RENIN AND THE THERAPY OF HYPERTENSION

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INTRODUCTION

The measurement of the activity of the circulating proteolytic enzyme, renin, has come to hold a unique place in modern concepts of hypertension. Recognized since its initial discovery by Tigerstedt & Bergman (1) as capable of inducing an elevated blood pressure, the overactivity of renin (and overproduction of the vasoactive octapeptide angiotensin II) is now thought to be directly responsible for high blood pressure in but a minority of humans afflicted with this disease. The implication of renin as a causative factor in this small, but important, subgroup of patients (with predominantly renal, renovascular, and malignant hypertension) belies its current importance, for it has facilitated the classification of hypertension, both primary (essential) and secondary in humans and experimental animals, yielding important new information on the variety of hypertensive states. The purpose of this paper is to summarize recent concepts of the etiology and therapy of hypertension based on knowledge of the activity of the renin-angiotensin system and its modification by therapeutic and diagnostic agents.

FACTORS AFFECTING RENIN RELEASE

Since most agents used in the therapy of hypertension affect plasma renin activity in some way, it is worthwhile to discuss briefly those mechanisms affecting renin release. Several recent reviews (2–5) outline this subject in greater detail.

Renin is a specific enzyme of 40,000 mol wt that is synthesized, stored, and released from specialized granular cells in the arteriole at the vascular pole of the renal glomerulus. Although extrarenal sources of renin or isorenins have been described, notably the brain (6), uterus (7), and adrenal glands (8), the physiologic significance of these enzymes remains undefined. The associated periglomerular grouping of the afferent arteriole, efferent arteriole, lacis cells, and the group of

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specialized cells at the origin of the nearby distal tubule known as the macula densa form the "juxtaglomerular apparatus" (9), a microstructure involved in the fine control of renin release. Although the specific intracellular mechanisms responsible for renin secretion remain speculative, its modulation by the physiologic variables of vascular volume, blood pressure, sympathetic nervous tone, sodium, and potassium appears to involve the juxtaglomerular apparatus (10, 11).

The baroreceptor hypothesis (that the afferent arteriole responds to a decreased (or increased) mean renal perfusion pressure with an altered stretching or a decreased transmural pressure in this vessel by an increase (or decrease) in renin release) followed from the observation of altered juxtaglomerular cell granularity with varied perfusion pressures (12, 13). Further experiments in the nonfiltering kidney preparation (13), in which an influence on renin release by alterations in intratubular sodium concentration was excluded, specifically in the area of the macula densa, have established strong support for this hypothesized mechanism (14). That an altered sodium concentration in the region of the macula densa can regulate renin release has been suggested by several studies (15–17), although whether the stimulus to renin secretion is an increase (17) or decrease (16) in this concentration is unresolved.

The following illustrate the intimate relation between sympathetic nervous activity and plasma renin activity: observations of the close histologic association of sympathetic nervous fibers with the juxtaglomerular apparatus (17–19a), the induction of renin release by renal nerve stimulation (20), the reduction of resting plasma renin activity in response to volume depletion by renal sympathectomy (21), and the blunting of renin responsiveness after administration of ganglionic blocking agents (22). The closely related stimulation of renin release by circulating catecholamines is further considered under the section on propranolol.

Although β, and not α, receptors (23) are thought to control adrenergic modulation of renin, the cellular mechanisms involved are controversial, but are thought by many to involve β-receptor mediation of the intracellular cyclic adenosine monophosphate (cAMP) system (24–27). Michelakis et al (26) have shown in vitro stimulation of renin release into the incubating medium by both catecholamines and cAMP, and Nolly and co-workers (30) have demonstrated potentiation of catecholamine-stimulated release by the phosphodiesterase inhibitor theophylline. Similarly, Winer and colleagues (24) demonstrated in vivo stimulation of renin release by cAMP, but because propranolol prevented cAMP-induced renin release, also suggested an adrenergic site of action distal to cAMP. Reid (28), however, found that propranolol did not prevent theophylline-stimulated renin secretion in vivo. Also controversial is the observation of Beck et al (29) that lithium pretreatment in vitro and in vivo, which prevented isoproterenol-induced increases in intracellular and excreted cAMP, did not affect isoproterenol-induced renin release. Hence, the precise role of intracellular cAMP in this scheme is at present unclear, since the sequence of activation of a juxtaglomerular cell membrane-bound β-receptor and adenylate cyclase stimulation leading to increased intracellular cAMP and renin release does not conform to several experimental findings.

Of related interest are the demonstrated experimental alterations in renin release by central nervous system interventions, specifically stimulation of medullary and

hypothalamic centers (31) and inhibition by intracerebral 6-hydroxydopamine administration (32), which, together with other central mechanisms of blood pressure regulation, appear to be mediated through the peripheral sympathetic nervous system. The demonstration of a central pressor action of the active product of renin activity, angiotensin II, probably via an action at the area postrema and again mediated by the autonomic nervous system (33) highlights the variety of interrelationships of the central nervous system, renin activity, and blood pressure control.

Renin release is affected by changes in serum potassium concentration and excretion, which in turn are often affected by the treatment of hypertension with various types of diuretics and/or necessary potassium supplementation. Administration of potassium to humans tends to reduce plasma renin activity despite an induced natriuresis from this cation (34), directly related to alterations in plasma concentration and urinary excretion. Potassium depletion results in the converse rise in plasma renin activity, despite an induced sodium retention (and lower aldosterone secretion), and both these effects appear mediated through a renal tubular mechanism, possibly at the macula densa (35).

The control mechanisms of renin release are all interrelated, with several feedback cycles. The end product of renin activity, angiotensin II, inhibits renin release directly by an effect presumably at the renin-containing afferent arteriolar cells (36–39) independent of vasoconstrictive activity (37), and indirectly by several mechanisms. First, angiotensin II stimulates aldosterone production by the adrenal zona glomerulosa (40) with consequent increased distal tubular sodium reabsorption, expansion of the extracellular fluid volume, a sensed increased perfusion pressure by the afferent arteriole, and hence a depressed rate of renin release. Second, the direct systemic vasoconstrictor effect of angiotensin II would effect the same sensed increased perfusion pressure and renin inhibition, as would the third indirect step, the mentioned central pressor effect of angiotensin II. Other postulated indirect actions are afferent or efferent arteriolar vasoconstriction in response to locally formed angiotensin II from an increased distal sodium load as sensed by the macula densa and the consequent increased renin secretion (41), or a converse single nephron feedback system with suppression of renin release upon distal sodium delivery (42). Of all these mentioned indirect feedback inhibitory factors upon renin release, that via aldosterone stimulation and vascular volume expansion is thought to be the most physiologically significant.

Before considering the classification of hypertension and the use of such subgrouping, attention should be focused on the variations of the renin activity during antihypertensive therapy, which are related to the above-mentioned control mechanisms of renin release.

EFFECT OF ANTIHYPERTENSIVE DRUGS ON PLASMA RENIN ACTIVITY

Virtually all the drugs currently employed as antihypertensive agents affect plasma renin activity in some manner, although these effects may not necessarily be related to the mechanism of the antihypertensive effect. The effects of single agents on renin activity are discussed below. Because evidence of the relation of the adrenergic

nervous system to renin has evolved through study with a multitude of antiadrenergic drugs, each with a unique effect on the sympathetic nervous system, the concepts of this relation are discussed relative to the mechanism of action of each drug.

Diuretics

The mechanism of the antihypertensive action of diuretic agents is unknown, but appears related to an initial negative sodium balance (43), possibly with sustained plasma volume reduction (50). Certain types, such as those of the thiazide and chlorthalidone group and those affecting the loop of Henle, may also act through a direct dilatory action on arteriolar smooth muscle or through alterations in the electrolyte or water content of the arteriolar wall (44, 45). However, whether this latter mechanism is significant is unclear (46), since the blood pressure of normotensive individuals is not reduced by these drugs and the antipressor activity can be nullified by a high sodium diet (47) and can be duplicated by sodium restriction (48) or diuretic agents with no demonstrated direct arteriolar action, such as mercuhydrin (43). A diminished vascular reactivity to sympathetic stimulation possibly via effective chronic sodium depletion after thiazide administration has also been shown (49), which may blunt a compensatory blood pressure rise upon volume depletion, and may also in part account for the well-known potentiation of the antihypertensive effect of other agents by the oral diuretics. With chronic diuretic therapy, the plasma renin activity is usually increased and remains so (50). Although possessing a somewhat lesser chronic antihypertensive effect than the thiazide or chlorthalidone group (51) [although nonetheless effective as single agents for mild hypertension (52)], the loop of Henle diuretics, ethacrynic acid and furosemide, promote a greater initial diuresis with consequent volume depletion, often leading to a rise in plasma renin activity. This phenomenon has been used to stimulate renin release for renin subgroup classification (61). That the mechanism of acute stimulation of renin release is not completely via volume depletion, and may involve an increased sodium delivery to the macula densa, is suggested by the incomplete inhibition of renin release by simultaneous urine reinfusion by uretero-venous anastamosis (53), although effective vascular volume reduction by extrarenal effects, such as an effect on postcapillary capacitance vessels (54), may also occur.

Spironolactone

This drug is a specific competitive antagonist of aldosterone, and competitively inhibits the sodium-retaining and kaliuretic effect of this steroid (and other mineralocorticoids) at the distal tubular site of the nephron. It is devoid of diuretic effect in adrenalectomized subjects (55). A possible mechanism of action of spironolactone may be a competitive inhibition of endogenous mineralocorticoid action on the arteriolar resistance vessels, suggested by findings of a direct extrarenal effect of aldosterone and other mineralocorticoids on the maintenance of vascular tonicity (56, 57). When employed in the treatment of unselected patients with essential hypertension, some workers have reported a therapeutic potency comparable to the thiazide diuretics (58), although others have found a greater hypotensive effect in the subset of patients with low renin essential hypertension (59–61), in contrast to

those with normal renin values. Also spironolactone has been shown by Spark and co-workers to restore normal renin responsiveness to posture and furosemide stimulation (62), in contrast to lack of a similar response after chronic thiazide administration. These studies, and others discussed below, have been taken as evidence for an excessive secretion of mineralocorticoid as a cause for low renin essential hypertension, with spironolactone being as effective a specific antagonist as it is for the alleged prototype of such hypertension, primary aldosteronism.
and unexplained effect of spironolactone in such patients is a prolonged restoration of renin responsiveness for many weeks after discontinuation of the drug, although the hypertensive state itself is soon resumed (63).

Diazoxide

This agent, with a benzothiadiazine (thiazide) structure and antinatriuretic action, is currently used in North America solely by rapid intravenous injection for the treatment of hypertensive emergencies, although it is possibly also effective by oral administration (64). Its action in hypertensive patients is via direct arteriolar smooth muscle relaxation and consequent reduction of total peripheral resistance and blood pressure (65). The hypotensive response is dissociable from the rise in plasma renin activity, the latter occurring maximally two hours after injection in two thirds of patients (66). The remaining one third, although showing a comparable hypotensive response, show no or little change in plasma renin and probably correspond to low renin essential hypertensives as defined by other techniques, such as dietary sodium restriction and upright posture (66). The mechanism of renin release in hypertensive patients responsive to diazoxide is more complex than one would expect. It is dissociable from changes in extracellular fluid volume (67) and may be related to a sensed decreased renal blood flow by the juxtaglomerular apparatus (68) or a compensatory increased adrenergic activity, as adrenergic blocking agents prevent the diazoxide-induced renin release (69). Involvement of an intracellular increase in cAMP with enhanced renin release has also been hypothesized (70), as diazoxide is a phosphodiesterase inhibitor (71) (as are the other thiazide diuretics).

Other Direct Vasodilators

Similar to diazoxide, other vasodilating drugs exert their antihypertensive effect by relaxation of arteriolar smooth muscle and decreased total peripheral resistance. Agents in this group include sodium nitroprusside (72) (used intravenously only for hypertensive emergencies), minoxidil (73), hydralazine (74), and guancydine (75). The vasodilating drugs have similar secondary effects that may limit their usefulness as solitary antihypertensive agents. They promote a reflex increase in sympathetic activity, causing increased heart rate and cardiac output (72–74), and can induce sodium retention with extracellular fluid and volume expansion (76), which may blunt the hypotensive effect. Vasodilating drugs consistently increase the plasma renin activity (73, 77, 79), possibly by a changed renal perfusion pressure and an increased renal sympathetic discharge (69, 77). An enhanced renin release by direct renal vasodilation has been stressed by Kaneko and colleagues (78), as small amounts of a vasodilator infused directly into a renal artery without significant

systemic vasodepression produce large increases in plasma renin activity. The combination of vasodilating drugs with adrenergic blocking agents to prevent the reflex cardiac and renal responses, and addition of diuretics to counteract the induced sodium retention caused by these drugs has been shown to result in an effective combination capable of controlling virtually all degrees of hypertension, from mild to severe, without consideration of the baseline renin subgroup of such patients (80–82).

Clonidine

This potent antihypertensive drug, an imidazoladine derivative, differs from most other antihypertensive agents in its mechanism of action. Parenteral administration results in an acute brief hypertensive response from direct vascular adrenergic stimulation not related to catecholamine release (83). This effect is not seen with chronic oral therapy. The antihypertensive action of the drug is due to a long-acting central inhibition of medullary vasomotor and cardiac centers (84), as indicated by the absence of its effect with reserpine pretreatment, and in the spinal animal, and by the vasodepressor response following minute doses injected into the cisterna magna.

The effect of clonidine on plasma renin release is primarily inhibitory. In the anesthetized dog, intravenous injection after the initial pressor response leads to a decreased mean arterial pressure and a parallel drop in plasma renin activity, suggesting that the renin suppression is from central sympathetic inhibition (83). Intracisternal injection effects a similar depression of renin release. That renin activity is suppressed in the face of a decreased renal perfusion pressure, itself a stimulus to renin release via the juxtaglomerular apparatus sensing mechanism, has been taken as evidence that centrally controlled sympathetic tone has a predominant role in controlling renin release. However, other more direct interventions against sympathetic nervous control such as ganglionic blockade have been shown to raise plasma renin under certain conditions in the face of the parallel hypotensive response (85). Thus the relative hierarchy of control over renin release is not clear cut, as discussed below. The administration of clonidine to patients with essential hypertension also lowers the plasma renin activity (83), but as mentioned above this relation to the antihypertensive effect is uncertain.

Guanethidine

This potent drug exerts its antihypertensive action by interfering with neurotransmission at the adrenergic postganglionic nerve terminals by both preventing norepinephrine release and depleting norepinephrine stores at these terminals (86). The sympatholytic effect on cardiac innervation, with decreased heart rate, stroke volume, and hence cardiac output, contributes to the effect on blood pressure as with other agents affecting the sympathetic nervous system. The dependence of the antihypertensive action on upright posture (87) reflects its greater effect in a condition with enhanced sympathetic discharge from the postural reflex, and accounts for the common side effect of orthostatic hypotension. Similar to other drugs that impair adrenergic function, sodium retention and plasma volume expansion may

result from its chronic use (88), which would have a depressive influence on the plasma renin activity. However, the net effect of guanethidine on plasma renin is variable. When given to hypertensive patients under conditions of sodium depletion, guanethidine was shown by Jose, Crout & Kaplan to augment renin increase after assumption of upright posture (89), probably via renal detection of the unbuffered blood pressure decline and lessened perfusion pressure. Lowder & Liddle (90) have demonstrated that low-renin hypertensive patients on a normal diet, with suppressed renin values despite oral furosemide (three doses of 40 mg over a 15-hr period) and upright posture, do respond with significant renin elevations to the same maneuvers after concurrent guanethidine therapy. Presumably, furosemide induces an effective sodium-depleted state in this interval. Without sodium depletion, guanethidine diminishes the renin response to upright posture (91), probably reflecting a greater dependence of the sympathetic reflexes on renin release in the sodium replete state.

Reserpine

Reserpine and the other rauwolfia alkaloids exert their antihypertensive action primarily by lowering total peripheral resistance through interference with neurotransmission at the postganglionic adrenergic nerve terminus by norepinephrine depletion, and to a lesser degree by interference with sympathetic discharge by a central action on the hypothalamus and vasomotor centers. The interference with intraneuronal storage of catecholamines appears to be the primary mechanism for impairment of adrenergic neurotransmission (92). As reserpine is thus an effective antiadrenergic drug, it would be expected to blunt reactive rises in renin activity from volume-depleting stimuli, and indeed reserpine pretreatment in rats does lessen the posthemorrhage increase (93) and in man the thiazide-induced saliuretic rise in renin activity (94). However, baseline plasma renin activity after reserpine injection has been reported to increase in dogs with renovascular hypertension (85). Morphologic evidence suggests an increase in renal renin synthesis (with a parallel decrease in plasma renin activity) after reserpine treatment, with the lack of functional sympathetic terminals impairing the release of these increased renin stores (95). Thus, reserpine may dissociate the mechanisms of renin synthesis, which are stimulated by the sensing by the juxtaglomerular apparatus of a decreased perfusion pressure from those of renin release, which are impaired by a functional sympathetic nervous blockade.

α-Methyldopa

Although this widely used drug appears to reduce the blood pressure in patients with essential hypertension by a decrease in peripheral arteriolar resistance (96), the major mechanism of action of α-methyldopa is probably central. Interference with the peripheral biosynthesis of norepinephrine (by dopa decarboxylase inhibition) or conversion to α-methylnorepinephrine with action as a *peripheral* "false" neurotransmitter appears not to account for the chronic antihypertensive effect (97). Recent studies have suggested that the hypotensive action is mediated by an effect on the central nervous system (98–100), primarily from evidence of effect from

intravertebral artery and intraventricular injections of systemically subpressor doses of the drug. The mechanism is probably brain entry of the drug and *central* conversion to and accumulation of α-methylnorepinephrine with either displacement of the more potent natural central nervous system neurotransmitter norepinephrine (101) or direct stimulation of inhibitory α-adrenergic neurons in the brainstem (101a). This concept is consistent with the earlier observation by Sjoerdsma and co-workers (102) that administration to a hypertensive patient of the potent peripheral dopa decarboxylase inhibitor MK-485 (which does not cross the blood-brain barrier, but does prevent *peripheral* formation of α-methylnorepinephrine) has no effect on the hypotensive response to α-methyldopa.

Chronic oral administration of α-methyldopa to hypertensive and normotensive humans (103, 111) usually lowers the plasma renin activity in both the supine and upright positions and attenuates renin release from similar maneuvers and renal nerve stimulation in the dog (104). Similarly, a decrease in the renin activity in Bartter's syndrome (105) and the severe hypertension with hyperreninemia in end-stage renal failure (106) have been shown, and Kaplan's (107) demonstration of a blunting of the thiazide-induced rise in plasma renin activity in hypertensive subjects is in accord with the observations by Sweet and co-workers on renal hypertensive dogs (112). The peripheral "false transmitter" hypothesis has been invoked to account for this suppression of renin activity, since infused α-methylnorepinephrine has been demonstrated by Privitera & Mohammed to possess but one third the potency of the natural neurotransmitter in producing renin release (108). However, the convincing evidence for a primarily central effect of the drug and the observed analogous depression of renin activity by the centrally acting drug clonidine (83) make such a mechanism unlikely.

That the antihypertensive effect of α-methyldopa depends upon the suppression of the plasma renin activity (and a lessened production rate of angiotensin II) is also improbable. First, the drug appears to produce a supersensitivity to the pressor effects of exogenous (and by implication endogenous) angiotensin II (109), which would be expected to offset any induced lowering of the renin activity. Second, the hypotensive effect of the drug and its effect on renin, as with certain of the other antiadrenergic drugs, are dissociable. Holuska & Keiser (110) reported that in dogs with unilateral renal vessel ligation and denervation of the contralateral kidney, α-methyldopa infusion consistently lowered the blood pressure without changing the peripheral renin activity. And Lowder & Liddle (90) have recently shown that α-methyldopa therapy, which adequately controlled the blood pressure of low- and normal-renin hypertensive humans, neither lowered the baseline renin activity nor altered the renin subgroup classification by concurrent provocative testing (furosemide and upright posture), again illustrating this dissociation. Observed correlation between the antihypertensive effect of α-methyldopa and decrease in the plasma renin activity in patients with essential hypertension (111) probably reflects simply parallel effects, and not a cause and effect relationship.

Propranolol

In the past 10 years multiple studies have demonstrated the efficacy of the β-receptor blocking agents as antihypertensive drugs, both alone (113–118) and in

combination with other medications (79–82). The mechanisms of this antihypertensive effect remain controversial, mostly in relation to the suppression of the plasma renin activity as a primary antihypertensive mechanism.

Propranolol antagonizes endogenous cardiac β-adrenergic stimulation, both from circulating catecholamines and from norepinephrine at the sympathetic nerve terminus. A reduction in myocardial contractility, heart rate, and cardiac output follows with a subsequently reduced blood pressure from but a minimal compensatory rise in total peripheral resistance (117–119) in responsive hypertensive patients. This lack of parallel rise of resistance with chronic propranolol administration appears to differentiate those responding from those not responding to the hypertensive effect, and includes those with both essential and renovascular hypertension (118). Although intravenous propranolol induces a reduction in cardiac output similar to chronic oral therapy, total peripheral resistance rapidly rises (119) and accounts for the usual lack of acute antihypertensive effect (120). The mechanism for a lack of compensatory rise in resistance with chronic therapy is unknown, although an enhanced sensitivity of the baroreceptor reflex has been suggested (119). In addition, little change in plasma volume is seen in most hypertensive patients (123), in contrast to the usual volume expansion with other solitary antiadrenergic drugs, probably deriving from the lack of effect on α-adrenergic-mediated vascular reflexes.

A central antihypertensive effect of propranolol has been proposed (121, 124) but not established for therapeutic antihypertensive levels of the drug in man. Introduction into the carotid or vertebral artery (122) and cerebral ventricles (125) induces hypotension in animals, and brain-tissue entry of the drug from the bloodstream has been demonstrated (126).

That suppression of renin release constitutes a primary mechanism for the antihypertensive effect of the β-blockers has been proposed by Bühler and co-workers (127), and extended as a proposal that β-blockade represents specific therapy for hypertensive patients with high baseline renin values (including high renin essential, malignant, and renovascular hypertension), primarily from observations of correlation of hypotensive effect with both preexisting renin values and lowering of renin activity during treatment. However, subsequent studies by Michelakis & McAllister (133), Stokes et al (134), and others (136, 137) have failed to confirm either correlation with long-term β-blockade, and increasing evidence indicates that the suppression of renin release is not a primary antihypertensive mechanism of the β-adrenergic blockers.

In hypertensive patients, the dissociation between the effect of chronic propranolol therapy on the plasma renin activity and the blood pressure response suggests a separate mechanism for each effect. Suppression of plasma renin is easily attained in most hypertensive and normal subjects, including baseline measurements or stimulation by posture or other agents (69, 133, 134), although total suppression is rarely achieved. Yet, as mentioned, the antihypertensive response is variable. Significantly, the suppression of the plasma renin occurs with relatively lower doses of the drug, and the antihypertensive effect in those so responding occurs only with greater doses and relatively higher plasma levels (133, 134). Analysis of the dose-response relationships between plasma propranolol levels, plasma renin, and degree of blood pressure reduction in hypertensive patients by Leonetti et al (134a) showed

a dissociation of the latter two effects with virtually complete renin suppression occurring at propranolol levels having no effect on the blood pressure. Thus, a lack of correlation and a different behavior of the hypotensive and renin-suppressing responses to propranolol appear to suggest different mechanisms of action.

The varying response to acute and chronic propranolol administration under conditions of long-term stimulation of renin synthesis has led to the concept that renal β-receptor stimulation is involved primarily in renin release and not in synthesis. Acute propranolol administration to hypertensive patients with high plasma renin levels from chronic diuretic treatment lowers these levels (153), whereas chronic oxyprenolol (138) or propranolol (154) therapy does not, despite the pronounced antihypertensive effect obtained on addition of the second drug. Analogously, Guthrie and co-workers (154a) have noted that neither renal renin content nor plasma renin activity (nor brain or adrenal gland isorenin activities) is changed in rats after two weeks of propranolol treatment; that is, long-term synthesis is unaltered. The distinction between renin synthesis and release (135) may also in part account for the maintenance of renin elevations during long-term propranolol therapy (154). The antihypertensive effect of propranolol is thus maintained in the face of persistent plasma renin elevation from diuretics, clearly dissociating the antirenin from the antihypertensive effect.

Propranolol inhibits the acute renin release induced by various exogenous [epinephrine (128) or isoproterenol (70, 129–131) infusion] and endogenous adrenergic stimuli [from sympathetic discharge (132) and catecholamine release during upright posture (133), volume depletion (69) or hypoglycemia (139)]. Such inhibition appears to derive from competitive blockade of a renal β-adrenergic receptor (140, 141) by L-propranolol contained in the racemic mixture of the drug.

Distinct subpopulations exist among the various tissue β-receptors, with the cardiac receptor classified as β-1 [stimulating cardiac contractility and rate (142)] and receptors in muscle and liver (stimulating glycogenolysis) and bronchial smooth muscle (stimulating relaxation) classified as β-2 (143). Recent evidence suggests that the renal receptor mediating renin release is of the β-2 type on the basis of studies with selective β-2-agonists (144) and antagonists (144–146, 151). However, this classification has been disputed (147). Propranolol is nonspecific in that it competitively blocks both types of β-receptors, in the same way as do other nonspecific β-blockers such as oxyprenolol and prindolol. But the use of the specific β-1-adrenergic blocking agent, practolol (148), has clarified the relationship of the plasma renin activity to the antihypertensive response from β-blockade. This drug lowers the blood pressure when administered chronically to hypertensive patients (149) without significantly changing baseline plasma renin activity (150, 151). Concurrent isoproterenol infusion, an agonist to both β-1 and β-2 receptors, raises the plasma renin while effecting a markedly lessened increase in the heart rate (151). Propranolol in comparison blunts both responses (70). Intravenous practolol has no acute effect on blood pressure or renin activity (151), whereas intravenous propranolol, again in comparison, may have no effect on blood pressure but usually lowers the plasma renin activity in hypertensive patients (136). A similar potent antihypertensive effect in man without suppression of either recumbent or upright

plasma renin activity during treatment with another cardioselective β-1 antagonist (ICI 66,082) has been reported (145). And animal studies using a selective β-2 adrenergic blocker (H35/25) have confirmed the impression that renin release is mediated by the β-2 receptor, as this agent significantly reduced the plasma renin activity without affecting baseline blood pressure (146).

The conclusions suggested by these studies using the selective β-blockers are that the antihypertensive effect of a nonselective blocker such as propranolol derives from β-1-receptor blockade only. The suppression of renin activity by the drug appears to be but a parallel renal β-2 blockade that does not cause the blood pressure response, supporting the view that there are isolated mechanisms for renin and blood pressure reductions.

However, conflicting data suggest that a solitary β-1 cardiac mechanism for the hypotensive effect of propranolol is not conclusively established. A correlation between the hypotensive response to 1-sarcosine 8-alanine angiotensin II and propranolol in hypertensive patients has been reported by Streeten et al (152), supporting an earlier correlation between propranolol response and renin subgroup classification by Bühler et al (127). Recent reports by Pettinger and co-workers (155, 156) have also concluded that lowering of blood pressure following addition of propranolol to antecedent vasodilator drugs is mediated by the former compound's inhibition of vasodilator-induced renin relase, because 1-sar-8-ala angiotensin II infusions potentiated the vasodilator-induced hypotensive response before but not after propranolol therapy in rats and hypertensive humans. Furthermore, the "short feedback" direct inhibition of renin release by angiotensin II was thought to be proximal to the site of propranolol inhibition of renin release in these studies, as propranolol failed to prevent the 1-sar-8-ala–induced rise in plasma renin activity (156).

CLASSIFICATION OF HYPERTENSION BY RENIN VALUES

The use of the plasma renin determination has proved of some value in defining subpopulations of hypertensive patients with characteristic physiologic traits. Patients found to have a plasma renin activity subresponsive or nonresponsive to appropriate stimuli, including upright posture alone or combined with dietary sodium restriction or various drugs stimulatory to renin release, have been classified as low renin hypertensive, and have attracted much recent attention. Variations in methods of definition of this low renin group have proved a source of difficulty in comparison of data from different laboratories. A standardized technique of in-hospital dietary sodium restriction (10 meq per day) for three to five days and subsequent renin determination before and after four hours of upright posture is often inconvenient, whereas outpatient techniques using oral or intravenous furosemide have been used with moderately good agreement with the dietary technique (61, 157–159). However, Drayer et al (160) have noted a poor correlation between the ability of oral furosemide and sodium restriction to identify low renin patients, although five days of oral chlorthalidone did compare well. It appears that when diuretics [or hypotensive agents (66)] are used to stimulate renin release and to

identify low renin patients, their administration must be standardized and shown to compare with the results of sodium restriction. The technique of an ad libitum sodium intake with indexation of the plasma renin activity against the measured 24 hr sodium excretion as used by Brunner et al (161) is probably insufficiently discriminating to identify accurately the low renin group, especially with sodium intakes near or above 150 meq per day.

The assumption that low renin hypertension is a stable, well-defined state may not be valid. Crane et al (162) have found that fully 22% of patients they defined as belonging to the low renin group had normal renin responsiveness on retesting. Analysis of the data of Brunner et al (163) by Dunn & Tannen (164) determined that one third of their patients did not have reproducible renin determinations, and Genest et al (165) have noted an inconsistent and variably suppressed plasma renin activity in many subjects. These findings suggest that the phenomenon of renin unresponsiveness may be labile for a given patient. Furthermore, the time when the renin determination is made may influence the value, since prolonged antecedent diuretic therapy may result in the elevation of renin activity, even in patients previously classified as being of the low renin type (158, 166).

Racial idiosyncrasies may affect the classification of hypertension by renin values. Black patients have a greater incidence of low renin hypertension; the frequency has been found to be 42% by Mroczek et al (167), 42% by Brunner (163), and 43% by Gulati et al (168), in contrast to an incidence of 9–30% (165–170) in white populations. The degree of renin stimulation by furosemide also appears lower in normotensive and hypertensive blacks than whites, as shown by Kaplan's group (171), suggesting fundamental racial differences in the renin response.

The age and sex of patients appear to influence the renin classification. Crane and co-workers (162) found twice as many females as males in his hypertensive low renin group; Gulati et al (168) found a male to female ratio of 1:1.2; and Mroczek (167) found 75% of their low renin patients to be female. Several studies have shown that the low renin hypertensive state is correlated with the age of the patient. Gulati (168) reported a significantly higher incidence in his older than 50 group for both races compared to younger groups. Genest et al (169a) and Tuck et al (169) have found that approximately 9% of 20- to 30-year-old essential hypertensives are of the low renin type (compared to age-matched normal controls), compared to about 30% in the 35–65 year age group similarly matched. In addition, Tuck and co-workers (169) demonstrated a correlation of a low renin subgrouping with level of diastolic pressure. An increased frequency of low renin hypertension in older patients may reflect the known decline in renin responsiveness in normotensive humans with advancing age (172) or may relate to a subtle renal or adrenal defect impairing sodium excretion, which some workers (94) feel is established in the hypertensive state over a period of time.

Finally, the inherent lability of the renin-angiotensin system combined with the variability of the renin determination itself can make reproducible values for classification difficult, especially in distinguishing a high from normal renin value. Even indexation against an outpatient timed urinary sodium excretion, which has not

been established to accurately reflect average daily sodium intake, leaves much room for uncertainty of classification, especially since Laragh and colleagues (172a) collect the major fraction of urine (21 hr of the 24 hr volume) *after* the corresponding renin determination.

Renin as a Prognostic Factor for Cardiovascular Disease

The pretreatment plasma renin activity has been proposed as a prognostic factor for the development of subsequent morbid cardiovascular events in hypertensive patients by Brunner et al (163). Their study of 219 hypertensive patients observed retrospectively over a ten-year period revealed that 59 low renin patients suffered no heart attacks or strokes in this interval, whereas 11% of the normal renin group and 14% of the high renin group did incur one of these events. This original study has been criticized on several grounds (165, 174). One is a lack of comparability between the normal control group (used to define the boundaries between a normal and abnormal renin profile) and the hypertensive patients. The normal control group contained no blacks, whereas the hypertensive patients were 27% black, and this racial group appears to have a higher incidence of hypertension and its resultant complications despite a greater frequency of suppressed renin activities (175). Furthermore, the high renin group contained patients with higher blood urea nitrogen levels and mean diastolic pressures, implying both established renal (and vascular) disease and increased risk from the level of blood pressure. Other criticisms have pointed out (*a*) that misleading conclusions have been arrived at because of the retrospective nature of the study, because a heart attack (by an alteration in cardiac output and vascular dynamics) or stroke may have altered the plasma renin activity (and subgroup classification) or established renal vascular or glomerular disease at the time of the renin determination may have changed a given patient's past renin profile; (*b*) that low renin essential hypertensive patients respond well to antihypertensive therapy, especially diuretics (176), implying a correlation with blood pressure control; (*c*) that a renin subgroup classification is labile, since renin levels may change unpredictably (162, 165) or decline with age.

More importantly, however, the conclusion that low renin essential hypertensive patients are at lesser risk for a morbid cardiovascular event has not been supported by subsequent independent studies (165, 167, 168, 177–179) save one (180) with major qualifications. Although these studies have employed varying techniques for the renin determination and for provocative testing, and have used differing definitions of a normal, low, or high renin classification for the hypertensive group, their conclusions are surprisingly similar. Most classify approximately 20–30% of hypertensive patients as being of the low renin type, and find a similar incidence of vascular complications in the low and normal renin groups. The speculation that a low plasma renin activity is protective against strokes or heart attacks, allegedly by a lesser degree of vascular damage from circulating renin, is not supported by these reports. Also deemed improbable is the implication that an induced rise in the plasma renin from treatment may be harmful, for Doyle and co-workers (179) have reported that those low renin patients with a plasma renin stimulated into the

"normal" range by chronic antihypertensive therapy suffered an incidence of morbid events similar to that suffered by patients whose plasma renin remained suppressed.

That a low renin essential hypertensive patient may be at lesser risk than his normal or high renin counterpart will not be disproved until prospective studies are completed that match age, sex, race, and degree of blood pressure control in the comparison groups; that employ standardized techniques for both renin subgroup classification and the renin determination; and that establish a stable renin profile (if this is possible) during antihypertensive therapy. Until then, all patients with fixed diastolic hypertension, regardless of their renin profile, are best treated to attain maximal practical blood pressure control, since most evidence indicates that the elevated blood pressure itself is the most significant risk factor for mortality (184) and cardiovascular morbidity, including heart attack (185), stroke (186), and congestive heart failure (187), and that effective blood pressure control does lessen the incidence of strokes (184, 185) and possibly myocardial infarctions (183).

Renin as a Guide for Evaluation and Therapy

The plasma renin activity is useful as a guide in several stages of the evaluation of hypertensive patients. A major objective of the modern clinical evaluation of hypertension is to identify currently known curable causes of the hypertensive state, not so much to effect immediate correction of the primary abnormality (although this is usually done), but to provide the physician with information to aid his management of the patient. Virtually all of the secondary hypertensive states can be successfully controlled with currently available drugs, as an alternative to surgical correction of such diverse conditions as renovascular hypertension, an aldosterone-producing adrenal adenoma, or even a pheochromocytoma for a limited period. But if the alternative of life-long pharmacotherapy is deemed too great a burden or risk to the patient, as it most often is, surgical therapy may hold reasonable promise for a permanent cure. Expanded arguments for (188, 189) and against (190, 191) a vigorous search for secondary hypertension may be found elsewhere. The plasma renin activity aids in such an evaluation by the presence of abnormally high or low values.

A low plasma renin activity is seen in a variety of secondary hypertensive states characterized by the production of excessive amounts of adrenal mineralocorticoids, with excessive distal renal tubular sodium retention and sustained expansion of the extracellular fluid volume, thus leading to chronic renin suppression (192, 193). An often associated hypokalemia is from the mineralocorticoid-induced kaliuresis (193). Known causes of mineralocorticoid-induced low renin hypertension include aldosterone overproduction from an adrenal adenoma or bilateral hyperplasia of the adrenal cortex or zona glomerulosa (194), 11-deoxycorticosterone (DOC) overproduction either from a 17α-hydroxylation deficiency (195) with associated elevations of corticosterone (B) and 18-hydroxycorticosterone or as an isolated non-ACTH-dependent overproduction (196), 11β-hydroxylation deficiency in children with

DOC and 11-deoxycortisol overproduction (197), and mixtures of mineralocorticoids with adrenal carcinomas (198) or ectopic ACTH-producing tumors. Overproduction of 18-hydroxy-DOC in some patients with low renin hypertension has been reported by Melby et al (199) and Genest et al (200), and recently Liddle et al (201) have reported increased urinary excretion of the C-19 steroid 16β-hydroxydehydroepiandrosterone (16β-OH-DHEA) in some patients with low renin hypertension, shown by them to be a weak mineralocorticoid in adrenalectomized rats, although others report a lack of binding of this compound to the renal mineralocorticoid receptor (201a). However, the elevated secretion of 18-OH-DOC and 16β-OH-DHEA is not yet a firmly established cause of low renin hypertension owing to an as yet incomplete confirmation of their reported oversecretion and to the lack of a demonstrated mineralocorticoid effect of these compounds in man.

The postulated existence of excessive mineralocorticoid activity in patients with low renin essential hypertension is a topic stimulating active current research, as much direct and indirect evidence, reviewed elsewhere (164, 170), suggests such a possibility. Some workers suggest that the secretion of an "abnormal" steroid may be responsible (199, 201–203). Other evidence suggests a disordered regulation of aldosterone metabolism, since plasma levels and secretion rates for aldosterone are not found depressed appropriate to the low renin levels (204–206), or a decreased metabolic clearance rate for aldosterone may be a contributory factor (207), possibly from an altered binding to a plasma globulin fraction as recently shown by Nowaczynski et al (208).

Other mechanisms have been postulated to account for the renin unresponsiveness of low renin essential hypertension. Laragh and colleagues (209) have suggested that an impairment of the ability to normally excrete potassium may be at fault, although little available data support and many studies discount this explanation, as reviewed elsewhere (164). An impaired peripheral β-adrenergic responsiveness has been proposed, with the suppression of renin merely reflecting inadequate adrenergic renin release and the hypertension resulting from an unopposed α-adrenergic activity. An observed blunted rise in urinary norepinephrine excretion in such patients to postural stimuli (210, 211) suggests an adrenergic dysfunction, but further work is needed to explore this proposal. Finally, Schalekamp and co-workers (173) and others (169) argue that low renin essential hypertension may be but a late state of the hypertensive state itself, with a low plasma renin the result of a long-term effect of an elevated blood pressure on the kidney. Evidence supporting this view is a lack of bimodality in the frequency distribution of renin levels in hypertension (212) and the known inverse relation of renin activity to age in normotensive and hypertensive patients. Because individuals with low renin essential hypertension are quite probably a heterogeneous group, several pathogenic mechanisms may be involved.

A suppressed plasma renin activity can guide the evaluation of hypertensive patients first by providing an indication that available steroid measurements ought to be taken, most commonly a 24-hour aldosterone excretion during augmented sodium intake to detect the estimated 0.5% of hypertensive patients with primary

aldosteronism (189). Additional steroid determinations such as measurements of DOC, or 18-OH-DOC levels may provide evidence that a glucocorticoid-suppressible type of hypertension is present, such as partial or complete 17α-hydroxylase deficiency. And since chronic low dose dexamethasone therapy is generally without side effects and well tolerated, usually much more so than most other antihypertensive therapy, such a search may prove quite rewarding to the patient. Thus, a supressed plasma renin together with other clinical and laboratory data can aid in the detection and treatment of known causes of mineralocorticoid hypertension.

A low plasma renin activity is useful as a guide to the therapy of a patient with essential hypertension primarily as an indication that effective diuretic treatment must be begun. Many groups have observed that diuretics appear to effect a greater antihypertensive response in patients whose renin values are suppressed than in normal or high renin hypertensive patients (176, 213–215). And since such therapy if effective is relatively inexpensive and well tolerated compared to other drugs, the indication to so attempt blood pressure control may prove rewarding.

The reason for the sensitivity of low renin essential hypertensive patients to diuretic treatment is controversial. Some have taken this observation as evidence that such patients possess a volume-expanded type of hypertension and that diuretics correct this primary abnormality by inducing volume depletion. Whereas some types of hypertension such as fluid retention from chronic renal failure (216), primary aldosteronism (217), and 17α-hydroxylase deficiency (195) clearly represent volume-mediated hypertensive states, many reports of direct measurements of plasma and extracellular fluid volumes and exchangeable sodium spaces have not produced convincing evidence that low renin essential hypertension is so mediated. For example, the data of Jose et al (89), Helmer & Judson (218), Birkenhäger and co-workers (219), and Woods et al (202) all show no significant difference between the plasma or blood volumes of low- compared with normal-renin essential hypertensive patients. Measurements of the exchangeable sodium space by Schalekamp and co-workers (216) are not different for the two groups, conflicting with an earlier report by Woods et al (202), that low renin hypertensives possess a larger space than do normal renin patients, although no difference was found between the low renin group and their matched controls. The sum of results from most studies fails to support the presence of an expanded extracellular fluid volume in low renin hypertension, most certainly not of a degree comparable to that of established hypermineralocorticoid states.

The response to spironolactone therapy by low renin essential hypertensive patients is of special interest partly as supporting evidence for an occult hypermineralocorticoid state. Yet several groups (176, 213–215) report comparable efficacy to the more conventional diuretics, which suggests that a nonspecific natriuresis and not an antagonism to occult mineralocorticoids is responsible for the action of the drug. In view of the high doses of spironolactone (200–400 mg per day) necessary for blood pressure control in such patients and the consequent expense and relatively higher incidence of undesirable side effects than with other diuretics, the latter drugs are best tried first.

The presence of a high baseline plasma renin activity in a hypertensive patient usually prompts a search for a correctable renal or renovascular abnormality, and thus may be of aid in detecting the estimated 5% incidence of a renovascular cause among an unselected hypertensive population (189). Yet the absence of a peripheral venous renin elevation does not exclude renovascular disease, since approximately 40% of patients with such hypertension have a normal baseline renin value (220), and up to 15% may remain normal after stimulatory maneuvers (221). Selective renal venous renin determinations and presence of a greater than 1:1.5 ratio of uninvolved to involved side values are the current criteria for detection and operability of renal and renovascular hypertension.

Studies with 1-sar-8-ala angiotensin II by Streeten et al (152) on unselected hypertensive patients have shown that most (13 of 16) reacting with a hypotensive response had an elevated baseline plasma renin activity, and that all had some type of renal or renovascular disorder. Such results suggest that high renin *essential* hypertension may be a misnomer, as a renal abnormality may be common to all such patients, concordant with earlier findings by Hollenberg et al (222) that patients with high renin essential hypertension without overt structural lesions by arteriography possessed renal cortical ischemia by ^{133}xenon washout techniques. Moderately advanced renal disease and hypertension without marked azotemia or fluid retention, such as in some cases of chronic pyelonephritis, may occasionally be associated with a suppressed renin activity (O. Kuchel and J. Genest, unpublished observations) and bilateral renal artery stenosis may also be associated with low or normal peripheral renin values (223). Hypertension from a renin-producing renal tumor has recently been reported by Hollifield and colleagues (224) with a normal peripheral plasma renin value (although previously reported cases of reninomas have noted elevated peripheral renin activities). Such reports illustrate that the peripheral renin value may be an inconsistent marker, and although this fact can be valuable as a piece of diagnostic information, it does not rigidly define subgroups of patients with essential or secondary hypertension.

The presence of an elevated renin value as a guide to the selection of specific antihypertensive drugs has been proposed by some workers in an attempt to direct specific "antirenin" therapy against the presumed pathophysiologic state (225). Such an approach is intellectually appealing but is often not appropriate to our current inadequate knowledge about essential hypertension. As mentioned above, the hypotensive response to the antiadrenergic drugs is quite probably not via their effect on the plasma renin activity. But most importantly, the blood pressure of almost all essential hypertensive patients can be controlled by an empiric approach, as by the initiation of diuretic therapy followed by an antiadrenergic drug, with the later addition of vasodilators if necessary. Such a scheme produced the impressive reduction of morbidity in the Veterans' Administration Cooperative Study (181, 182) and other workers have testified to its efficacy. But since the degree of successful response to antiadrenergic drugs alone has been shown to correlate with an antecedent elevated renin activity, the use of such agents by themselves may be of value for patients with an elevated renin activity who are intolerant of other drugs or not compliant with a multiple drug regimen.

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