Lewis K. Dahl Memorial Lecture

The Renin System and Four Lines of Hypertension Research
Nephron Heterogeneity, the Calcium Connection, the Prorenin Vasodilator Limb, and Plasma Renin and Heart Attack

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Introduction to the Lewis K. Dahl Memorial Lecture

I am most pleased to have been chosen to give this Lewis K. Dahl Memorial Lecture. I knew, admired, and respected Lew throughout my career. He was a thoughtful and gracious man whose contributions to hypertension research are of longstanding value. In particular, his definition of the role of salt in experimental hypertension and his creation of genetically salt-sensitive and salt-resistant rat strains are monumental achievements. His work nicely complements our parallel and subsequent research, derived largely from human studies that have defined the major endocrine control of sodium metabolism and arteriolar vasoconstriction, which I propose to summarize for you herein.

As the major regulator of arterial blood pressure and sodium balance, the renin axis supports normotension or hypertension via angiotensin-mediated vasoconstriction and angiotensin plus aldosterone-induced renal sodium retention. In this endocrine servo control, renal renin is released by hypotension or salt depletion; conversely, with hypertension or volume excess, plasma renin activity falls to zero. Accordingly, any renal renin secretion is abnormal in the face of arterial hypertension. Human hypertensive disorders comprise a spectrum of abnormal vasoconstriction-volume products (renin-sodium profiles). Excess plasma renin activity for the sodium balance is created by nephron heterogeneity in which a subpopulation of ischemic nephrons hypersecretes renin and retains sodium. This excess renin impairs adaptive natriuresis of neighboring normal nephrons. Research defining the pivotal role of vascular cytosolic calcium for transducing sodium or renin-mediated vasoconstriction explains the selective value of calcium antagonists for correcting the sodium-volume-mediated, and \( \beta \)-blockers or angiotensin converting enzyme inhibitors for correcting renin-mediated, arteriolar vasoconstriction. The renin precursor prorenin appears to be physiologically active, causing selective vasodilatation that offsets renin-mediated vasoconstriction. Overactivity of prorenin may be involved in the hyperperfusion vascular injuries of diabetes mellitus and toxemias. Prorenin underactivity may facilitate renin-mediated ischemic vascular injury. In essential hypertension, undue plasma renin activity is powerfully and independently associated with heart attack risk. Conversely, patients with low renin activity are protected from heart attack despite higher blood pressures and greater age. Also, renin or angiotensin administration consistently causes vascular injury in the heart, brain, and kidneys of animals. These data suggest new potentials for the prevention of cardiovascular sequelae (heart attack and stroke) by using explicit strategies to curtail plasma renin activity. (Hypertension 1992;20:267-279)

KEY WORDS • renin • angiotensins • hypertension, essential • aldosterone • myocardial infarction
Nephron Heterogeneity as a Factor in Essential Hypertension

By this time it is generally accepted that a high plasma renin value, when properly assayed and indexed against the current state of salt balance, indicates a renin-mediated hypertension likely to respond favorably to antirenin treatment. Conversely, a low renin value often points to a sodium-mediated disorder most likely responding to natriuretic treatments. However, for many clinicians, confusion and skepticism confound diagnostic and treatment strategies when the patient with essential hypertension shows plasma renin values equal to those found in normotensive individuals. Yet, that there is indeed a renin factor operating in such situations would appear to be indicated by the fact that many such patients experience a partial or complete correction of blood pressure on treatment with an ACE inhibitor. Two questions arise: 1) how can it be reasonably concluded that a patient has renin-mediated disease when his plasma renin value is "normal"? and 2) what does this say about the reliability of the renin-sodium profile?

An important step toward answering such questions can be made with the realization that a normal plasma renin value in any hypertensive person is inappropriate (indeed, abnormal in the context of the patient's hypertensive disease) and reflects a dysfunction of the renin system. In truly normal, healthy human subjects or animal models almost anything that will raise blood pressure will reduce renin secretion, most often to zero. Accordingly, because the word "normal" in this context of servo control is misleading, we have come to use the word "medium" instead.

We offer a hypothesis that may illuminate the physiological processes behind this phenomenon: that heterogeneously functioning nephrons coexist in a major portion of patients with essential hypertension, particularly those with medium-range plasma renin values. The renin output of each kidney is but the net sum of about two million nephrons, each individually contributing its share according to its capacity. In this context we have proposed that the kidneys of a major fraction of patients with essential hypertension harbor two functionally abnormal nephron populations: a minor subgroup of hypofiltrating nephrons with impaired sodium excretion, chronically hypersecreting renin, and a larger subgroup of normal but adapting, hyperfiltering nephrons, appropriately reacting to the elevated blood pressure with chronic renal suppression because of increased glomerular filtration rate (GFR) and distal sodium supply. Such discordant nephron populations, acting at odds with one another, may underlie the appearance of plasma renin "normality" even when sodium retention and response to ACE inhibitors and saline infusions are clearly abnormal.

Pathological evidence supports this hypothesis. Biopsies performed in the 1950s, when thoracolumbar sympathectomy was performed in many patients with hypertension, often mild and uncomplicated, show impressively narrowed afferent arterioles side by side with normal arterioles (Figure 1). The investigators, after studying 1,800 renal biopsy specimens, identified this phenomenon as the hallmark renal vascular lesion of uncomplicated essential hypertension. However, what is not generally appreciated is the surprising finding that this lesion is not diffuse but multifocal; abnormal nephrons are intermingled with a larger population of normal nephrons. The lesions may be compared with the more widespread diffuse changes occurring in typical human Goldblatt-type hypertension, a condition in which all nephrons in the stenotic kidney have diminished blood flow and reduced perfusion pressure. As a result, the juxtaglomerular cells that produce renin become hyperplastic and heavily granulated. These morphological changes are associated with elevated plasma renin activity (PRA) and the characteristic renin-dependent hypertension. The unclipped contralateral kidney has no such changes, and its renin activity is markedly suppressed.

An analogous situation may occur in essential hypertension, but among individual nephrons rather than between two kidneys. In this hypothesis those individual nephrons rendered ischemic by narrowed afferent arterioles secrete large amounts of renin while the intermingled normal nephrons have augmented blood flow and suppressed renin secretion. Such a conclusion is supported by the observation that some juxtaglomerular cells are significantly hyperplastic in the kidneys of patients with essential hypertension, particularly when significant arteriolar thickening is present. The same study found that only 8% of glomeruli were obsolescent...
in patients with essential hypertension, an amount insufficient to explain their morbidity in terms of nephron loss and overt renal insufficiency.13

The concept of a dysfunctional subpopulation of ischemic nephrons in patients with essential hypertension is further supported by the way they differ from normal subjects in their response to external stimuli. When sodium intake, a major stimulus for changes in renin secretion, is reduced the normal subject experiences a 250% rise in plasma renin, and when dietary salt is increased plasma renin levels drop by 50%. However, patients with essential hypertension cannot suppress their plasma renin to the same extent under conditions of high salt intake nor, except for those in the high-renin subgroup, can they increase it as briskly.11 The abnormal renin/sodium-volume secretory response is blunted. In contrast, blood pressure nonresponders to thiazide show brisk changes in plasma renin and aldosterone secretion, much as do the high-renin hypertensive patients and normotensive subjects. Parallel phenomena are seen when normotensive subjects and hypertensive patients are compared in their renin secretion decrements to saline infusion.13 Normal subjects show a far greater, and appropriate, suppression of PRA per millimole salt excreted per liter than do patients with low-renin or medium-renin levels or renovascular disease.

Thus, patients with essential hypertension differ from normotensive subjects in their responses to stimuli affecting renin release and sodium conservation. Were their responses normal and appropriate, there might be no hypertension. A normal PRA level, in our theory, is but a sum expression of overreacting and underreacting nephrons. However, the concept that a normal PRA level is abnormal in hypertension is confirmed by the corrective depressor response to antirenin agents.

It is thus probable that in the presence of hypertension, a normal but inappropriate circulating renin level impairs sodium excretion in ischemic and hyperfiltering nephrons alike. In the ischemic nephron GFR is reduced because of underperfusion, and the nephron's attempt to overcome this by increasing the plasma renin level to induce more efferent constriction is overpowered by the compensating effects of healthy, adapting nephrons, which have turned off their renin secretion. At the same time these hyperfiltering, adapting nephrons acquire an increased proximal sodium reabsorption because they, too, are exposed to an inappropriate amount of angiotensin II created by the ischemic nephrons. Thus, the healthy nephrons are overreabsorbing sodium while the ischemic nephrons continue to hypo-filter because their plasma renin compensatory response is diluted by the response of the normal nephrons, which have adapted appropriately to the high arterial pressure.

Unsuppressed and inappropriate renin secretion from ischemic nephrons impairs renal function in ischemic and hyperfiltering nephrons alike. To maintain GFR and an adequate excretion of sodium, ischemic nephrons need a higher rate of renin secretion than they receive (at low perfusion pressures angiotensin II–induced efferent arteriolar constriction is needed to maintain GFR). At the same time, the compensating hypernatriuretic nephrons become unable to excrete dietary sodium fully because they are exposed to an unwanted, inappropriately high angiotensin II level coming from the ischemic nephrons, the direct effect of which is to promote proximal sodium reabsorption by acting on the proximal tubules and by inducing afferent vasoconstriction. In sum, all nephrons are exposed to angiotensin levels inappropriate to their needs; the nephrons are unable to excrete sodium properly and the hypertension is perpetuated.

Since any circulating renin is inappropriate in the face of hypertension, this helps explain why ACE inhibitors reduce blood pressure even when renin levels appear normal. It suggests that in both high- and medium-renin patients, the physician must consider the possibility of a renin factor and be prepared to test for and treat it.

The Abnormal Renin/Sodium–Volume Products of Hypertension

We have developed, and usefully employed, an analytic and diagnostic format that seeks to identify the pathogenesis of a hypertensive situation in terms of the...
reciprocity of two forms of long-term vasoconstriction, one mediated by renin release and the other by sodium retention. The powerful vasoconstrictive force of renin's active agent, angiotensin II, is well recognized, but it must be remembered that angiotensin additionally musters the pressor effects of sodium by its stimulation of aldosterone biosynthesis as well as its direct sodium-reabsorbing effect on renal proximal tubules.

While the hydraulic action of the fluid accumulation attending sodium retention, either subsequent to angiotensin's actions or to diet, makes a substantial contribution to blood pressure, such a sodium–volume excess also appears to mediate a direct vasoconstrictive action of its own, one probably equally important even though its mechanism has eluded definition. In tracking the biochemistry of vasoconstrictive processes, evoked by either angiotensin or sodium, one becomes increasingly aware that calcium plays a role on both sides of the vasoconstriction equation, suggesting a unity in nature's master plan. The pursuit of calcium's physiological roles, directed by Lawrence Resnick, is essential to understanding hypertension, and it accounts for an important element of our research effort.

The Calcium Connection

Calcium is involved in renin-mediated events. Available evidence suggests that all factors affecting renin release do so by changing the intracellular concentration of calcium or cyclic adenosine monophosphate, perhaps in coordination with adenine and prostaglandins. Cytosolic calcium change is further involved in the early stages of angiotensin's stimulation of aldosterone biosynthesis (cholesterol to pregnenolone) as well as in the vasoconstrictor action of angiotensin II on vascular smooth muscle.

As for sodium-mediated events, a number of findings suggest that the still poorly understood pressor action of dietary salt may be mediated by its ability to alter calcium metabolism. Three lines of evidence, together with the growing impression that patients with low-renin hypertension appear to display a relative or absolute calcium deficiency and are most likely to be those with sodium-mediated hypertension, support this concept.

1. Calcium feeding can correct the low-renin form of hypertension but is usually of no value or may even be pressor in high-renin patients. These effects have also been observed in prototype experimental models.

2. The pressor effect of sodium feeding seen in salt-sensitive patients is accompanied by calcitropic hormonal responses to a perceived calcium deficit and can be blocked by calcium administration.

3. The calcium channel antagonists nifedipine and verapamil are most depressor in patients with low-renin and lower serum-ionized calcium levels and least depressor in high-renin patients with higher calcium values.

We have recently undertaken further study of this possible sodium–calcium interaction as a mechanism involved in low-renin vasoconstriction. In metabolic balance ward studies patients were ingesting the high salt diet (which lowered renin values) as when they were on the low salt diet, probably even more so. These findings thus describe the first antihypertensive drug species in which sodium depletion does not add to effectiveness and may actually retard it. This means that patients receiving these drugs can enjoy the possible advantages of a normal salt intake. Similar results have been obtained by others when using either dietary or diuretic sodium depletion in combination with a calcium antagonist. These results further confirm that calcium channel antagonists are most effective in opposing the abnormal vasoconstriction of the nonrenin, sodium volume–mediated type identifiable in many low-renin patients and, conversely, associated with high sodium intake.

Since among hypertensive patients higher blood pressures are uniformly associated with commensurately higher levels of free intracellular calcium, how do both low-renin, lower calcemic vasoconstrictive and high-renin, higher calcemic vasoconstrictive states activate a similar final common pathway in which cytosolic calcium is increased? The same paradoxical relations between intracellular and extracellular environments obtain with the magnesium level: extracellular magnesium values vary inversely with renin levels. However, inside the cell, free magnesium values are uniformly reduced in hypertensive patients.

The following hypothesis, accommodating several clinical and pharmacological observations, may reconcile this postulated intracellular uniformity with different extracellular environments. The hypothesis begins with the assumption that with vasoconstriction the elevation in diastolic blood pressure is proportionate to the elevation in vascular smooth muscle cytosolic free calcium. In the low-renin, sodium-related form of vasoconstriction, extracellular ionized calcium levels are reduced because of an increased steady-state accumulation of cellular calcium from the extracellular space, i.e., the intracellular abnormality is opposite to that outside the cells. For this lesion we propose a change (Type I defect) in the plasma membrane, which normally maintains a gradient of 10,000:1 between the extracellular and intracellular calcium concentrations. This plasma membrane has become slightly more permeable to calcium or is less capable of extruding it, with more calcium accumulating inside the cells from outside sources. The result is the metabolic pattern observed in the low-renin state, with lower extracellular and higher intracellular calcium concentrations. The hypothesis may be consistent with a number of possible membrane defects in hypertension, many already postulated. Several studies suggest an abnormal influx via voltage-operated channels. Our own research and that of others supports the concept of increased calcium influx in this Type I defect. Indeed, salt loading of rats not only lowers PRA but has also been shown to increase the number of voltage-dependent calcium channels. Furthermore, in dogs the ability of salt loading to lower PRA and to elevate blood pressure both appear to be mediated by cellular calcium accumulation from the extracellular space.

Most recently, nuclear magnetic resonance spectroscopic techniques have been used to directly demonstrate dietary salt–induced elevations in cytosolic free calcium via extracellular calcium uptake.
ings are consistent with our finding that both the ionic and the blood pressure effects of salt loading are exquisitely sensitive to correction by calcium channel-blocking drugs, which reduce calcium entry through voltage-operated channels in the cell membrane. In this correction the low extracellular calcium levels are restored, while intracellular free calcium is commensurately reduced.

As for high-renin vasoconstriction, the same final common pathway, in which intracellular calcium ions are increased, operates. However, in this condition we find that levels of ionized calcium are also increased outside the cell. We call this relation the Type II defect. In this situation the excess intracellular calcium ions are apparently not coming from the outside plasma source but are mobilized from intracellular sites. In this situation, we postulate an abnormal angiotensin II–dependent intracellular partitioning between intracellular stored or bound calcium and cytosolic free calcium. Accordingly, with such a change in the intracellular partitioning of calcium, one would expect an otherwise normal plasma membrane to pump out the excess free cytosolic calcium, resulting in the observed increases in extracellular calcium levels. A primary increase in mobilized intracellular calcium becomes the cause of observed higher serum-ionized calcium.

The following chain of events may occur. Increased plasma angiotensin II engages specific angiotensin receptor–operated channels in the cell membrane of vascular smooth muscle. This engagement then, via the IP3 pathway,57 triggers the intracellular mobilization of calcium stores from the sarcoplasmic reticulum, thereby producing more vasoconstriction. In the process, a number of other downstream molecular abnormalities, including changes in mitochondrial function and abnormal calcium–protein partitioning in the sarcoplasmic reticulum, might possibly be involved.

Whatever the final intracellular pathways, patients with renin-mediated vasoconstriction, as would be predicted, are less sensitive to the depressor effects of calcium channel blockade because the increased intracellular calcium level is not primarily dependent on influx from the outside. Second, the pressor effect of salt feeding and the depressor effect of salt depletion are not observed in the high-renin state, presumably because these maneuvers operate by modifying calcium influx from outside sources. Furthermore, the preexisting increase in intracellular calcium could operate to gate its own calcium channels. Finally, as also would be required by this model, this vasoconstrictor mechanism is supremely sensitive to deletion of angiotensin II by an ACE inhibitor.

Calcium may also be involved in neurally mediated vasopressor phenomena because calcium is required for stimulus–secretion coupling of neurotransmitter release. However, the contribution of such phenomena in neural tissue to long-term hypertension is moot, and the pathways linking neural activity to sodium and calcium transport are poorly understood. Nevertheless, there is evidence at the experimental level that calcium channel antagonists may have a spillover antagonist effect on nearby postsynaptic α-adrenergic receptors. Thus, the effectiveness of calcium blockers, α-blockers, and diuretics in low-renin hypertensive patients suggests a functional link between sodium, calcium, and α-adrenergic receptor activity.

The more we untangle the web of calcium's participation in hypertensive phenomena, the closer we refine our marksmanship in the rational, targeted management of hypertension. Indeed, as we will discuss, since it is clear that angiotensin II via its vascular receptor acts powerfully to mobilize cytosolic calcium, overactivity of this endocrine servo control may be a key factor in causing or amplifying vascular disease in the heart, brain, and kidneys of hypertensive patients.

The Greater Renin System: Its Prorenin-Directed Vasodilator Limb?

Until now the renin system has been associated, in either its physiological or pathological manifestations, principally with vasoconstriction. Our attention was first captured by the formidable vasoconstrictive effect of angiotensin II even though its additional sodium-retaining effect from eliciting aldosterone was recognized as an important contribution to the defense of blood pressure. However, the sodium contribution to blood pressure, whatever its source, was considered primarily to be a hydraulic, volumetric function of sodium's role in retaining fluid. The more recent recognition of the sodium–calcium interaction described above, coupled with our understanding of calcium's intracellular role in smooth muscle constriction, supported the realization that two forms of vasoconstriction, renin-mediated and sodium-mediated, are operative in hypertension. In the larger picture, these two forms of vasoconstriction are reciprocal elements in the servo control of normotension. To the extent that the stimulated renin system could muster sodium retention to a common goal, they were also mutually supportive. However, as we shall see, when the servo control becomes deranged and sustains an excess of one relative (notably renin) to sodium, a situation develops that can cause or amplify ischemic vascular disease.

A Prorenin Vasodilator Pathway

New evidence suggests that the renin system is even more comprehensive and versatile in its normal dominion over blood pressure than we thought. The startling possibility appears that the renin system, when seen in an entirety that includes its precursor forms, now appears capable of selective vasodilation. If so, a redefinition of the renin system and its domain may be in order. This pioneering research odyssey has been led by Dr. Jean Sealey, who discovered prorenin as a cryoactivatable reservoir of renin that became active when samples were stored at 0–4°C.

The precursors of active renin prorenin is a protein that for its conversion to renin, requires that a prosegment be enzymatically cleaved. This occurs in the juxtaglomerular cells, from which active renin, along with prorenin, is released. In the blood, prorenin remains inactive, a statement convincingly supported by the total absence of renin activity in nephrectomized patients. However, prorenin can be activated in vitro in several ways, a characteristic that has confounded many a clinical assay of plasma renin. Proteolysis with trypsin or other proteases can result in cleavage of the prosegment and the irreversible formation of active renin. Of more curious interest and significance, how-
ever, is the finding that prorenin can be reversibly activated in vitro when acidified to pH 3.3, only to be deactivated when incubated at neutral pH and 37°C. We have also found that when purified human prorenin is chilled to 0°C it develops reninlike activity that disappears when the sample is warmed to 37°C. Indeed, during such activation at 0°C prorenin is capable of binding to a renin inhibitor, behaving just like renin. It has been suggested that acidification or freezing causes the prorenin molecule to physically unfold its prosegment and thus expose its active site, while refolding and shielding of the active site takes place upon neutralization or warming (Figure 2).

With these observations in mind, we turn to the frequently controversial topic of tissue renin systems. The concept for such systems might be supported by the observation that although circulating renin disappears after nephrectomy, circulating prorenin does not. Where does prorenin come from and what is its physiological function, if any?

One source that can be offered as a model of tissue renin systems is the human ovary, which secretes large amounts of prorenin into the circulation for about 3 days during the luteinizing hormone surge at the middle of the menstrual cycle. The process, apparently via the ovarian follicle, doubles the concentration of plasma prorenin. There appears to be no renin secretion from the ovary, and there is no increase in plasma renin during the surge of ovarian prorenin secretion, suggesting that the ovarian prorenin system functions independently of plasma renin.

Indeed, human and animal studies reveal an independent and completely functional renin-angiotensin system in the ovary, with the concentration of prorenin being two orders of magnitude higher than the plasma levels. Angiotensin is present in follicular fluid at the same or higher concentrations as in plasma. Angiotensin messenger RNA can be found in the rat ovary, and ACE is present in ovarian tissue and oolemma of rabbit oocytes. Angiotensinogen is present in ovarian follicular fluid, and angiotensin II receptors have been demonstrated in the ovary, changing with physiological stimuli. Since prorenin is the primary product of renin gene expression in the ovary, local ovarian angiotensin, which we know as a product of active renin, must be a product of prorenin.

But how can prorenin behave like active renin without having its prosegment cleaved? Taking our cue from what we know about the reversible activation of prorenin in vitro, we propose that a similar reversible mechanism may prevail in the ovary. In some way, the biochemical environment of the ovary makes possible, when a particular effect is needed, the unfolding of the prorenin prosegment so that the active site, uncovered, can initiate a local reninlike cascade to produce angiotensin II, which binds to its receptor for a local effect. The reversibility of this prorenin activation, the subsequent refolding and shielding of the prorenin active site, ensures that the effect will be parochial. If the prosegment had been cleaved and active renin formed from the extraordinarily high levels of prorenin present in the ovary, it would be virtually impossible for the effect not to escape the ovary and produce unwanted systemic cardiovascular effects—and this does not happen.

What is the local effect? It has been tempting to impute a local reproductive function for this insular renin system, and the temptation was stimulated by the finding that blockage of ovarian angiotensin with saralasin appeared to reduce the number of eggs in the fallopian tubes of rats after ovarian hyperstimulation. Is prorenin a sex hormone? For a time the temptation became compelling with the finding that other reproductive organs such as the placenta and uterus have high concentrations of prorenin together with other components of the renin-angiotensin system. Lower levels of prorenin secretion have also been measured from the human testis.

However, prorenin production has been identified in other than reproductive organs such as the human adrenal and pituitary glands. The presence of large amounts of prorenin in all the organs mentioned (and some others under study) suggests that prorenin, rather than active renin, may be the mediator of local tissue renin-angiotensin systems. Prorenin is processed to active renin only in the juxtaglomerular cells of the kidney. However, prorenin itself is also found in abundance in human kidneys, and the kidneys secrete 10 times more prorenin than renin into the circulation; the possibility...
of a local tissue renin system functioning here, too, cannot be excluded. But for what purpose? And can such a purpose fulfill a common physiological need in all these tissues that express the renin gene?

Recent experiments in our laboratories59,81 suggest a possible answer, one that has the attraction of making teleological sense. Infusion of recombinant prorenin into animals, to our great excitement, produced a vasodilator effect. This suggests to us that prorenin in certain vital tissues may normally play a locally protective vasodilator role opposing the broad and relatively unselective vasoconstrictive role played by the renin system as we know it, thus ensuring adequate blood flow within these tissues. Tissue renin systems—or, as they might more properly be called, tissue prorenin systems—may soon be considered a newly revealed, autoregulatory limb of the renin system. In much the same way that the alpha and beta limbs of the sympathetic nervous system regulate blood pressure and regional blood flow over the short term, renin and prorenin may perform similar relative roles over the long term.

If the mounting pace of research into tissue renin systems proves the above thesis real, the implications reach deeply, broadening the pathophysiological terrain and suggesting new therapeutic and prophylactic approaches in the management of hypertension and its sequelae and in prevention of the devastating vascular consequences of diabetes mellitus.85

Recently it was reported84 that increased plasma prorenin in insulin-dependent diabetes mellitus predicts the development of microvascular disease. Hyperperfusion injury is the presumed basis for much of the vascular damage of insulin-dependent diabetes mellitus.85 Our recent work suggests that prorenin may actually cause the vascular damage in patients with diabetes mellitus by inducing localized vasodilation in kidneys, eyes, and other organs and exposing these tissues to abnormally high perfusion pressure. Indeed, the concentration of prorenin is so high in these organs that it has the potential of catalyzing the production of many times more angiotensin II than can circulating renin, invoking actions of angiotensin II previously considered to be pharmacological, such as vasodilation and tachyphylaxis to the vasoconstrictor effect of lower concentrations.

There is considerable indirect evidence suggesting such prorenin-mediated localized vasodilation. Besides the vasodilator effect in primate studies cited above, after ureteral obstruction in dogs the highest prorenin levels are associated with the highest renal blood flows.86 In animals and in humans, organs with high rates of blood flow—kidney, eye, ovary, pregnant uterus, and placenta—all produce high concentrations of prorenin.67,87-89 During pregnancy the 10-fold rise in blood prorenin coincides with the increase in GFR and renal blood flow (RBF), the initial fall in blood pressure, and the appearance of insensitivity to infused angiotensin II.88,89 all of which could be the result of prorenin-mediated vasodilation. Increased plasma prorenin is also associated with the increases in GFR and RBF that occur in teenagers with diabetes mellitus before they develop gross nephropathy.91

The physiological evidence cited above is consistent with a vasodilator effect of prorenin in the renal afferent arteriole. This is compatible with immunohistochemical data. Prorenin was detected in increased amounts in the afferent arteriole after we infused the enzyme into monkeys (W.C. Campbell, T. Lenz, and J.E. Sealey, unpublished results) at the very site where angiotensin II levels are so high they can be detected by immunohistochemistry.86 Extraordinarily high levels of angiotensin II have also been detected in microdissected samples from Bowman's capsule.92 Thus the level of angiotensin II at the glomerular afferent arteriole may be so high as to cause vasodilation.

Increased Prorenin Levels and Hyperperfusion

Vascular Injury in Diabetes and in Toxemia of Pregnancy

Diabetes mellitus and pregnancy have certain similar hormonal and hemodynamic features: 10 times the normal level of prorenin, high RBF, high GFR, and the appearance of proteinuria when the blood pressure increases. Our current concept is that increased levels of prorenin in these conditions dilate the afferent arterioles, leading to glomerular hyperperfusion, which is not detrimental in pregnancy when blood pressure is low but is destructive when blood pressure is normal or high, as in preeclampsia or diabetes mellitus.

This effect of prorenin may explain, in part, the beneficial effect of ACE inhibitors in insulin-dependent diabetes mellitus.84 These agents may not only lower blood pressure and reduce the renal efferent arteriolar constriction imposed by circulating renin, but by blocking a localized prorenin action, they may also increase afferent arteriolar constriction, thus protecting the glomerulus from the full force of the arterial pressure. In this context, the hypotensive action of these drugs would reflect the sum of their downstream blockades of both renin-mediated vasoconstriction and prorenin-mediated vasodilator activities.

Thus, localized prorenin activity, driving a vasodilator limb of the renin system, may protect vital organs from the ischemic effects of circulating renin. In states with normal arterial pressure (i.e., pregnancy and congestive heart failure) this targeted activity is beneficial. In patients with higher arterial pressure (i.e., pregnant women with preeclampsia) this effect is destructive, leading rapidly to hyperperfusion injury. In diabetic patients with normal blood pressure a pathological hyperproreninemic response leads to retinal injury as well as to progressive glomerular damage proceeding to renal failure. Conversely, the lower plasma prorenin level of patients with essential hypertension is consistent with their characteristic afferent arteriolar constriction and low incidence of progressive renal failure.

Renin as a Risk Factor for Heart Attack and Stroke: New Evidence and Review

Considering the evidence that excessive or inappropriate renin activity is vasculotoxic, there are good reasons for protective mechanisms against renin-mediated vasoconstriction, particularly when it is inappropriately invoked. The first such evidence appeared as long ago as 1972, when we presented evidence that the baseline PRA could be predictive of vulnerability to heart attack or stroke. Our 5-year study of 219 patients with moderate-to-severe hypertension showed that those with a normal or high PRA had an 11% or 14% frequency, respectively, of heart attack or strokes.85
The findings of that study were compellingly confirmed and extended by a recently reported prospective trial involving 1,717 patients with mild-to-moderate hypertension followed-up for 8.3 years. The new study found that the pretreatment renin profile, accomplished in all subjects, was independently associated with the risk of myocardial infarction (but not mortality from all causes). Using our methodology, patients fell into three subgroups, suffering poorer tissue perfusion, particularly in vascular beds, are likely to be more susceptible to ischemic vascular damage in target beds such as the coronary and cerebral circulations.

Other Evidence Relating Plasma Renin-Angiotensin Levels to Cardiovascular Damage

There is a long and convincing history of experimental and clinical evidence that excessive or inappropriate PRA may be vasculotoxic. In 1939 Winternitz et al showed that injections of renin produced severe vascular damage in nephrectomized dogs whose sodium balance could be expected to be maximally positive. Since that time a large experimental and clinical literature has accumulated that relates PRA to vascular injury (Table 1). The human evidence begins with studies showing that malignant hypertension is caused by an abnormal renal–adrenal interaction causing excess renin and aldosterone secretion. This condition is associated with diffuse vascular damage and fibrinoid change. Significantly, the entire syndrome can be reversed by specific antirenin therapy, which corrects the hypertension and hyperaldosteronism and leads to healing of the vascular damage.
Recent experimental evidence supports the thesis. In the stroke-prone spontaneously hypertensive rat (SHRSP) we found that strokes were closely associated with very high prestroke plasma renin levels and that normal or low values were closely associated with the absence of a stroke. Moreover, feeding potassium supplements to SHRSP causes marked suppression of plasma renin levels, and this is associated with marked protection from stroke even though blood pressure is often unchanged. Blocking renin activity with ACE inhibitors also produced marked protection from stroke in rats whose blood pressures were not reduced.

The case for renin’s culpability is also supported by numerous clinical studies showing that total nephrectomy can reverse the malignant hypertensive syndrome, normalize the blood pressure, and lead to healing of the vascular disease as shown by biopsy. Patients with curable renovascular hypertension due to renin excess are also more prone to malignant vasculitis with vascular damage in the brain and heart. Moreover, there is an increasing awareness that high-renin essential hypertension, too, seems associated with more vascular sequelae, a stormier course, and a shorter survival.

Many other clinical situations associated with high plasma renin levels are accompanied by striking vascular damage, stroke, or heart attack. These include patients with scleroderma, renal trauma, acute closure of a renal artery graft, or a renin-secreting tumor. After use of the angiotensin II–blocking agent saralasin as a diagnostic test, four patients with renal hypertension and hyperreninemia developed marked rebound hypertension, with encephalopathy in two and coma in one. Finally, in patients with scleroderma, marked vascular damage and early demise is correlated with the amount of plasma renin.

**The Role of Blood Pressure**

How can we account for the proposition that renin-mediated hypertension engages greater risk of heart attack than does sodium-mediated hypertension despite equal degrees of elevated blood pressure? Skepticism flows from the long-held conviction, logical enough on the surface, that the dangers of hypertension stem mainly from the hydraulic force of expanded fluid volume rupturing blood vessels.

It is true that elevated blood pressure, if great enough, might damage any vascular structure; experimentally induced increases in blood pressure can disrupt a blood vessel. Human and animal studies have indicated that the malignant phase of hypertension occurs or can be induced when the blood pressure surpasses a critically high level. In this situation arteriolar necrosis develops, especially in those beds exposed to the high pressure, whereas the vasculature beyond the induced constriction is protected. It also appears that beyond a critically high pressure level, “breakthrough” of autoregulation occurs so that the resistance vessels are no longer able to constrict in response to the elevated blood pressure. Instead they give way, transmitting the high pressure load to the more distal and fragile vasculature, where a blowout occurs.

However, all this does not necessarily mean that high blood pressure is the critical or only factor in causing vascular damage. Moreover, it may not be appropriate to extrapolate to long-term situations in human subjects what has been observed mostly in short-term animal studies. It is well known that chronic high blood pressure produces adaptive change in the vascular wall—specifically, hypertrophy—which reduces the lumen-to-wall ratio and may substantially raise the breakthrough point for autoregulation. That this occurs has been suggested by research in hypertensive subjects and experimental models.

Further, many of the acute studies in animal models that have been used to support the pressure hypothesis have employed vasoconstrictor substances, usually renin-angiotensin or adrenergic agents, to induce the high pressure. This type of study must also be considered to show that the administration of vasoconstrictors can induce vascular damage correlated to the degree of hypertension. Rarely do the investigators ask whether a similar degree of hypertension induced by volume expansion would produce commensurate vascular injury.

There is another, perhaps even more important, criticism of the pressure hypothesis. Many hypertensive...
patients and animal models exhibit and tolerate extremely high blood pressure levels without vascular damage. Conversely, marked vascular damage can occur in a variety of clinical and experimental situations at blood pressure levels well below what is thought to be critical. These compelling observations suggest that factors in addition to an elevated blood pressure may be necessary to induce vascular damage.

Actually, a number of experiments suggest that vascular damage in hypertensive or normotensive situations may be more closely related to the induction of hypovolemia, with compromised blood flow and consequent ischemia of the tissues. This impression is supported by observations in animals and humans that indicate that malignant hypertension due to renin excess actually can be remitted by saline infusions. These infusions, even though they may raise blood pressure, improve blood flow and relieve hypovolemia and ischemia. Recent studies have defined two animal models in which sustained hypertension is induced or maintained by sodium depletion and corrected by saline administration. This broadens the evidence that sodium depletion and consequent reduced blood flow can be critical factors for inducing vascular stenosis and hypertension.

Despite the association of high plasma renin levels with many hypertensive situations in the clinic and laboratory, most advocates of the pressure hypothesis refute a role for renin in vascular damage by citing two situations in which vascular damage occurs with renin activity either blocked or absent. However, both of these situations are ambiguous. For example, the first type of study shows that when the pressor actions of renin are offset by the concurrent administration of a vasodilator drug such as hydralazine, vascular damage does not occur. But this proves nothing because at the same time the arterial pressure is also reduced, restoring adequate blood flow and creating an entirely different situation.

The second circumstance invoked to discredit the role of renin in vascular damage is the deoxycorticosterone acetate (DOCA)-salt hypertension model. In this model vascular damage develops in association with massive sodium retention and a reactivity low plasma renin level. However, it should be recognized that the vascular damage produced by DOCA takes much longer to develop than does that induced by renin. In the final analysis, DOCA-induced damage is probably also associated with ischemia and reduced blood flow in consequence of slow edematous deterioration of the vascular wall. Actually, it has been shown that onset of the malignant syndrome in DOCA-salt-treated rats usually follows paroxysms of natriuresis with resultant hypovolemia, high blood viscosity, lowered blood flow, and tissue ischemia. Furthermore, there is evidence that both the hypertension and the malignant syndrome of DOCA-salt hypertension are in fact sustained by abnormal vascular condition.

Möhring and associates have further defined the key role of renin in the malignant vasculitis of experimental renovascular hypertension and have demonstrated the beneficial effect of sodium administration in inducing remissions, presumably by restoring blood flow and suppressing renin. In this model, like the DOCA model, the malignant phase was preceded by natriuresis with hemoconcentration and by higher renin levels, while blood pressure levels remained unchanged. Accordingly, in both the DOCA-salt- and renin-induced renovascular models the findings suggest that sodium depletion with hypovolemia, reactive vasoconstriction, resultant poor blood flow, and tissue ischemia may be critical in precipitating vascular injury. Altogether, the data also show that severe vascular injury can occur in the absence of renin, as in the DOCA model, but that very likely another vasoconstrictor agent (vasopressin) is critically involved instead.

These experiments and others indicate that renin is not necessary for vascular injury to develop in the presence of hypertension. However, before one can conclude that the cause of vascular injury can be purely elevated blood pressure of any etiology, it must be shown that other vasoconstrictor substances besides renin (i.e., vasopressin or catecholamine hormones) are not involved.

Meanwhile, the available evidence suggests that severe vasoconstriction, with its attendant adverse effects, even in the absence of hypertension, may be a key prerequisite for inducing vascular damage. Such vasoconstriction leads to translocation of fluid from the vascular to the interstitial space, hypovolemia, hemoconcentration, higher blood viscosity, and finally ischemia from reduced tissue blood flow, particularly to the microcirculation. This helps explain the many clinical and experimental situations in which vascular damage occurs at blood pressure levels well below the so-called critical range. It might also explain results from numerous clinical trials in which successful antihypertensive therapy failed to protect from myocardial infarction. In all such studies diuretic therapy was part of the regimen. Such therapy would be expected to lower blood pressure at the price of reducing effective blood volume and flow and inducing reactive renin-induced vasoconstriction. Conversely, protection from myocardial infarction has been demonstrated in those clinical trials using -blockade alone—for example, the large Göteborg trial involving 7,500 subjects. This form of drug therapy can be expected to suppress renin-mediated vasoconstriction.

Today, reliable renin assays are available and, as I have attempted to note here, our appreciation of the scope of the renin system's pathophysiological relevance has grown greatly. More frequent use of the renin assay can generate the large-scale studies needed to further clarify or disprove the cardiovascular hazards we propose for renin and so set the stage for sharper diagnosis and more aware management of essential hypertension. The renin assay helps reveal the mechanisms of an individual's hypertensive state and directs the choice of appropriate treatment. Reduction of blood pressure alone is no longer a major accomplishment; any number of contemporary drugs can do that. The objective is to reduce blood pressure by means that protect from heart attack and stroke and thereby safeguard the quality and duration of life.

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Lewis K. Dahl Memorial Lecture. The renin system and four lines fo hypertension research. Nephron heterogeneity, the calcium connection, the prorenin vasodilator limb, and plasma renin and heart attack.

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