the drug informs the diagnosis.

16. Q: WHY WERE LEADING INVESTIGATORS UNABLE TO DEMONSTRATE SUPPRESSION OF PLASMA RENIN BY β-BLOCKERS? IS IT TRUE THAT EUROPEAN SCIENTISTS RETRACTED THESE CLAIMS? HAS THIS MODIFIED YOUR METHODOLOGY?

A: Serious scientists from Europe and Australia were unwittingly measuring, along with renin, a then unknown precursor substance called prorenin and this caused a gross error in their results and thus their interpretation of the plasma renin test. In fact, the acid conditions that they used to process their renin samples resulted in the conversion of large amounts of precursor prorenin into renin; they were actually measuring the true plasma.
that gradually became aware of this significant error and a zero. No kidneys, in whom we always find active renin to be renin in all of their patients, even in those who had no kidneys, in whom we always find active renin to be zero.

To the credit of the British and Australian groups they gradually became aware of this significant error and a Belgian group graciously published a retraction stating that $\beta$-blockers really did indeed produce a powerful reduction in renin.

After our discovery of large amounts of prorenin in plasma, the most important change we made in the renin test was to modify the way in which blood is processed for the renin test. Prorenin can be artifically (cryoactivated) into renin in plasma that is stored cold, without being completely frozen. Fortunately, the changes greatly simplified the way we process blood for the renin test. Blood is collected into a purple-top Vacutainer, which can stay for up to 24 h at room temperature. It can be centrifuged at room temperature, eliminating the need for a refrigerated centrifuge. The separated plasma can remain at room temperature for a few hours but then must be frozen if the assay cannot be performed immediately.

17. Q: IS THERE A ROLE FOR THE PRA TEST IN THE PATIENT WITH HEART FAILURE?

A: The PRA level is a valuable, but underappreciated tool for the evaluation and treatment of patients with CHF. For example, in the CONSENSUS trial of enalapril in heart failure, ACE inhibitor treatment greatly improved survival in those patients who presented with plasma angiotensin II levels above the median (see Lesson XII). Conversely, ACE inhibitor treatment was no more effective than placebo in patients whose baseline renin angiotensin II levels were below the median. Once again this prompt and sustained benefit implicates PRA levels and more specifically angiotensin II (AII) levels in the pathogenesis and progression of coronary vascular disease.

Furthermore, another study indicates (Packer M, Medina N, et al, Am J Cardiol 1984;54:771–777) that the reactive increase in PRA during ACE inhibitor treatment in patients with heart failure is a marker for efficacy. Patients with significant increments in the PRA level (>4 ng/mL/h) are most likely to have symptomatic and hemodynamic benefits. In contrast, as in patients with hypertension patients with CHF with lesser or no increases in baseline PRA (<0.65 ng/mL/h) are unlikely to benefit from this type of treatment.

A recently presented trial found that, in symptomatic heart failure patients, hemodynamic benefit and reduced morbidity can occur when an ARB is added to a CEI (Cohn JN, Tognoni G, et al, Val-HeFT (valsartan) trial, submitted to N Engl J Med 2001 [In Press]). This beneficial response was associated in a pilot study with a significant decrease in circulating aldosterone, and a rise in plasma K$^+$ verifying that further interruption of the renin system has occurred during this additive antirenin therapy.

Cody RJ, Couti AB, et al (J Clin Invest 1986;77:1441–1452) demonstrated that the low renin state de novo or induced by cautiously feeding salt to patients with CHF eliminates the striking unloading (antivasoconstrictor) hemodynamic response to captopril, which could then be restored by diuretic-induced sodium deprivation to increase plasma renin levels. They further showed that treated CHF patients exhibit the full range of renin values from low to high resembling those encountered in untreated hypertensives. In these patients either captopril or enalapril fails to reduce peripheral resistance in the low renin state, but these drugs are dramatically beneficial in the higher renin (>0.65 ng/mL/h) states. In contrast it was found that a dihydropyridine CCB greatly reduces systemic vascular vasoconstriction in low renin but not in high renin patients with heart failure.

In summary, in cardiac as in hypertensive patients, the PRA level predicts the response or lack of response to antirenin R or antisolium V drug therapy. Moreover, sizeable increases in renin during ACE inhibitor treatment (PRA >6.5 ng/mL/h) can identify patients in whom the ACE inhibitor is being overcome and for whom the R drug program may need to be strengthened. Conversely, a persisting low renin value indicates in heart failure or hypertensive patients the presence of a predominant sodium volume V factor in their pathophysiology for which strengthening of the V drug limb and stopping the R drug is indicated.

18. Q: CAN A PRA MEASUREMENT BE HELPFUL DURING AN ACUTE MI?

A: A meta-analysis of more than 100,000 patients given a CEI in the post-acute MI (see Lesson XII) situation found that ACE inhibitor treatment during acute MI prolongs survival and reduces the risk of heart failure and of recurrent MI. In the vast majority, these benefits accrue within the first week of treatment. There is also abundant evidence that the PRA level is elevated in many patients both before and during an acute MI (Blumenfeld JD, Sealey JE, et al, Am J Hypertens 2000;13:855–863). It has not been determined whether the PRA level during acute MI predicts the response to ACE inhibition. However, data from its use in hypertensive and heart failure patients suggest that a high PRA level will similarly identify those
acute MI patients most likely to benefit from antirenin therapy.

Although ACE inhibitor treatment is of established benefit to many patients during acute MI, the risk of sustained hypotension and acute renal failure doubles during this treatment. In fact, up to 20% of all CEI-treated acute MI patients can develop sustained hypotension. These complications are known to occur in many clinical situations when the renin system is already activated before CEI treatment (eg, diuretic-induced sodium depletion). It is likely that a very high PRA level before CEI treatment will identify the acute MI patient at greatest risk of hypotension and acute renal failure. Therefore, the PRA test can identify patients for whom a lower initial ACE inhibitor dose is most appropriate.

In summary, a high PRA level during acute MI identifies those patients who are most likely to benefit from R treatment, but, at the same time, may be at greatest risk for drug-induced hemodynamic complications. A low renin value is unusual during an acute MI, but if present indicates a sodium volume excess possibly requiring V drug treatment.

19. Q: IS THERE A ROLE FOR THE RENIN TEST IN THE PATIENT WITH CHRONIC RENAL DISEASE?

A: Two major randomized placebo-controlled trials, one in diabetic patients (Lewis EJ, Hunsicker LG, et al, N Engl J Med 1993;329:1456–1462) and the other in nondiabetic patients (Maschio G, Alberti D, et al, N Engl J Med 1996;334:939–945) have shown that ACE inhibitor treatment significantly decreases the rate of progression of renal disease. In these studies, the ACE inhibitor-treated patients were less likely to require dialysis. However, PRA levels were not measured in either of the studies. Nevertheless, some important information can be drawn in relation to other disorders that benefit from ACE inhibitor treatment and in which the PRA level predicts treatment response.

More recently, a HOPE trial substudy has demonstrated a similar effectiveness on proteinuria for the CEI ramipril in type II diabetes. This trial has been followed by similar results for two angiotensin receptor blockers, losartan or irbesartan, with both claiming to reduce proteinuria in type II diabetes in oral presentations at the annual American Society of Hypertension (ASH) 2001 meeting. A problem with all of these reports is that <20% of patients derive any benefit. Thus, some 80% have no chance of benefit. It is likely that plasma renin testing could identify those in need of R drug therapy and spare the other 80% the cost and risk of what turns out to be a placebo. It might even open the door to another type of therapy, perhaps effective V therapy instead. Whatever the case, focused and mechanically targeted therapy is likely to be wiser than just treating everybody as alike.

20. Q: WHY SHOULD I USE A RENIN TEST WHEN DEMOGRAPHIC CHARACTERISTICS ARE REPORTED TO BE USEFUL FOR SELECTING INITIAL DRUG TREATMENT?

A: In a study comparing demographic criteria and PRA testing as a means of selecting initial drug treatment, PRA testing determined that 100% of patients with high PRA levels had a significant antihypertensive response to an ACE inhibitor (Preston RA, Materson BG, et al, JAMA 1998;280:1168–1172). This study thus confirmed the powerful value of the renin test for directing treatment for high renin patients. However, their renin test failed to discriminate medium from low or subnormal renins, and recorded an astonishing 70% incidence of low renin values (national average = 32%) possibly caused by the nomograms used, details of which were not given.

Demographic, ethnic, racial, age, or sex-related differences in renin levels among various populations are, at best, weak statistical indicators, not powerful enough to use in the care of individual patients or to identify pathophysiology or to replace an accurate renin test in the man to man practice of medicine. Thus, although it commonly has been said that the elderly have less renin-related hypertension, a recent study of octogenarians using plasma renin testing totally refuted this view (Trenkwalder P, James GD, et al, Am J Hypertens 1996;9:621–627).

21. Q: DO ALL LABORATORIES USE THE SAME UNITS FOR PLASMA RENIN TEST RESULTS?

A: Most laboratories in the United States use the same units for renin test results, which are expressed as the rate of angiotensin generation units (ng Ang I/ml/h). Renin is measured by an enzyme kinetic assay. It provides the level of sensitivity necessary to measure the incredibly small amounts of renin present in blood. Renin is not the active hormone of the renin–angiotensin system. Angiotensin is the active hormone. Renin is an enzyme that circulates in the blood and extracellular fluids, where it continuously cleaves angiotensin I from a large circulating protein called angiotensinogen. The plasma renin test mimics the production of angiotensin in the blood by measuring in a test tube at 37°C the hourly rate at which angiotensin I is formed. The advantage of this approach is that the reaction can be carried out in the test tube for as long as it takes to produce enough angiotensin to be measured accurately.

Primarily in Europe, there are laboratories that measure plasma renin levels directly in the blood. They usually report values as a concentration, such as units per milliliter. These insensitive direct assays are called IRMA (for immunoradiometric assay). We do not recommend this approach as it is not sensitive enough to either identify or discriminate among low renin patients and to clearly sep-
arate these values from those in the normal range. Certain and consistent discrimination of the low renin patient (ie, one with a PRA level <0.65 ng/mL/h) is essential for the performance of all of the Protocols that we use. Only this approach can always separate the renin R from nonrenin V forms of hypertension.

22. Q: ARE ALL RENIN TEST RESULTS COMPARABLE AS LONG AS THEY USE AN ENZYME KINETIC ASSAY?

A: In general terms the results are comparable. However, some laboratories are more accurate than others, especially in probing the low range. To understand why some laboratories are more accurate requires knowledge of how the renin assay is carried out. The plasma renin test measures the hourly rate at which angiotensin I is formed by the plasma renin in a test tube at 37°C. This is called the angiotensin generation step. That is followed by quantification of the angiotensin I generated by radioimmunoassay. In calculating the rate of angiotensin formation some laboratories measure the plasma angiotensin level twice: before the angiotensin generation step and after a 1-, 2-, or 3-h angiotensin generation step. The pre- and postincubation levels of “angiotensin” detected are almost identical in patients with low PRA levels. Unfortunately, these very low numbers are often not real. They are to a large extent the result of assay artifacts. In fact, sometimes there is less angiotensin after the generation step than in the preincubation tube, because the cause of the artifact disappears during the angiotensin generation step. This results in a negative number, which is usually reported as zero (see Lesson XIX).

The best laboratories routinely generate angiotensin for 3 h, and then on the next day they carry out an 18-h generation step for those plasmas that they find have low PRA levels (<0.65 ng/mL/h). This longer Ang I generation time for low renin samples makes it possible to ignore the preincubation blank value because the amounts of angiotensin I (thousands of copies of Ang I) generated during 18 h of incubation become so great as to make the preincubation tube, because the cause of the artifact disappears during the angiotensin generation step. This results in a negative number, which is usually reported as zero (see Lesson XIX).

The level of 6.5 ng/mL/h was chosen as a cutoff point because it is higher than the lowest PRA level at which a renin factor participates in BP control. A 10-fold increase in PRA is likely to overcome the effects of most antirenin system drugs because they are only partial blockers and can rarely counteract more than 90% of renin system activity.

A patient treated unsuccessfully with an antirenin drug who has a PRA level above 6.5 ng/mL/h is likely to benefit from a second antirenin drug. Such a high plasma renin level in a treated patient often means that the drug has induced a large increase in circulating renin and has overcome the drug’s effectiveness. In such a patient a second antirenin system drug may be needed for complete the blockade.

In contrast, a treatment PRA level below 6.5 ng/mL/h on an antirenin drug means that the patient may still have a sodium volume component to the hypertension that needs to be blocked. In such a patient the addition of an antivolume drug is less likely to induce such a large reactive increase in circulating renin that could overwhelm the effects of the antirenin system drug that the patient is already taking.

The 6.5 ng/mL/h level is also the cutoff for determining in which patient unsuccessfully treated with an antivolume drug, this drug should be stopped before adding an antirenin system drug. At a PRA level above 6.5 ng/mL/h the antivolume drug should be stopped because the patient is unlikely to have a volume component sustaining the hypertension. At treatment PRA level below 6.5 ng/mL/h, combined therapy with antirenin and antivolume drugs is likely to be effective because the patient needs antisyndrome volume therapy (the increase in PRA levels is insufficient to overwhelm the antirenin system therapy).

23. Q: WHAT WAS THE BASIS FOR CHOOSING 0.65 ng/mL/h FOR DETERMINING DIFFERENT TYPES OF TREATMENT FOR THE UNTREATED HYPERTENSIVE PATIENT?

A: A level of 0.65 ng/mL/h is used to determine which untreated patient should be started on an antivolume drug and which should be started on an antirenin system drug. A PRA level <0.65 ng/mL/h has little effect on BP. The value of 0.65 ng/mL/h is also the lowest level of renin usually found in young normal subjects on a normal sodium intake.

24. Q: WHAT IS THE BASIS FOR USING 6.5 ng/mL/h AS A SECOND DISCRIMINATING PRA LEVEL FOR CHOOSING FURTHER DRUGS FOR THE UNSUCCESSFULLY TREATED PATIENT?

A: The level of 6.5 ng/mL/h was chosen as a cutoff point because it is higher than the lowest PRA level at which a renin factor participates in BP control. A 10-fold increase in PRA is likely to overcome the effect of most antirenin system drugs because they are only partial blockers and cannot rarely counteract more than 90% of renin system activity.
(1) The patient with treatment PRA <0.65 ng/mL/h taking one or more antirenin drugs. That patient is taking the wrong type of drug. **Switch to an antivolume drug.**

(2) The patient with treatment PRA >6.5 ng/mL/h taking one or more antivolume drugs. That patient is taking the wrong type of drug. **Switch to an antirenin drug.**

(3) The patient with treatment PRA >6.5 ng/mL/h taking one antirenin drug. That patient is taking the correct type of drug but the renin system may have overreacted and is overcoming the effect of the drug. **Add a second antirenin drug. Work-up the patient for renovascular hypertension.**

(4) The patient with treatment PRA >6.5 ng/mL/h taking both V and R drugs. In a patient with a high renin level and no sodium volume factor contributing to the high BP, an antivolume drug can counteract the effect of the antirenin drug by inducing an excessive increase in renin secretion that could overwhelm the effect of the antirenin drug. **First stop the antivolume drug. Then, if BP is still not satisfactorily corrected, add a second antirenin drug. Work-up the patient for renovascular hypertension.**

26. **Q:** WHAT IS THE RELEVANCE AND ROLE OF THE NEW ANGIOTENSIN RECEPTOR BLOCKERS FOR TREATING HYPERTENSION AND RELATED CARDIOVASCULAR DISEASES?

**A:** The angiotensin receptor blocking drugs are conceptually a most exciting new class of drugs because, so far as we know, the only thing these drugs do is block your own circulating angiotensin II from binding to its specific receptors lining the walls of blood vessels. Accordingly, this is the most specific antirenin system drug class yet developed. Thus, as my friend Harry Gavras likes to say, anyone who has doubted the roles of circulating angiotensin II for causing high BP and for triggering a series of downstream events leading to vascular injury, fatal heart attack, heart failure, kidney failures or stroke will now find it extremely difficult to deny this key relationship. Actually, for many of us working in the field we didn’t need this, β-blockers and CEIs had proven the point to us.

Practically speaking, this is a spectacular new class of drugs. They seem to do just about everything that CEIs do so that a growing number of head-to-head trials are bearing out an extremely similar effectiveness for BP control per se, for improving CHF, and in renal disease, for improving proteinuria, for openers.

Moreover, these agents do not cause any cough and they seem to have no known toxicity or even unpleasant side effects so that exploration of higher doses will be possible. The only caution I see now is that they can produce huge increases in plasma renin levels when they lower BP. I’m not sure about the long-term effects of this, but I see no red flags.

To sum up, in addition to their conceptual value for pinpointing the key causal roles of circulating angiotensin II, these drugs already have captured a big and partially unique place in cardiovascular therapeutics.