The discovery of angiotensin I converting enzyme inhibitors (ACEI) and of their efficiency in the treatment of high blood pressure and cardiac insufficiency constitutes one of the major advances in medicinal chemistry and therapeutics of the last decade. The design of captopril and its congeners resulted from a rational and systematic study of the interactions of carboxypeptidase A and angiotensin converting enzyme (ACE) with their substrates and inhibitors. Not only were ACEI found to be effective for treating high renin-dependent forms of hypertension, but unexpectedly, they were also active in normal and low renin hypertension. Very productive research on the ways of blocking the renin-angiotensin system has been undertaken by several academic and drug company laboratories with the aim of finding drugs that could be at least as potent but more selective. Indeed, long-term treatment by ACEI seems not to completely suppress the circulating renin-angiotensin system as plasma angiotensin II (Ang II) and aldosterone levels tend to return toward pretreatment values. In addition, ACE is not a specific enzyme in that it can hydrolyze substrates other than angiotensin I (Ang I), such as bradykinin, substance P, and enkephalins. The side effects observed with all ACEI, such as the rare cases of angioneurotic edema and the more frequent occurrence of cough, may be related to this lack of selectivity.

It could be anticipated that potent and specific renin inhibitors would constitute an interesting alternative to ACEI for two reasons: 1) the first step in the renin-angiotensin system, the hydrolysis of angiotensinogen by renin, is rate limiting; and 2) renin has a unique specificity for angiotensinogen as there is no other known substrate for this enzyme. Research on renin inhibitors has been facilitated by the recent progress made on the molecular structures of renin and angiotensinogen and by the elucidation of the molecular mechanisms of action of aspartyl proteases and their inhibitors. Several other factors were apparently promising for the rapid design of a renin inhibit: the discovery of pepstatin, a lead compound inhibiting the class of aspartyl proteases to which renin belongs; the use of simple biochemical assays for testing renin blockade; and the knowledge accumulated on the pathophysiology of the renin-angiotensin system in animals and humans. However, the design of an orally active renin inhibitor proved to be so difficult that, although many ACEI are now available to treat hypertension, no renin inhibitor is available, even though the research on renin inhibition started with antibodies and peptides a long time before the discovery of captopril. The main reasons for the difficulties encountered in their research will be analyzed in this review, which will also insist on the need for well-designed comparisons between ACE inhibition and renin inhibition. The short-term administration of renin inhibitors to primates and, recently, to normotensive and hypertensive men has provided an interesting but still limited comparison between the effects of ACEI and renin inhibitors on hemodynamic and hormonal parameters.

Molecular Structures of Renin and Angiotensinogen

The elucidation of the molecular structures of renin and angiotensinogen has greatly facilitated the design of renin inhibitors by revealing the homology between renin and other aspartyl proteases and the unique amino acid sequence of human angiotensinogen compared with angiotensinogens of other species.

The primary structure of the renin precursor prorenin was deduced from the complete nucleotide sequence of mouse submandibular gland (SMG) renin complementary DNA (cDNA) and human kidney renin cDNA. Biosynthetic experiments in renal tissues showed that human renin was processed from prorenin by removal of a 43 amino acid prosegment, followed by release of a Lys^-Arg^ peptide. Misono and Inagami showed that renin could be irreversibly inhibited by chemical reagents that formed a covalent bond with the amino acids of the active site, thus implying that renin belonged to the aspartyl protease superfamily, a class of proteases that includes pepsin, chymosin, and cathepsin D. Renin cloning confirmed that renin was an aspartyl protease and had, as do the other members of this class of proteases, two critical aspartic acids in the catalytic site followed by the conserved sequence Thr-Gly-Ser(Ala). Like other aspartyl proteases, renin is inhibited by peptides derived from its own prosegment, but the inhibitory effect of these peptides is too small to provide new lead inhibitory compounds at the present time. Renin is unique

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Among aspartyl proteases in its specificity for angiotensinogen and its action at neutral pH.

Three-dimensional x-ray crystallography studies of several aspartyl proteases revealed that these proteins are bilobal with a pronounced cleft between the two lobes where the two aspartyl residues of the catalytic site are located close together, one on each side of the cleft. From these data, Tan et al.13 hypothesized that these proteases evolved by duplication of an ancestral gene coding for a protein of about 100-150 residues with a structure resembling that of one of the pepsin lobes and that their activity was generated by dimerization. Indeed, it has been recently shown that aspartyl retroviral proteases may represent the ancestral enzyme of this family because they contain the conserved aspartyl protease sequence Asp-Thr-Gly and they function as a dimer.14,15 This observation is of considerable importance as pepstatin, the universal aspartyl protease inhibitor, has been shown to inhibit the retroviral aspartyl protease activity.16 It is likely that our knowledge of renin inhibitors will facilitate the design of retroviral acid protease inhibitors.

Computer models of the three-dimensional structure of mouse and human renin17-19 have been based on the crystallographic coordinates of other members of the superfamily and used to formulate hypotheses on the structure of the catalytic site, the interactions of renin subsites with its substrate, and the interactions of renin inhibitors with other aspartyl proteases.20 The recent crystallization of recombinant human renin and the elucidation of its atomic coordinates at 2.5-8.0 Å21 show that most of the assumptions made from molecular modeling were correct and will help in the design of renin inhibitors.

Another important advance was the elucidation of the primary amino acid sequence of human angiotensinogen.22,23 Human angiotensinogen differs from rat or hog angiotensinogen by the presence of a Leu10, Val11 cleavage site instead of a Leu10-Leu11 bond, and also by the nature of the residues that immediately follow on the C-terminal side of the scissile bond. This explains the high specificity of human renin for human angiotensinogen and its low catalytic activity for rat angiotensinogen. It also implies that renin inhibitors should be modeled on human angiotensinogen sequence and tested in primates.

**Molecular Mechanism of Action**

The molecular mechanism of action of renin and of its inhibitors has been deduced in large part from the studies performed by Marciniszyn et al.24 and Rich et al.25 on the mechanism of peptide bond hydrolysis by aspartyl proteases. During the attack by the two aspartic acids of the active site, the planar carbon atom of the peptide bond becomes tetrahydral, forming a transition state. Because the C-N bond is relatively fragile, it can be hydrolyzed by the water molecule buried in the active site. Synthesis of a molecule that mimics the tetrahydral carbon atom, but whose C-N bond is replaced by a virtually uncleavable bond such as a C-C bond (transition state analogue), leads to inhibition of aspartyl proteases (Figure 1). Studies of the action of renin on various synthetic substrates derived from angiotensinogen have also shown that the minimal substrate recognized and cleaved by renin is an octapeptide.

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**Figure 1.** Schematic representation of mechanism of peptide bond hydrolysis by acid proteases and of mode of action of the inhibitor pepstatin. Of the two active-site aspartic acid residues (32 and 215), 215 is protonized and 32 is not. A water molecule is bound to these residues by hydrogen bonding. The CO-NH peptide bond to be cleaved is hydrolyzed after formation of an intermediary, which renders the carbon atom tetrahydral (gray dotted area). Central statine residue of pepstatin (the only one shown here) displaces the water molecule through its hydroxyl group and binds reversibly to two aspartate residues of catalytic site through its stable tetrahydral carbon atom. E indicates enzyme; S, substrate; I, inhibitor. (From Rich et al, in Vida JA, Gordon M (eds): Design and Discovery of Aspartyl Protease Inhibitors, ACS Symposium Series N. 251, Conformationally Directed Drug Design. Washington, DC, American Chemical Society, 1984, pp 221-237).
(His-Tyr\textsuperscript{23}) including the cleavage site.\textsuperscript{26} The amino acids surrounding this cleavage site also interact specifically with different renin subtypes, which vary from one renin species to another.\textsuperscript{27}

These unique features of renin and angiotensinogen explain why it is difficult to design potent and specific competitive human renin inhibitors. Most of the rational designs were based on the sequence of human angiotensinogen surrounding the Leu\textsuperscript{10}-Val\textsuperscript{11} cleavage site and on the assumption that a relatively large number of renin subtypes had to be occupied to ensure sufficient inhibitor specificity and affinity.

Renin is strongly species specific, but primate renin shares enzymatic and immunological properties with human renin.\textsuperscript{28} Primates are therefore the best model to date for the study of human renin inhibitors. However, they may have a pronounced stimulation of their renin system in basal conditions that is not observed in human hypertension as will be discussed below. Some of the inhibitors synthesized are active against dog renin,\textsuperscript{29} allowing useful investigations to be performed on the renin inhibitors mechanisms of action.\textsuperscript{30} The recent synthesis of inhibitors able to block plasma renin activity (PRA) in rats should allow studies in this species that would be extremely helpful for comparison of renin inhibition with ACE inhibition in the most convenient animal species for experimental hypertension.\textsuperscript{31} The inhibitory properties of human renin inhibitors have generally been tested in vitro by their effects on PRA, which is dependent on the pH of incubation, the protein content of the medium, and the amount of available angiotensinogen. Therefore, difficulties in screening procedures are associated with the difficulties encountered in drug design.

**Renin Inhibitor Peptides and Pseudopeptides**

**Early Renin Inhibitors**

An ideal renin inhibitor should have high affinity and unique specificity for renin, good oral availability, metabolic stability allowing a long duration of action, and no toxicity.

The first renin inhibitors, synthesized by Kokubu et al,\textsuperscript{3} were derivatives of the tetrapeptide Leu\textsuperscript{10}-Leu\textsuperscript{11}-Val-Tyr\textsuperscript{23} found in equine angiotensinogen and had a $K_I$ for renin in the millimolar range. Haber's group (Poulsen et al\textsuperscript{32}) then modified the Leu\textsuperscript{10}-Leu\textsuperscript{11} cleavage site of the octapeptide renin substrate by replacing one of the leucyl residues by its D enantiomer (dLeu\textsuperscript{10} or dLeu\textsuperscript{11}). These peptides were not cleaved by renin and had inhibitory constants in the micromolar range. The same group substituted a hydrophobic dipetide (Phe\textsubscript{2}-Phe\textsubscript{11}) for the cleavage site. Renin inhibitor peptide (RIP) Pro\textsuperscript{1}-His-Pro-Phe-His-Phe-Phe-Val-Tyr-Lys\textsuperscript{13}, again based on hog angiotensinogen sequence, inhibited human renin with a micromolar concentration and was sufficiently water soluble. RIP was studied in the sodium-depleted normotensive monkey and in a renin-dependent model of hypertension.\textsuperscript{33} In both cases, this inhibitor produced a drop in blood pressure similar to that observed with teprotide, a converting enzyme inhibitor. In humans, RIP decreased blood pressure, but unexpectedly produced a sinus bradycardia and profound hypotension.\textsuperscript{34} These latter phenomena have not been observed with latter renin inhibitors and are probably not related to renin inhibition itself.

**Transition State Analogue Inhibitors Based on Statine and Statinelike Compounds**

Present-day analogue inhibitors contain a nonhydrolysable analogue of the transition state for the scissile peptide bond hydrolyzed by renin. The most extensively studied series of inhibitors, both theoretically and experimentally, is that derived from pepstatin. Pepstatin, a natural pentapeptide isolated from Actinomyces cultures by Aoyagi et al,\textsuperscript{35} is a universal protease inhibitor with an exceptionally high affinity for pepsin and a much lower inhibitory potency for human renin ($K_I$ about $10^{-7}$ at pH 7.4). Pepstatin (Isoval-Val-Val-Ala-Ala-COOH) contains two statine (Sta) residues of which only the central one acts as an analogue of the transition state. The mode of inhibition of pepsin and renin by pepstatin and its analogues has been studied in detail by several authors, particularly by Rich et al.\textsuperscript{36,37} Acute administration of pepstatin or its soluble derivatives has been shown to inhibit the pressor effect of renin and decrease blood pressure in rats with renovascular hypertension.\textsuperscript{38,39} However, its experimental use was limited because of its lack of specificity and its low affinity for rat renin.

The synthesis of more specific renin inhibitors with a greater affinity for human renin was achieved by retaining the central statine of pepstatin and by replacing the amino acids surrounding it by amino acids present in human angiotensinogen or chemical entities displaying a high affinity for the corresponding renin subtypes. Boger et al\textsuperscript{41} suggested that statine could be considered as a dipetide analogue of the transition state complex replacing Leu\textsuperscript{10}-Val\textsuperscript{11} because of its two extra carbonyl groups. These authors and Evin et al\textsuperscript{42} synthesized peptides with 1,000 to 10,000 times more affinity for human renin than pepstatin itself and a markedly reduced affinity for pepsin and cathepsin D. They found that the presence of a phenylalanine residue at P\textsubscript{1} and a histidine at P\textsubscript{2} position conferred a high affinity for human renin inhibitors, a finding that has been amply confirmed, as most recent renin inhibitors contain an aromatic group at P\textsubscript{1} and a histidine (or a histidine analogue) at P\textsubscript{2}. On the other hand, the P\textsubscript{3} and P\textsubscript{4} positions seem less critical as they tolerate many different chemical entities (Figure 2). Tetrapeptide, tripeptide, and even dipetide renin inhibitors containing a statine have been synthesized with an IC\textsubscript{50} of around $10^{-8}$ to $10^{-9}$ M. Statine has also been replaced by derivatives, e.g., norstatine,\textsuperscript{48,49} difluorostatine,\textsuperscript{50} cyclohexylalanine analogues of statine (ACHPA),\textsuperscript{51-53} and cyclostatine.\textsuperscript{54} Some new compounds containing ACHPA
have subnanomolar inhibitory constants and are extremely specific for human renin.\textsuperscript{52}

Other Peptides and Pseudopeptide Inhibitors of Renin

Many other peptides that are able to inhibit human renin with a remarkable affinity (IC\textsubscript{50} values ranging from $10^{-8}$ to $10^{-11}$ M) and have a restricted specificity for other aspartyl proteases have been recently synthesized. In these peptides or peptidelike structures, statine is replaced by another transition state analogue, and they contain other chemical structures designed to optimize their interactions with the various renin subsites.

Szelke et al\textsuperscript{55,56} made a fundamental contribution by preparing an interesting series of renin inhibitor peptides in which the scissile bond (-CO-NH-) was reduced (reduced "isostere," -CH\textsubscript{2}-NH-). They conceptualized and designed analogues of the transition state (Figure 2). These peptides were investigated in detail in primates and in humans (see below). Other isosteric compounds have been synthesized by Szelke et al\textsuperscript{57} by inserting a hydroxy isostere (CHOH-CH\textsubscript{2}) in the scissile bond of the human renin octapeptide.

Following this approach, the Leu\textsuperscript{10}-Val\textsuperscript{11} scissile bond has been successfully replaced by a dehydroxyethylene isostere,\textsuperscript{58} sulphur nucleophils,\textsuperscript{59} amino alcohol dipeptide,\textsuperscript{60} and miscellaneous structures.\textsuperscript{61-63} It is also possible to synthesize compounds in which the C-terminal residue is an aldehyde (leucinal or phenylalanilal) and acts as a precursor of the transition state analogue.\textsuperscript{64,65} Because aldehydes are chemically and metabolically unstable, a similar approach was taken with the synthesis of more stable peptides with an alcohol at the C-terminal position of angiotensin I or of dipeptide glycol renin inhibitors.\textsuperscript{66}

Present Status and Limitations of Renin Inhibitors

At the present time, two of the objectives for the design of a renin inhibitor have been achieved: affinity and specificity. Most presently available compounds inhibit human renin with a nanomolar or subnanomolar K\textsubscript{i}; they are extremely specific for renin as they are 10,000 times less potent for inhibiting pepsin or cathepsin D.

However, several limitations still remain that restrict their use in the treatment of human hypertension.
Metabolic stability. The administration of a renin inhibitor is immediately followed by an increase in renin secretion, which is dose-dependent. Therefore, its concentration must be sufficiently high and remain so long enough to fully inhibit the new renin molecules released into the circulation. In fact, all renin inhibitors investigated up to 1989 were cleaved or metabolized rapidly as blood pressure usually recovers within minutes after stopping an intravenous infusion. Although the metabolic rate of renin inhibitors has not yet been reported in detail, it seems that several renin inhibitors are excreted by the liver into the bile, which contributes to their rapid metabolism. Various modifications to the peptide backbone have been made to increase metabolic stability (e.g., retroinverso amino acids, where the amide bond -CO-NH- is inverted to -NH-CO-), design of unhydrolyzable protecting groups at the N-terminus, and conformationally restricted renin inhibitor peptides. Such modifications increase the in vitro resistance of these compounds to proteolytic enzymes, but there has been no report showing a dramatic increase in their metabolic stability in vivo.

Oral availability. The most difficult area of the current research on renin inhibitors is the production of a compound with sufficient oral availability. There are several difficulties: little or nothing is known of the general rules governing the intestinal absorption and transport of peptides or pseudopeptides; the most efficient compounds still often have a molecular weight around 600-700 and contain a dipeptide like Phe-His at the P2-P3 position; it may be difficult to design compounds shorter than dipeptides for the reasons explained above (in fact most “dipeptides” contain additional bulky groups at their N- and C-terminals); the renin inhibitor must be resistant to the digestive proteolytic enzymes. Several renin inhibitors have been shown to be actually absorbed per os in primates, either directly by recovery in the plasma of a radiolabeled compound given per os or by its detection in the plasma, or indirectly by following inhibition of PRA and blood pressure decrease. However, most compounds require doses of 30-60 mg to produce a complete inhibition of PRA, which lasts for 5 hours with the highest doses used, but PRA, as discussed later, is not the most appropriate index to investigate the reality of renin inhibitor in vivo.

Solubility. Because most of the compounds produced to date exhibit very low oral availability, it was important to develop compounds that were water soluble and could be evaluated in animal models by continuous intravenous administration. Bock et al recently reported the synthesis of statine- and ACHPA-containing tetrapeptides whose aqueous solubility was enhanced by adding selected polar groups to the C-terminal. These peptides have a long duration of action when administered intravenously but still a low oral availability.

Importance of the renin system in human hypertension. As shown below, renin inhibitors have been studied in primates with pronounced stimulation of the renin system to obtain clear hemodynamic and biochemical effects. Marmosets have a spontaneously highly stimulated renin system even in the absence of sodium depletion. Obviously, these experimental conditions do not reflect the usual status of the renin-angiotensin system in humans, where basal levels of PRA are generally much lower. To obtain a 10% drop in blood pressure, Kleinert et al used doses of the renin inhibitor A-6466 ranging from 0.01, 0.1, and 1.0 mg/kg in salt-depleted, normal, and anephric animals, respectively. Thus, high dosage levels of renin inhibitors or high levels of stimulation of the renin axis may be necessary to obtain a hemodynamic response in human hypertension.

Hemodynamic Effects of Renin Inhibitors
Acute and Chronic Hypertensive Effects in Primates

Intravenous bolus injection or short-term infusion of renin inhibitors induces a rapid fall in blood pressure in conscious, normotensive, and sodium-depleted primates. The onset of the response usually occurs within 5 minutes of administration and affects both systolic and diastolic pressure. The nadir of the hypotensive response is equally rapid (within 30 minutes), the magnitude of the decrease in blood pressure is dose related, may be profound, and is sustained as long as infusion is continued. The recovery of blood pressure depends on the dose and the pharmacological characteristics of the renin inhibitor. It generally returns to its pretreatment level quickly after discontinuation of low dose infusions, but some inhibitors are said to be long acting. No blood pressure rebound has been observed so far after cessation of treatment. The in vivo specificity of the inhibitors has been indirectly tested by their effects on blood pressure in various renin-dependent states. The minimum effective dose required to reduce mean arterial pressure is lower in sodium-depleted primates where renin is elevated than in controls fed a normal sodium diet. Renin inhibition significantly lowered blood pressure in a primate model of transient renin-dependent hypertension induced by renal infarction. Very similar results were obtained in sodium-depleted and renin hypertensive dogs. Finally, in primates pretreated with ACE inhibitors, blood pressure was not affected even when high doses of renin inhibitor were administered by intravenous bolus injection of renin inhibitors into normotensive primates on a low sodium diet for 1 or 2 weeks induced a sustained reduction in blood pressure, without tolerance.

Effects on Heart Rate and Peripheral Resistance

Renin inhibitors do not usually modify heart rate, whatever the dose used or the hypotensive response obtained, thus sharing a common hemodynamic profile with other inhibitors of the renin-angiotensin system, such as ACEI and saralasin. They reduce total peripheral resistance in sodium-
depleted dogs\textsuperscript{30} and primates\textsuperscript{79} without altering of cardiac output. Renin inhibition reduces afterload and left ventricular end-diastolic pressure in anesthetized dogs with acute left ventricular failure.\textsuperscript{87}

**Renal Effects**

The intrarenal administration of a renin inhibitor in small quantities without measurable systemic effect on renal function markedly increases urinary sodium excretion and glomerular filtration rate.\textsuperscript{88} These effects are completely blocked by concurrent intrarenal administration of Ang II, demonstrating that this hormone acts intrarenally to control renal sodium and fluid homeostasis. Renal blood flow selectively increases in sodium-depleted marmosets with a concurrent decrease in renal vascular resistance, but mesenteric flow remains unchanged.\textsuperscript{89} Under conditions of sodium depletion, glomerular filtration rate is lowered by renin inhibitors\textsuperscript{90}; urine flow and sodium excretion are unaltered; and potassium excretion is normal or slightly reduced.\textsuperscript{84,91} No data are yet available on the long-term effects of renin inhibitors on the renal functions of a clipped kidney, an important issue for the treatment of renovascular hypertension.\textsuperscript{91}

**Human Studies**

After the promising results in nonhuman species, investigation of renin inhibitors in humans has recently started and is under way in several laboratories. Two different renin inhibitors have been infused in normal volunteers on a normal sodium diet to study their pharmacodynamic and pharmacokinetic properties.\textsuperscript{92-94} Neither affected blood pressure or heart rate, although PRA and plasma Ang II fell in a dose-dependent manner. In similar sodium regimens, captopril also had a minimum effect on blood pressure in recumbent volunteers, suggesting that the renin system participates to a minor effect in maintenance of blood pressure under these conditions.\textsuperscript{92} Infusion of the renin inhibitor CGP 38560A did not reduce blood pressure when a slight sodium depletion was previously induced by 40 mg furosemide,\textsuperscript{94} but another inhibitor, II142, decreased diastolic blood pressure during a more severe sodium depletion.\textsuperscript{95} Maximal renin inhibition and profound suppression of plasma angiotensins were achieved with all renin inhibitors tested so far. Finally, in a study recently conducted in 12 hypertensive patients selected for their diastolic blood pressure decrease in response to a single oral dose of 50 mg captopril, the infusion of two doses of CGP 38560A induced a modest but significant hypotensive response that was not equal to that induced by captopril (\(-5.3\%\) after CGP 38560A and \(-15.3\%\) after captopril).\textsuperscript{96}

**Hormonal Effects**

**Renin Secretion**

Inhibition of Ang I and Ang II formation during renin inhibition may be expected to produce a secondary increase in renin secretion due to blockade of the negative feedback control of Ang II on renin secretion. Even though the maximum number of immunoreactive renin molecules released can be sometimes increased 10-fold,\textsuperscript{96} there is a large molar excess of renin inhibitor under intravenous infusion that is able to block the newly released renin molecules. Blaine et al\textsuperscript{29} found that a 48-hour continuous infusion of the renin inhibitor SCRIP in dogs induced a sustained fall in PRA. Interestingly, PRA was increased during the infusion after SCRIP was removed and then returned toward basal values when infusion was stopped. The recently developed new direct immunoassays\textsuperscript{97} for total or active renin in human and primate plasma, which are independent of the presence of renin inhibitor, provided a direct evidence of these changes.\textsuperscript{67} A comparable fall of blood pressure was observed using the renin inhibitors CGP 29287, enalaprilat, or hydralazine in sodium-depleted marmosets.\textsuperscript{57} The two inhibitors of the renin system produced an increase in total plasma immunoreactive renin of up to 300\% of pretreatment values, whereas hydralazine did not increase as much plasma immunoreactive renin. Similarly, a dose-dependent rise in active renin was observed after administration of SR 43845\textsuperscript{58} in primates. A 30-minute infusion of CGP 38560A induced a dose-dependent increase in active renin in normal volunteers, with a peak at the end of infusion and a progressive decrease thereafter.\textsuperscript{92-94} Even though blood pressure was not affected, this large increase in active renin secretion emphasizes the crucial role of the negative feedback of Ang II on renin release. The lack of rise in plasma active renin was extremely useful to demonstrate the weak oral availability of CGP 38560A and its absence of effect after oral administration to normal volunteers (50-200 mg). This absence of increase in active renin release confirmed the limited value of the conventional PRA assay, the suppression of which would have falsely suggested in this investigation an efficacy of the compound after oral administration.

**Plasma Aldosterone**

Plasma aldosterone decreased during a 1-week infusion of the renin inhibitor A-64662 in primates but differed significantly from the vehicle group only on the second and third days of infusion.\textsuperscript{86} Short-term infusion of the presently available renin inhibitors in humans did not affect plasma aldosterone.\textsuperscript{92-94}

**Relation Between the Circulating Renin-Angiotensin System and Blood Pressure During Administration of Renin Inhibitors.**

Most in vivo studies have described a dose-related inhibition of PRA during continuous infusion and after intravenous bolus or oral administration of low doses of various renin inhibitors in dogs and primates, under normal or low sodium conditions.\textsuperscript{29,47,54,78} The inhibition of PRA occurred within 5 minutes after intravenous bolus. On cessation of the inhibitor infusion, PRA returned to control values with a dose-
dependent time recovery. Some renin inhibitors exhibited a prolonged inhibition of PRA.54,72
Wood et al47 showed a parallel between PRA inhibition and blood pressure decrease in an acute study using CGP 29287. A 7-day renin inhibitor infusion resulted in sustained inhibition of PRA to very low levels.86 However, marmosets given a 14-day intraperitoneal infusion of a renin inhibitor showed a recovery of PRA to pretreatment level on the last day in the group treated with the highest dose of renin inhibitor, whereas the hypotensive response persisted.86 As early as 1984, Blaine et al29 emphasized their perplexing results on the dissociation between blood pressure lowering and plasma renin inhibition by showing that mean arterial pressure recovered faster than did PRA after a 48-hour infusion of SCRP. In addition, there was no parallel between PRA inhibition and mean blood pressure changes during short-term infusion of increasing doses of this inhibitor. Similar observations have been made by other investigators, mostly in anesthetized animals.54,76,79

The existence of a dissociation between circulating Ang II concentration and blood pressure after acute administration of renin inhibitors is still a matter of debate. These two parameters may55-57 or may not83-86 be correlated, depending on the experimental models and the methods used for measuring angiotensins.98 As already mentioned, CGP 38560A and enalkiren decreased the Ang II levels of normal volunteers in a dose-dependent manner within 10 minutes, but their blood pressures remained unchanged.92,93 Modest changes in blood pressure were found to parallel those of plasma Ang I and Ang II in hypertensive patients.96 This study clearly showed the persistence of PRA inhibition as tested by the usual assay, whereas the in vitro generation of Ang I measured by the Ang I-trapping method99 suggested that the inhibition of PRA was disappearing (Figure 3). This latter measurement was more closely related to plasma Ang I concentrations and blood pressure than the conventional PRA measurement, which illustrates the numerous methodological difficulties that are encountered in assessing renin blockade in the circulation.

From these studies, it is clear that a dissociation can occur between blood pressure changes and PRA inhibition, whatever the method used. The most reliable index for testing in vivo plasma renin blockade is the reduction in plasma Ang I and Ang II concentrations. However, dissociation between the circulating renin-angiotensin system and blood pressure is conceivable in two opposite directions. Blood pressure can stay low when plasma Ang I and Ang II are coming back to their initial levels as already shown with ACEI,2 and blood pressure can stay high when plasma Ang I and Ang II are suppressed because of an extravascular generation of angiotensins.100

Comparison Between Angiotensin Converting Enzyme and Renin Inhibition
Careful studies designed to compare ACEI and renin inhibitors would have important theoretical and practical implications. The hypothetical antihypertensive effect of ACEI mediated by bradykinin potentiation and eicosanoid production would be substantiated if an ACEI appeared to be more potent than a renin inhibitor during acute and chronic administration. There might also be certain forms of experimental hypertension that would respond better to one or the other agent, which would help to discriminate between these two types of drugs in their therapeutic indications.

A precise comparison between the effects of ACE and renin inhibitors on blood pressure decrease, however, is extremely difficult to make for several reasons. A dose-response curve would have to be established for both compounds to find the maximal hypotensive dose for each. Both drugs should completely inhibit either circulating ACE or renin at the same time. The, hemodynamic and hormonal conditions should be similar. Finally, it would be important to see whether dissociations observed in acute conditions still hold for long-term treatment of different forms of hypertension. These requirements have not yet been met. Several studies report an equivalent antihypertensive effect of both inhibitors in normotensive monkeys and hypertensive dogs.77,85,87,101 However, Blaine et al3 showed that when a complete renin inhibition was
achieved by SCRIP, enalaprilat promoted a further fall in mean arterial pressure. In the reverse experiment, SCRIP did not affect the blood pressure of dogs first treated with enalaprilat. Mento et al\textsuperscript{102} have recently reported that the blood pressure-lowering effects of either renin inhibition or ACEI do not necessarily correspond to decreased plasma Ang II concentrations and that combined renin and converting enzyme inhibition causes a greater decrease in blood pressure and lowering of plasma Ang II concentrations than either agent alone. This is not surprising in view of the results of Nussberger et al\textsuperscript{98} which showed the presence of true immunoreactive Ang II in plasma during acute and chronic treatment with ACEI. However, the validity of the experiments performed in rats by Mento et al\textsuperscript{102} is impaired by the report of normal PRA values after ACE inhibition, which does not fit with what is well known on renin release under these circumstances. Many more studies are clearly required with different renin inhibitors at different doses to unambiguously demonstrate any possible difference with the endocrine and hemodynamic profiles of the other inhibitors of the renin-angiotensin system.\textsuperscript{103}

In conclusion, inhibitors with an exceptionally high specificity and affinity for renin have been developed in recent years. However, most of the structures published to date are still peptidic in essence and have relatively large molecular weights, which might explain their low oral availability and their rapid metabolism. Pharmacological experiments in primates indicate that these inhibitors are effective in lowering blood pressure, especially in renin-dependent states, without causing any major alteration in heart rate or unwanted hemodynamic effects and, as with ACEI, not provoking any counterregulation by the organism during the decrease in blood pressure. All renin inhibitors block PRA, suppress plasma Ang I and Ang II levels, and increase renin secretion.

There is usually no clear relation between the lowering of blood pressure and suppression of PRA under acute administration of renin inhibitors. The most reliable and accessible hormonal parameters for following renin blockade seem not to be PRA but the plasma Ang I and Ang II concentrations. Indeed, PRA measurement by conventional assays, can still be inhibited, whereas angiotensins have returned toward pretreatment values. The existence of dissociation between blood pressure and angiotensin levels should be looked for very carefully; this issue needs to be more precisely addressed, as well as the questions of the generation of Ang I in the extravascular compartment, the distribution of renin inhibitors in these compartments, and the relative importance of this extravascular compartment production of angiotensins.

Whether a renin inhibitor will be more, equally, or less tolerated than an ACEI in all or some cases of human hypertension is also unknown. Nevertheless, the clinical development of renin inhibitors is a challenge for the next decade to eventually enlarge our range of antihypertensive drugs and undoubtedly to improve our understanding of the renin-angiotensin system.

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