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The Pharmacologic Alteration of Renin Release* † ‡

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* This review is dedicated to Dr. Andres Goth on the occasion of his retirement after 25 years as Chairman of the Department of Pharmacology of the University of Texas Southwestern Medical School, Dallas.

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I. Introduction

In 1934, Goldblatt and his co-workers (392) reported that persistent arterial hypertension could be produced by constriction of the renal artery and suggested that a circulating pressor substance of renal origin served as a mediator of the hypertension. It was soon determined that the substance "renin," which was originally described as a pressor agent of renal origin (1094), was actually an enzyme that catalyzed the formation of a peptide with potent vasoconstrictor properties (861). Braun-Menéndez et al. (129) confirmed that the pressor substance found in the venous blood of ischemic kidneys was the same as that formed when renin was incubated with blood proteins. This peptide was called either "angiotonin" (861) or "hypertensin" (129) until 1958 when the compromise term "angiotensin" was suggested (130). After synthetic angiotensin became available in 1957 (162), it was discovered that the compound possessed numerous pharmacologic activities, each of which could contribute to the elevation and maintenance of blood pressure (61, 82, 92, 108, 275, 544, 545, 575, 580, 599, 789, 863, 879, 998, 1162, 1272).

With the development of sensitive radioimmunoassay

techniques for the measurement of angiotensin I(AI) and angiotensin II(AII) a great volume of literature appeared concerning the physiologic control of renin release and its relationship to human hypertension. In the course of these studies it became apparent that the amount of renin circulating in the blood was the major rate-limiting step in the formation of AII. Finally, interest in the relationship between the renin-angiotensin system and hypertension was spurred by the advent of selective competitive antagonists of AII in the early 1970s (698, 872, 1244). These receptor blocking agents soon became a major tool in defining the role of angiotensin in experimental [see Davis et al. (257) for a review] and clinical (151, 152, 895, 1057) hypertension. As clinical and experimental studies on the role of the renin-angiotensin system in the etiology of hypertension have progressed, it has become apparent that antihypertensive drugs and other therapeutic agents alter the rate at which renin is released from the kidney. More important, these drug-induced changes in circulating renin activity can limit or alter the pharmacologic response to antihypertensive agents.

Despite the fact that the scientific literature concerning the physiology and pharmacology of renin release is voluminous, a critical evaluation of the mechanisms by which drugs alter renin release has not been published to date. It has been some time since Braun-Menendez (128) and Peart (881) reviewed the subject of renin release in this JOURNAL, and these reviews dealt more with the pharmacology of AII. An excellent review has been published recently concerning the physiologic control mechanisms governing renin secretion (256), but the authors have emphasized the effect of physiologic perturbations on the rate of renin release rather than the mechanisms by which drugs alter renin release. The importance of renin in the etiology and treatment of hypertension, the publication during the past 20 years of a large volume of primary research data concerning the mechanisms that control renin release, and the alterations of renin release induced by a wide spectrum of drugs indicate that a review of the mechanisms by which pharmacologic agents affect renin release is timely and appropriate.

This review consists of a survey of the literature through 1979.

A. Scope and Definitions

We will use the term "renin release" to indicate the movement of renin molecules from the granular juxtaglomerular cells of the kidney, where renin is synthesized and stored, into the blood flowing through the afferent glomerular arteriole. By the strictest definition, renin secretion is the "minute output of renin by the kidney into the renal vein" (256), and is calculated by multiplying the renin plasma flow times the renal vein plasma renin activity minus the aortic plasma renin activity. Here the term "renin secretion" will be used only when true secretion rates have been determined or when renin is secreted from renal tissue slices in vitro.

In our analysis of reports of primary data, we have assumed that changes in plasma or serum renin activity, as measured in samples of peripheral blood, are a faithful reflection of changes in the amount of renin released into the renal afferent arterioles. Furthermore, we have used the word renin to refer to the proteolytic enzyme released from the kidney and not the renin isozymes found in other tissues such as the uterus (85), brain (374a), and salivary gland (1203). Renin also has been identified in the arterial wall and a portion of this renin is of renal origin (1093a).

It has been impossible to include each report that has dealt with the changes in renin release caused by certain drugs, e.g. furosemide, because of the enormous number of papers published. We have attempted to examine in detail those papers that 1) provide historical perspective, 2) delve into the mechanism by which certain drugs alter renin release, or 3) include comparisons between different drugs or classes of drugs. With regard to animal studies, we have stressed those experiments performed with conscious animals since anesthesia causes artifactual changes in renin release that can and have complicated the interpretation of experimental results. Finally, areas in which further experimentation is required to clarify the mechanisms by which certain drugs alter renin secretion have been pointed out with the hope of stimulating new investigations into this fascinating subject.

B. Abbreviations

AI = angiotensin I
AII = angiotensin II
AVP = arginine vasopressin
ECF = extracellular fluid
GFR = glomerular filtration rate
JG = juxtaglomerular
MAP = mean arterial pressure
PG = prostaglandin
PRA = plasma renin activity
PRC = plasma renin concentration
RBF = renal blood flow
RPF = renal plasma flow
SHR = spontaneously hypertensive rat
SRA = serum renin activity
SRC = serum renin concentration

C. Anatomy of the Juxtaglomerular Apparatus

A brief description of the anatomical relationship of the structures comprising the juxtaglomerular apparatus or complex is prerequisite for any discussion of the mechanisms controlling renin release. More detailed descriptions of the anatomy of the juxtaglomerular apparatus may be found elsewhere (51–53, 81, 447, 450, 636, 820). Each nephron has a region known as the juxtaglomerular (JG) apparatus, which is composed of 1) granular cells, 2) the macula densa, 3) agranular cells, and 4) mesangial cells (fig. 1).

The granular JG cells, which synthesize, store, and secrete renin, are differentiated smooth muscle cells that

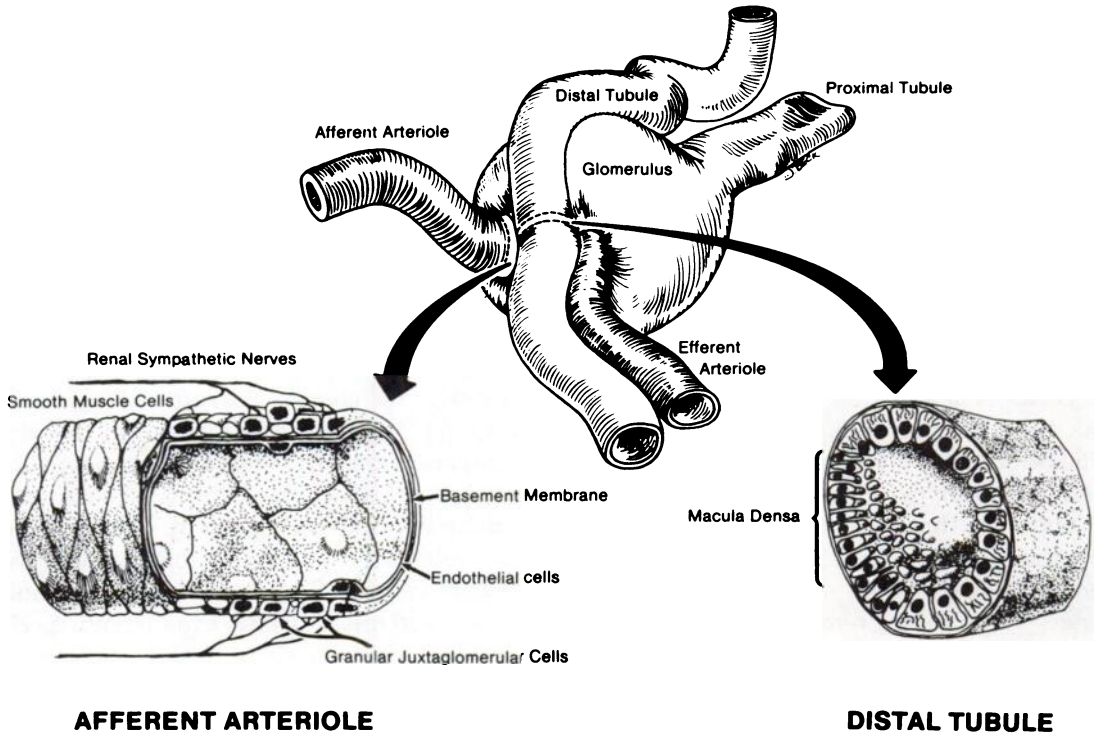

FIG. 1. The anatomical relationship of the granular juxtaglomerular cells, which synthetize and release renin, and the afferent arteriole, renal sympathetic nerves, and the macula densa cells of the distal tubule. This figure is adapted from Barajas et al. (51, 52, 53) and Netter (789a).

are usually found in the media of the renal afferent arteriole just adjacent to the glomerulus. Granular JG cells are sometimes found in the wall of the efferent arteriole and among the mesangial cells, but their presence in the afferent arteriole is more prominent. Myofibrils, which are characteristic of vascular smooth muscle cells, are observed in the granular JG cells. The granules found in these cells are relatively homogeneous and dense and are membrane bound. The granular JG cells have a well-developed endoplasmic reticulum and Golgi membranes, cytologic characteristics that are consistent with an endocrine function. The renal sympathetic nerves innervate the granular JG cells (fig. 1).

The macula densa segment of the distal tubule, a specialized group of heavily nucleated cells located on the glomerular side of the tubule, always lies in close contact with the vascular pole of the glomerulus from which the tubule originates (fig. 1). The cells of the macula densa, which may be columnar or cuboidal depending on the species studied, mark the transition from the ascending limb of the loop of Henle to the distal tubule. As the ascending limb of the loop of Henle approaches the glomerulus, it runs parallel with the efferent arteriole for some distance and then comes into brief contact with the afferent arteriole before becoming the convoluted portion of the distal tubule. The cells of the macula densa are in close contact with the granular JG cells of the afferent arteriole.

In the angle formed by the entrance of the afferent arteriole and the exit of the efferent arteriole of each glomerulus is a cell mass, termed the Polkissen or "polar mass," consisting mostly of agranular and occasional granular cells. These agranular JG cells are continuous with the cells composing the walls of the afferent and efferent arterioles, where they may replace some of the vascular smooth muscle cells, and they are in close contact with the macula densa. Like the granular JG cells, the agranular JG cells retain some of the cytologic characteristics of vascular smooth muscle cells. This JG cell mass extends to the glomerulus and becomes continuous with the mesangium of the glomerulus, i.e. the thin membrane that helps support the capillary loops in the glomerulus. A dense matrix between the cells of the JG apparatus binds them together in a compact mass closely adhering to the arterioles.

It also should be pointed out that at the hilus of the glomerulus, both the afferent and efferent arteriole have a lumen that is about two to five times the thickness of the vascular wall, but the wall of the efferent arteriole quickly thins to the point that the vessel resembles a thin-walled venule. The efferent arteriole then courses for some distance before branching into the peritubular capillaries.

D. Renin

A brief description of the enzymic steps involved in the renin-angiotensin system is an important prerequisite for readers not familiar with the subject of renin release. Renin is a proteolytic enzyme of approximately 40,000 mol. wt. that is released into the blood stream in response

to certain physiologic stimuli. Once in the blood, renin cleaves the leucyl-leucine bond that joins the amino-terminal decapeptide AI to the remainder of the renin substrate (also called angiotensinogen). Renin is synthesized and stored in the JG cells that line the afferent glomerular arteriole (fig. 1) whereas renin substrate (approximately 60,000 mol. wt.) is produced in the liver and is widely distributed in the blood and other extracellular fluids. After AI is released from renin substrate, converting enzyme (also known as kininase II) removes two amino acid residues from its carboxy-terminus to yield AII. The conversion of AI to AII was thought to occur predominantly in lung tissue, but it is now known that this reaction occurs in vascular endothelium (175a, 529a) throughout the body. In recent years, it has been discovered that the heptapeptide des-Asp-AII, which is formed from AII in vivo, also possesses many of the pharmacologic actions of AII. Goodfriend et al. (396) and later investigators (177) have suggested that the heptapeptide des-Asp-AII be called angiotensin III.

Angiotensin II has a very short half-life (~30 sec) in the blood (331) and its continued production is dependent on the presence of renin substrate and renin. However, the concentration of renin substrate in the blood is usually constant, and, in point of fact, it is the amount of renin circulating in the blood that is the major rate-limiting step in the production of AII in vivo. On the other hand, despite the fact that renin has a much longer half-life in the circulation (~4 to 15 min) (401, 421, 746, 813, 846, 894), a constant stimulus still is required to chronically increase the rate of renin release from the kidney.

Those readers interested in a more comprehensive review of the biochemistry of the renin-angiotensin system should consult Erdos (313) and Peach (878).

E. Brief Description of the Pharmacology of Angiotensin II

The octapeptide AII is a potent compound that has numerous pharmacologic effects, all of which are directed at increasing blood pressure. Its principal effect is that of vasoconstriction due to a direct action on vascular smooth muscle. In addition, AII increases cardiac contractility in vitro both by a direct action on the myocardium (108, 599) and by potentiating the release of norepinephrine from the cardioaccelerator nerves (108, 1036). By an action in the central nervous system, AII elicits an increase in efferent nerve activity to the peripheral sympathetic nervous system that results in an increase in cardiac output and total peripheral resistance (998), the two major determinants of blood pressure. Since the area postrema, which has been identified as one site of action of the central cardiovascular effects of AII (545), lies outside the blood-brain barrier, circulating AII has the potential to elicit these central nervous system-mediated events (1162). In addition, AII has remarkable dipsogenic effects when injected into the ventricular system of the brain (1006), but it is not known at this time whether circulating AII has free access to the receptors involved. In addition to increasing efferent sympathetic nerve activity through an action in the central nervous system, AII also can modulate the activity of the sympathetic nervous system in other ways. Angiotensin causes the release of epinephrine and norepinephrine from the adrenal medulla (879), facilitates the release of norepinephrine from the peripheral sympathetic neurons (1272), and blocks the uptake of norepinephrine by peripheral sympathetic neurons (580).

Aside from its vasoconstrictor effects, the best known and most widely studied action of AII is its ability to increase steroidogenesis in the zona glomerulosa of the adrenal cortex (61, 92). This action results in the increased production of the mineralocorticoid aldosterone (61, 92), which in turn acts in the distal tubule of the kidney to increase the reabsorption of sodium. As total body sodium increases, water reabsorption is increased and extracellular fluid volume is expanded. Along these same lines, AII itself possesses direct antinatriuretic effects at the tubular level when administered in small doses (789).

All of these effects of AII help to restore and maintain blood pressure when the body is threatened by hypovolemia and/or hypotension. Each of these effects of AII has a different response time and a different amount of gain in the maintenance of blood pressure. Thus, the direct and indirect "pressor" effects of AII represent a major homeostatic mechanism involved in the long-term maintenance and control of blood pressure. Against this background, it is apparent that drug-induced alterations of renin release are of great importance in experimental and clinical medicine.

F. Measurement of Plasma (Serum) Renin Activity and Plasma (Serum) Renin Concentration

Plasma renin activity is a measure of the ability of plasma to generate AI in vitro given the amount of renin and renin substrate present in the plasma sample (121, 429, 495). Plasma renin activity is usually expressed as nanograms of AI generated per milliliter of plasma per hour of incubation at 37°C (ng of AI/ml/hr) and is generally accepted as being a reflection of the level of activity of the renin-angiotensin system in vivo. Plasma renin concentration is a measure of the ability of plasma to generate AI in vitro given the amount of renin present in the plasma but with an excess of exogenous renin substrate (usually homologous) added to the sample. Plasma renin concentration is usually expressed as nanograms of AI generated per milliliter of undiluted plasma sample per hour of incubation at 37°C (ng of AI/ml/hr) and is generally accepted as being a reflection of the amount of renin circulating in vivo.

The kinetics of the reaction of renin with renin substrate has been thoroughly reviewed by Poulsen (915). However, several important points should be mentioned.

First, when renin activity is measured in samples that contain only endogenous renin and renin substrate, the reaction does not obey zero order (substrate-independent) kinetics. That is to say that "renin activity" is not the same as "renin enzyme activity" since the rate of generation of AI in vitro is dependent on the concentration of endogenous renin substrate as well as the amount of renin present (915). Thus, an increase in the circulating levels of renin substrate can lead to an increase in PRA even though the amount of renin in the plasma remains constant. This adherence to first-order kinetics by renin stems from the fact that the concentration of renin substrate in plasma is not high enough to result in substrate saturation (915). This problem can be circumvented by adding homologous renin substrate to plasma samples before their incubation at 37°C as is done in the measurement of PRC. However, even the addition of homologous substrate does not ensure that zero-order kinetics will always be obtained when measuring PRC [see Poulsen (915) for a complete discussion], so PRC cannot necessarily be considered to be an accurate physiologic index of the number of renin molecules circulating in the blood.

During short-term experiments with animals or humans, changes in PRA are almost always due to a change in the rate of renin secretion from the kidney since the concentration of plasma renin substrate is not subject to rapid changes. However, during long-term therapy, an increase in PRA may potentially be due to an increase in the production of renin substrate by the liver (175). If the investigator believes this to be the case, it is possible to measure the renin substrate concentration as well as PRA and PRC of a single plasma sample (725, 916). To a certain extent, the measurement of PRC obviates the need to determine all three of these parameters since variations in the endogenous concentration of renin substrate (unless the concentration is very high or very low) will have little effect on the PRC value obtained. It should be emphasized that many researchers consider PRA to be the most desirable parameter to measure since they consider this value to be an accurate reflection of the ability of the system to generate AII in vivo and thus to induce physiologic changes (70). For those researchers more interested in changes in the amount of renin released by the kidneys, regardless of its ultimate physiologic effects, PRC may be the more desirable parameter to measure. Whether measuring PRA or PRC, incubation times for the generation of AI should be kept as short as possible to ensure a linear rate of production of AI.

Although PRA and PRC were originally determined by a pressor-bioassay system in anesthetized rats treated with a ganglionic blocking drug, most studies performed during this decade have involved the measurement of AI by radioimmunoassay. The use of radioimmunoassay as a quantitative technique for measuring the concentration of circulating hormones was first described by Berson and Yalow (76, 1239) in 1957. Berson and Yalow (77) and Skelley et al. (1019) should be consulted for a basic review of the principles of radioimmunoassay. The reader may wonder why the rate of generation of AII in vitro could not be used to measure PRA. If PRA is to be determined by this method, angiotensin converting enzyme must be present, and it is not possible to inhibit the plasma angiotensinases selectively without also inhibiting converting enzyme. However, the simultaneous inhibition of plasma angiotensinases and converting enzyme does allow AI to accumulate and be measured.

Finally, for those readers interested in the relationship between PRA values determined by bioassay versus those obtained by radioimmunoassay, Sealey et al. (1000) have made a thorough study of the problem. Although a high degree of correlation ($r = .91$) was noted between PRA values obtained by bioassay and immunoassay, the immunoassay values were 2.2 times higher than those determined by bioassay. This disparity results from 1) the use of AII as the standard for most bioassay systems despite the fact that AI is being injected from the incubated plasma samples, 2) the 1.7 times greater pressor effect of AII as compared to AI when equal *weights* are compared, and 3) the longer time of incubation of plasma usually used in the bioassay technique.

With few exceptions, an increase in PRA levels leads to an increase in PRC. If PRA values are plotted against PRC values within a set of plasma samples ($n = 24$), a linear relationship ($r = .96$) is obtained with PRC values being approximately 1.7 times greater than their corresponding PRA values. This relationship was observed between PRA values of 2 to 100 ng of AI/ml/hr (K. Keeton, unpublished observations). Other researchers have noted a high degree of correlation between PRA and PRC (600). However, several drugs, e.g. oral contraceptives, have been found to alter this relationship, as will be discussed in subsequent sections.

II. Physiologic Control of Renin Release

An understanding of the basic physiologic mechanisms controlling renin secretion is a prerequisite for a discussion of drug-induced alterations of renin release. During the past 20 years, five basic mechanisms controlling renin release have been described. They are 1) an intrarenal baroreceptor, 2) the amount of sodium (or possibly chloride) ion sensed by the macula densa segment of the distal tubule, 3) the sympathetic nervous system and humorally released catecholamines, 4) other hormonal factors (e.g. angiotensin II, prostaglandins, steroids), and 5) plasma electrolytes (e.g. potassium, calcium).

A. Intrarenal Vascular Receptor or Baroreceptor

In 1934 Goldblatt and his co-workers (392) induced experimental hypertension in dogs by constriction of the renal arteries, and they suggested that the resultant renal ischemia led to release or formation of a circulating

pressor substance that served as a mediator of the hypertension. This first suggestion of renin release in response to a decrease in renal blood flow (RBF) was followed some years later by studies that suggested that a decrease in pulse pressure amplitude was the stimulus for increased renin secretion into venous blood (601). Interest in the subject was renewed in the late 1950s when Kolff (602) reported that renin was released in response to constriction of the renal artery whether flow was pulsatile or nonpulsatile.

A short while later, Tobian et al. (1098) proposed the existence of a renal baroreceptor that either increased or decreased renin secretion in response to a decrease or increase in mean renal perfusion pressure, respectively. They noted that juxtaglomerular cell granulation, i.e. renin content, decreased in association with an increase in renal perfusion pressure (1098). In a review (1096) of the evidence for this hypothesis, Tobian suggested that renin release from the granular cells of the JG apparatus was inversely related to the amount of stretch of the renal afferent arterioles, and that the amount of stretch was in turn determined by the mean renal perfusion pressure. However, "degranulation" of the JG cells also could have resulted from changes in RBF and/or GFR.

The first systematic studies concerning the effect of renal hypotension on renin release were performed by Skinner et al. (1023) Progressive renal arterial hypotension was produced in anesthetized dogs by a graded constriction of the aorta above the renal arteries. This resulted in a decrease in renal vascular resistance during renal autoregulation and was associated with an increase in renin secretion. Furthermore, when the decrease in blood pressure was associated with an increase in pulse pressure, as elicited by vagal stimulation and sympathetic blockade with bretylium, renin secretion was still increased.

In order to obviate the effects of sodium transport on renin release (see discussion of the macula densa mechanism controlling renin release in section II C), Blaine et al. (98) developed the nonfiltering canine kidney to explore the baroreceptor hypothesis. They found that both hemorrhage and suprarenal aortic constriction in conscious dogs elicited an increase in PRA in the absence of a functional macula densa (98). To isolate further the vascular receptor, renal denervation and bilateral adrenalectomy were performed during preparation of the nonfiltering kidney (97). Even after removing the influence of the macula densa, the renal sympathetic nerves, and humoral catecholamines, hypotensive hemorrhage and suprarenal aortic constriction still produced a significant (2-fold) increase in PRA in *conscious* dogs (97). To date, this study remains the most convincing evidence for the existence of a renal vascular pressure receptor controlling renin release. The tentative location of the renal baroreceptor was determined to be at the level of the afferent arteriole since papaverine, which prevents renal autoregulation by dilatation of the renal afferent arterioles, blocked hemorrhage-induced renin secretion from denervated, nonfiltering kidneys in anesthetized dogs (1231).

According to Tobian's "stretch" receptor hypothesis, high renal perfusion pressure or renal (afferent arteriolar) vasodilatation would stretch the walls of afferent arterioles (673). The JG cells also would be stretched, since they are located in the media of the afferent arterioles, and this increased stretch would result in a decrease in renin secretion. One of the major criticisms of this hypothesis was the subsequent observation by various investigators that either systemic or renal arterial hypotension-induced renin release was usually associated with renal vasodilatation (237, 301, 304, 405, 421, 446, 586, 987). As mentioned previously, Skinner et al. (1023) found this to be the case when renal perfusion pressure was decreased by constricting the aorta above the origin of the renal arteries in the anesthetized dog. Schmid (987), also in anesthetized dogs, found that lowering renal perfusion pressure from 128 to 88 mm Hg caused a 2-fold increase in renin secretion, a drop in renal vascular resistance, and no change in RBF or GFR. As renal arterial pressure was lowered to 70 mm Hg, RBF and GFR decreased while renin release continued to increase. However, in the latter case the decrease in GFR would lead to stimulation of renin secretion by the macula densa mechanism. In order to eliminate the cardiovascular control loops of the central nervous system, Cowley and Guyton (237) studied renal arterial hypotension-induced renin secretion in dogs after spinal cord destruction and decapitation. These decapitated dogs received a constant infusion of norepinephrine to maintain blood pressure. It should be pointed out that the renal vasoconstriction produced by an intrarenal infusion of AII or norepinephrine or an increase in sympathetic nerve discharge does *not* influence the autoregulatory vasodilatory response to a reduction in renal perfusion pressure (586, 588). A 2- to 3-fold increase in renal venous renin activity occurred when renal perfusion pressure was decreased from 100 to 80 mm Hg by a clamp on the renal artery, even though RPF was maintained. Net renin secretion continued to rise until perfusion pressure was dropped to 65 to 70 mm Hg, and then secretion remained constant due to the fact that the RPF decreased radically whereas renal venous renin activity continued to increase (237).

In anesthetized dogs with a single denervated nonfiltering kidney, Gotshall et al. (405) found that suprarenal aortic constriction, sufficient to reduce renal arterial pressure by 20%, induced a 3-fold increment in the rate of renin secretion without altering RBF. Further decrements in perfusion pressure resulted in a decrease in renal vascular resistance and a further increase in renin secretion despite the fact that RBF dropped considerably. Similarly, Eide et al. (301), by progressive constriction of the renal arteries in intact anesthetized dogs, determined that the lowest perfusion pressures at which RBF and GFR were autoregulated were 66 ± 3 and 72

± 8 mm Hg, respectively. Decreasing perfusion from 116 to 66 mm Hg resulted in a 7-fold increase in the rate of renin secretion; however, a further reduction to 44 mm Hg led to no additional increment in renin secretion. When renal perfusion pressure was lowered below the autoregulatory range for RBF and GFR, infusion of sufficient mannitol or isotonic saline to restore sodium excretion to above control levels failed to suppress the 7-fold increase in renin secretion (301). However, a very high sodium load will inhibit renin release even if secretion is stimulated by constriction of the renal artery (586). These studies indicate that renin secretion during renal autoregulation becomes maximal when the arterioles are maximally dilated and that this release mechanism is independent of renal sodium metabolism. It is also of interest to note that more than half of the increase in renin release elicited by renal arterial hypotension occurred within the lowest 15 mm Hg of the range of renal autoregulation of blood flow (301).

Since anesthesia per se has been shown to reduce RBF (106, 279, 683, 953, 1141, 1237) and increase renin release (373, 537, 643, 702, 896, 903), the effect of renal arterial hypotension on renin release also has been examined in conscious, chronically cannulated dogs (353, 421, 446). It should be mentioned, however, that while these studies have provided valuable information, no attempt was made to control the influence of the macula densa on renin release. When renal arterial pressure was decreased in conscious dogs from 107 to 75 mm Hg by an externally controlled snare, a 4-fold increase in PRA resulted while renal vascular resistance decreased and RBF increased (446). Gutmann et al. (421) used an inflatable cuff around the renal arteries of uninephrectomized conscious dogs to decrease renal perfusion pressure from 92 to 79 mm Hg, and they observed an increase in PRA from 0.67 to 1.91 ng of AI/ml/hr, no change in RBF, and a decrease in renal vascular resistance. After release of the cuff, PRA decreased rapidly to control levels. With 81 measurements made between 5 min and 7 hr after constriction of the renal artery, a close inverse relationship was found when the log of PRA was plotted against the renal arterial pressure. This is very similar to the relationship between the rate of renin secretion and renal perfusion pressure observed by Eide et al. (301) in anesthetized animals. Unfortunately, Gutmann et al. (421) did not measure renal sodium excretion in their conscious dogs, and even if RBF was maintained during renal hypotension, we cannot be certain that sodium transport was not reduced enough to stimulate renin release by a macula densa mechanism. Fray et al. (353) found that PRA was elevated 9-fold when the renal arterial pressure of conscious dogs was decreased from the control MAP of 77 mm Hg down to 50 mm Hg. During this maneuver, systemic MAP rose to 98 mm Hg due to the increase in PRA. Since control blood pressures were so low in these well-trained dogs, it is difficult to speculate as to whether autoregulation of RBF occurred at a perfusion pressure of 50 mm Hg. However, on the basis of similar studies in conscious dogs (421, 446), vasodilatation probably did occur but renal sodium excretion probably decreased. Thus, the 9-fold increase in PRA could have been due to activation of both the renal baroreceptor and macula densa mechanisms regulating renin release. Fray et al. (353) also discovered that prior salt depletion greatly potentiated the renin release caused by renal arterial hypotension whereas salt-loading blunted the response.

In contrast to the previously mentioned reports, the renin release induced by hypotensive hemorrhage was found to be associated with renal vasoconstriction in two studies (97, 1231). In dogs with a single denervated nonfiltering kidney, a rapid hemorrhage of 20 ml/kg increased PRA 2-fold in the conscious state (97). When the dogs were anesthetized, the same degree of hemorrhage increased renin secretion 5-fold. This degree of hemorrhage resulted in an average drop in MAP of 8 mm Hg in the conscious state and 47 mm Hg in the anesthetized state. Renal blood flow was not measured in the conscious state, but was decreased by 51% when the dogs were anesthetized despite the fact that mean arterial pressure (MAP = 76 mm Hg) remained above the minimum pressure necessary for renal autoregulation (301). However, it should be noted that the responses of RBF and MAP to hemorrhage are quite different in conscious and anesthetized dogs. Vatner and Braunwald (1140) have demonstrated that rapid hemorrhage (26 ml/kg) elicited renal vasodilatation in the conscious trained dog whereas it caused marked renal vasoconstriction in the anesthetized trained dog. This renal dilatation in the conscious dog during hemorrhage was not affected by renal denervation but rather appeared to be mediated by the intrarenal production of prostaglandins. In addition, after a hemorrhage of 20 ml/kg, the blood pressure of conscious trained dogs dropped 8 to 10 mm Hg whereas a decrement of 37 to 43 mm Hg was noted when the trained dogs were anesthetized (1140). Thus the blood pressure responses to a hemorrhage of 20 ml/kg observed by Blaine et al. (97) in conscious and anesthetized dogs were similar in magnitude to those observed by Vatner and Braunwald (1140). Based on these observations (1140), it is also likely that renal vasodilatation occurred in the conscious dogs subjected to hemorrhage by Blaine et al. (97). It also should be noted that anesthesia per se decreases RBF in trained dogs with chronically implanted cannulae, and this effect appears to be mediated by the intrarenal formation of AII since it was blocked by the selective angiotensin antagonist saralasin (170). It would be of great interest to know if an intrarenal infusion of papaverine could block hemorrhage-induced renin release in *conscious*, rather than anesthetized, dogs with a single denervated nonfiltering kidney.

In light of recent data, it is difficult to reconcile Tobian's original "stretch" receptor hypothesis with the fact that renal arterial hypotension-induced renin release is usually associated with increased stretch (autoregulatory

vasodilatation) of the renal afferent arterioles unless it is assumed that intravascular pressure rather than the radius of the afferent arteriole is the predominant factor that influences "stretch." Along these lines, Vander (1116) proposed that the actual baroreceptor stimulus to renin secretion might be 1) a decrease in the transmural pressure gradient (the difference between the intraluminal pressure and renal interstitial pressure), 2) a decrease in the tension within the wall of the afferent arteriole, or 3) a decrease in the intraluminal pressure of the afferent arteriole at the level of the juxtaglomerular granular cells. In point of fact, each of these variables are closely interrelated. In its simplest form, wall tension is the product of the transmural pressure gradient and the interior arteriolar radius (Laplace's law). By and large, a decrease in renal perfusion pressure, whatever its origin, will result in a decrease in intraluminal pressure and the transmural pressure gradient. Arteriolar wall tension may or may not change depending on how much the interior arteriolar radius changes in relationship to the change in intraluminal pressure. Since sympathetic stimulation, circulating pressor or depressor agents, or renal autoregulation affect arteriolar smooth muscle tone, i.e. interior arteriolar radius, they have the potential of altering intraluminal pressure, the transmural pressure gradient, and arteriolar wall tension. The transmural pressure gradient is usually controlled by renal perfusion pressure; however, an increase in renal interstitial pressure can decrease this pressure gradient. This being the case, several investigators (304, 550) have examined the effects of ureteral occlusion on renin release since this maneuver is known to increase renal interstitial pressure.

Kaloyanides et al. (550) found that clamping the ureter of an isolated blood-perfused canine kidney resulted in a 6-fold increase in renin secretion even though perfusion pressure was maintained at 100 mm Hg. If perfusion pressure was increased to 160 mm Hg while ureteral occlusion was continued, renin secretion fell back to control levels and RBF increased by 35%. If the experimental maneuvers were reversed, the suppression of renin release caused by a high renal perfusion pressure was counteracted by ureteral occlusion. Therefore, manipulation of the transmural pressure gradient did indeed elicit changes in the rate of renin secretion. In similar studies in anesthetized dogs with denervated filtering kidneys, Eide et al. (304) produced step-wise increments in ureteral pressure that caused step-wise increments in renin secretion despite the fact that RBF remained unchanged. More than half of the elevation of renin release took place during the final step in which ureteral pressure rose from 75 to 96 mm Hg. Complete ureteral occlusion caused ureteral pressure to rise to 95 mm Hg and renin secretion to increase 11-fold. Subsequent constriction of the renal artery sufficient to decrease renal arterial pressure radically resulted in no further increment in the rate of renin secretion and RBF fell off in proportion to perfusion pressure. In the absence of ureteral occlusion, renal arterial pressure had to be reduced to 65 mm Hg to stimulate renin secretion fully (13-fold increase), but if ureteral pressure was increased to 65 mm Hg by only partial occlusion, renin release became fully stimulated when perfusion pressure was dropped to 104 mm Hg.

Both ureteral occlusion and a decrease in renal perfusion pressure elicited afferent arteriolar dilatation, and thus RBF is not changed even though the transmural pressure gradient is lowered in both instances (304). In every case, maximal renin secretion occurred when the transmural pressure gradient was decreased enough to result in maximal afferent arteriolar dilatation. Although ureteral occlusion decreased sodium excretion, the renin release precipitated by this maneuver was not due to the macula densa mechanism since restoration of sodium excretion to control levels during partial ureteral occlusion did not blunt the increase in renin release (304). Renal interstitial pressure is usually quite low, but it can be increased enough during osmotic diuresis, high urine flow, renal venous pressure elevation, congestive heart failure, ureteral obstruction, or renal disease to result in a decrease in the transmural pressure gradient at the afferent glomerular arteriole. In each of these cases, high tubular or interstitial pressure elicits arteriolar dilatation until the hydrostatic pressure gradient across the glomerular membrane is reestablished, thereby maintaining GFR (589). In conclusion, a change in the transmural pressure gradient is a likely candidate for the baroreceptor stimulus to renin release.

Davis and Freeman (256) stated their belief that the intrarenal baroreceptor responds to changes in afferent arteriolar wall tension, but as Fray has pointed out (350), they presented no data or quantitative arguments to support this belief. They did, however, judiciously state that wall tension could be altered by "1) changes in the diameter of the renal afferent arterioles, 2) changes in the transmural pressure gradient, 3) renal sympathetic nerve activity that controls renal arteriolar tone, 4) intrinsic myogenic factors as exemplified in renal autoregulation, and 5) alterations in the elastic components of the vessel wall" (256). We previously stated that vascular wall tension is the product of the transmural pressure gradient and the internal arteriolar radius (Laplace's law). Since this form of Laplace's law applies only to thin-walled vessels, it cannot be applied to arterioles as their radius-thickness ratio can be 1:1 (343). As cogently pointed out by Fray (350), the circumferential (tangential) stress on the arteriole, which is expressed in either mm Hg or dynes/cm^2, is a more appropriate measure of wall tension since it takes into account the wall thickness of the vessel. The circumferential stress (σ_θ) can be calculated from the following formula derived by Fray (350):

$$\sigma_\theta = \frac{r_i^2 r_o^2 (P_i - P_o)}{r^2 (r_o^2 - r_i^2)} + \frac{r_i^2 P_i - r_o^2 P_o}{r_o^2 - r_i^2}$$

where r_i = internal radius, r_o = total radius, r = radius to

the point in the wall where the stress is exerted, P_i = intraluminal pressure, and P_o = interstitial pressure.

By using known values and making certain assumptions, values for wall tension (circumferential stress, σ_θ) can be estimated during both normotension and renal arterial hypotension.

Changes in internal radius (r_i) during renal autoregulation, in response to a drop in renal perfusion pressure, have recently been measured with great accuracy by Morkrid et al. (770), who used microspheres. When the renal arterial pressure of anesthetized dogs was reduced from an average of 129 to 69 mm Hg, the lowest autoregulatory pressure, the internal radius of the JG portion of the afferent arterioles increased from 8.7 μm to 10.7 μm (a 23% increase). Although the actual value of the intraluminal pressure (P_i) in the afferent arteriole during normotension and renal arterial hypotension cannot be determined from these experiments (770), the pressure drop from the renal artery to the glomerular capillaries of the Wistar rat has been determined to be approximately 50% of the MAP (138). While it is not known whether this pressure drop occurs in the interlobular arteries and/or the afferent arterioles (548, 770), it is apparent that the majority of the decrement in intraluminal pressure occurs proximal to the JG portion of the afferent arteriole. Robertson et al. (937a) have determined the effects of graded reductions in renal perfusion pressure on the hydrostatic pressure drop along the afferent arteriole. They found that the pressure (MAP minus glomerular capillary hydrostatic pressure) fell progressively with a slope of approximately 1 as renal perfusion pressure was lowered by partial constriction of the abdominal aorta in both plasma-expanded and hydropenic rats. Thus, the intraluminal pressure (P_i) of the JG portion of the afferent arteriole appears to decrease by the same absolute value (mm Hg) as does renal perfusion pressure during renal arterial hypotension. This being the case, if during normotension MAP equals 120 mm Hg and the afferent arteriolar pressure (P_i) in the JG area equals 60 mm Hg, then lowering renal perfusion pressure from 120 to 90 mm Hg would drop afferent arteriolar pressure in the region of the JG apparatus from 60 to 30 mm Hg, i.e., the same absolute change in pressure (937a). If we assume that interstitial pressure (P_O) under all pressure conditions is 5 mm Hg, that the wall thickness of the afferent arteriole is 5 μm during normotension (350), and that the granular JG cells are located in the media equidistant from the inside and outside of the arteriolar wall, then during normotension r_i would equal 8.7 μm (770), r_O would equal 13.7 μm, and r would equal 11.2 μm whereas during renal arterial hypotension r_i would equal 10.7 μm (770), r_O would equal 14.7 μm (wall thickness will decrease from 5 to 4 μm during vasodilatation), and r would equal 12.7 μm. Making these assumptions, the circumferential stress on the vascular wall in the JG portion of the renal afferent arteriole would be 88 mm Hg at control pressures (P_i equals 60 mm Hg), but would decline to 61 mm Hg when P_i falls to 30 mm Hg during renal arterial hypotension. This being the case, renal arterial hypotension would result in a 30% decrement in afferent arteriolar wall circumferential stress (tension) in the region of the granular JG cells since the decrease in intraluminal pressure would override the influence of the increase in arteriolar radius just as suggested by Davis and Freeman (256). Thus, the actual renal baroreceptor stimulus to renin release may be the change in arteriolar wall tension (circumferential stress).

Perhaps the most innovative study of the hemodynamic stimulus that activates the renal baroreceptor mechanism was conducted by Fray (350), who used the isolated rat kidney perfused with a Krebs-Henseleit solution containing albumin. He determined that decreasing renal perfusion pressure from 110 to 50 mm Hg for 60 min increased the cumulative perfusate renin activity 4-fold whereas increasing perfusion pressure to 160 mm Hg decreased renin accumulation in the perfusate by 80%. Since increasing or decreasing sodium excretion by altering the sodium concentration of the perfusate did not affect cumulative renin release, it was claimed that changes in sodium metabolism were of no importance in eliciting these changes in renin release. When perfusion pressure was held constant, papaverine increased RBF by 37% and caused the cumulative (60 min) renin release to decrease by 70%. Conversely, vasoconstriction with the alpha-adrenergic agonists phenylephrine or methoxamine led to a greater than 50% decrement in RBF and a 3- to 4-fold increment in cumulative perfusate renin activity. The stimulatory effects of phenylephrine on renin secretion were counteracted by either the addition of papaverine, which returned RBF to control levels, or by allowing the perfusion pressure to increase as vasoconstriction occurred.

Since vasoconstriction or low perfusion pressure increased renin secretion, and since vasodilatation or high perfusion pressure decreased renin release, Fray (350) applied Tobian's original "stretch" receptor hypothesis (1098). For purposes of mathematical analysis, he assumed that: 1) the renal preglomerular arteriole is a thick-walled cylindrical tube; 2) the wall of the arteriole is of a homogeneous composition and has elastic properties that obey Hooke's law; 3) the "stretch" is equal to the volume strain (amount of deformation of the vessel wall); 4) only small strains (changes in vessel volume) occur during vasodilatation and vasoconstriction; and 5) the rate of renin release is inversely related to the amount of volume strain [see appendix of Fray (350)] of the wall of the afferent arteriole. From these assumptions, he derived the equation:

$$\frac{RR}{K} = \frac{1 - (r_i/r_o)^2}{(r_i/r_o)^2 P_i - P_o}$$

where RR is renin release and K is a constant. By taking the first partial derivative of this equation and assuming that r_i = 15 μm, r_o = 20 μm, P_i = 60 mm Hg, and P_o = 5

mm Hg, the following equation was obtained:

$$\Delta RR = -0.0001\ \Delta P_i + 0.00054 \Delta P_o - 0.10086 \Delta (r_i/r_o)$$

As a result of these calculations, Fray concluded that a change in afferent arteriolar radius (r_i/r_o) was over 300 times more effective in altering renin release than a proportional change in the internal hydrostatic pressure (P_i). This idea was a radical departure from the original idea that a change in perfusion pressure per se was the stimulus to renin release.

However, it is important to recognize that certain difficulties arise when this type of mathematical modeling is applied to such a complex biologic system. Fray (350) assumed that the wall of the renal afferent arteriole is homogeneous and has elastic properties that obey Hooke's law, i.e., for an ideal elastic material the amount of strain (deformation of the material) is proportional to the amount of stress (force/unit area) exerted on the material and the ratio of stress/strain is a constant for any given stress or strain. However, the wall of the preglomerular arteriole is composed of both elastic (passive) and muscular (active) elements so the ratio of stress/strain will be different for each level of activity of the vascular smooth muscle. Therefore, any alteration in renal perfusion pressure, whether a decrease or an increase, that elicits autoregulatory changes in the afferent arteriole or any drugs that alter the tone of the vascular smooth muscle will modify the elastic properties of the vascular wall and, thus, the stress/strain ratio. This variable relationship between stress and strain probably disallows the application of Hooke's law to this system.

Secondly, the conclusion that a change in the afferent arteriolar radius (r_i/r_o) was 300 times more effective in altering renin release than a proportional change in internal hydrostatic pressure (P_i) was derived from the finding that the coefficient for the change in r_i/r_o was 300 times greater than the coefficient for the changing P_i. Fray (350) failed to consider the fact that a change in P_i will be expressed as a whole number (mm Hg) whereas a change in r_i/r_o will be expressed as a fraction that will always be less than 0.333 [see Morkrid et al. (770)]. Thus, a positive change in intravascular hydrostatic pressure (P_i) will, in fact, counterbalance a proportional negative change in the ratio of the radii (r_i/r_o). This point is best illustrated by considering Fray's studies (350) with vasoconstrictors. With his pressure and flow values, total renal vascular resistance increased by 225% (relative to the control values) when perfusion pressure was controlled at 110 mm Hg during phenylephrine infusion. Cumulative renin release rose by 360%. However, when perfusion pressure was allowed to rise to 200 mm Hg, cumulative renin release dropped to about 60% of the control values despite the fact that total renin vascular resistance was still 196% of the control values. Thus, in the presence of essentially the same degree of phenylephrine-induced renal vasoconstriction, the negative effect on renin release of increased renal perfusion pressure easily counteracted the positive effect on renin release of the decrease in r_i/r_o caused by phenylepherine. This is similar to the situation in which the positive effect on renin release of a decrease in P_i overrode the negative effect on renin release of an increase in r_i when changes in circumferential stress were calculated during renal arterial hypotension (vide supra). It may well be that changes in arteriolar radius (r_i/r_o) are of some importance in mediating baroreceptor stimulation or inhibition of renin release, since a change in this parameter can lead to a change in vascular wall tension (circumferential stress) or volume strain, but this effect is probably not as great as that proposed by Fray (350).

While the objections outlined above apply only to the more theoretical aspects of Fray's (350) studies, there are also certain limitations in the experimental techniques employed. It is important to note that RPF, GFR, filtration fraction, and net sodium reabsorption are radically different in the cell-free perfused kidney from what they are in the cell-perfused kidney (490). In fact, the hemodynamics and sodium metabolism observed in a red blood cell-perfused kidney correspond more closely to values obtained in the intact kidney (490). In addition, isolated perfused kidneys accrue weight during the course of an experiment, and this edema formation may alter the interstitial hydrostatic pressure and ion movements (490). Finally, the relationship between cumulative perfusate renin activity and the actual rate of renin secretion is not known.

In addition to the physical factors that might mediate baroreceptor-induced renin release, recent studies have suggested that renal prostaglandins may function as hormonal mediators of this control mechanism. The role of renally produced prostaglandins in the autoregulation of RBF has been the subject of some controversy. When Herbaczynska-Cedro and Vane (475) examined the release of PG-like material from the autoperfused canine kidney, they found a reciprocal relationship between renal vascular resistance and the release of PG-like material into the renal venous blood during pressure-dependent autoregulation of RBF. Since inhibition of renal prostaglandin synthesis with indomethacin prevented both the release of PG-like material and autoregulation of RBF during a reduction in perfusion pressure, the authors proposed that renal prostaglandins mediated autoregulatory vasodilatation. However, subsequent studies from several laboratories (19, 338, 549, 858, 1147) have failed to confirm the ability of inhibitors of prostaglandin synthesis to block renal autoregulatory vasodilatation. In perhaps the most complete study, Kaloyanides and co-workers (549), with an isolated canine kidney perfused by blood from a second donor dog, found that the increased rate of secretion of PGE_2 elicited by reducing renal perfusion pressure was completely blocked by indomethacin or meclofenamate. However, when renal perfusion pressure was lowered in a step-wise fashion, RBF remained unchanged in both the presence and

absence of inhibitors of prostaglandin synthesis. These data indicate that prostaglandins are probably not the mediators of renal autoregulation. These conflicting reports from Herbaczynska-Cedro and Vane (475) and subsequent investigators (19, 338, 549, 858, 1147) can only be resolved if it is assumed that increased renal prostaglandin release is secondary to autoregulatory vasodilatation rather than the cause of the dilatation.

The first study that suggested a relationship between renal prostaglandin production and renin release during renal arterial hypotension was that of McGiff et al. (715). When the renal arteries of anesthetized dogs were constricted enough to reduce RBF from 257 to 109 ml/min, PG-like material, as measured by bioassay, was released into the renal venous blood as renin release increased 10-fold. With anesthetized dogs with a single nonfiltering kidney, Data et al. (246) determined that suprarenal constriction of the aorta sufficient to reduce renal perfusion pressure from 121 to 61 mm Hg caused a 4-fold elevation of renal venous PRA. Renal blood flow was decreased from 65 to 30 ml/min (J. W. Hollifield, personal communication). When a similar reduction in renal arterial pressure was produced in dogs pretreated with indomethacin, renal venous PRA increased only slightly and RBF again dropped from 60 to 35 ml/min. Unfortunately, in both of these studies (246, 715), renal perfusion pressure was dropped to below the range of autoregulation of RBF. However, Blackshear et al. (94) determined the effects of indomethacin on renal arterial hypotension-induced renin release both above and below the range of autoregulation of RBF. When renal perfusion pressure was reduced from 120 to 90 mm Hg in anesthetized dogs, RBF did not change while renin secretion increased 4-fold. A further reduction in perfusion pressure to 60 mm Hg led to a large drop in RBF and a further elevation of renin secretion. When these studies were repeated in indomethacin-treated dogs, reduction of perfusion pressure from 120 to 90 mm Hg did not cause a significant change in RBF, and yet hypotension-induced renin secretion was blocked by 75% when compared to control animals. Dropping renal arterial pressure to 60 mm Hg greatly reduced RBF, but renin secretion rose the same amount as it did in control dogs. Thus, indomethacin prevented the rise in renin secretion, but not the autoregulation of RBF, as long as perfusion pressure was maintained above the autoregulatory range of the kidney. It would appear that in the filtering kidney (94), in contrast to the nonfiltering kidney (246), lowering renal perfusion pressure below the autoregulatory range releases renin by a non-prostaglandin-dependent mechanism.

Blackshear and Wathen (95) later determined the effects of indomethacin on renin release and RBF during ureteral occlusion. Blockade of renal prostaglandin synthesis prevented the increase in RBF and markedly blunted the increase in renin secretion normally observed during complete ureteral obstruction in the anesthetized dog. After ureteral clamping had increased renin secretion and RBF in untreated dogs, an infusion of PGE_2 into the renal artery caused no further increment in renin secretion or RBF. However, the infusion of PGE_2 into the kidneys of indomethacin-treated dogs after ureteral occlusion resulted in renal vasodilatation and increased renin secretion. It was concluded that an increase in the production of renal prostaglandins elicited the renal vasodilatation seen during ureteral occlusion. Furthermore, these prostaglandins, either directly by an action on the granular JG cells or indirectly via vasodilatation, appeared to be the stimuli to renin secretion during an increase in ureteral pressure. In this case, unlike hypotension-induced renal vasodilatation, the prostaglandins appear to mediate the vasodilatation rather than the vasodilatation causing the increase in the production of prostaglandins. In this respect, a mechanical rise in renal interstitial pressure has been shown to activate the synthesis of prostaglandins, and Olsen et al. (836) noted that ureteral occlusion elevated the urinary excretion of PGE_2 in anesthetized dogs.

We originally considered that ureteral occlusion activates the renal baroreceptor by lowering the transmural pressure gradient and thereby decreasing circumferential stress. We thought that the decrease in the transmural pressure gradient overrides the effect of arteriolar vasodilatation on circumferential stress. However, in the experiments of Blackshear and Wathen (95), the transmural pressure gradient *probably* was decreased during ureteral occlusion in indomethacin-treated dogs. According to our previous discussion of the renal baroreceptor mechanism, this decrease in the transmural pressure gradient should have stimulated renin release by decreasing circumferential stress. Indomethacin did not have a nonspecific paralytic effect on the arteriolar smooth muscle since PGE_2 relaxed this smooth muscle in the presence of indomethacin. Based on these observations, it would have to be concluded that 1) it is the act of vasodilatation per se, irrespective of changes in circumferential stress, that triggers baroreceptor-stimulated renin release, or 2) prostaglandins are mediators of baroreceptor-induced renin release, or 3) indomethacin exerts its effects at a final common pathway for renin release that is distal to the vascular mechanism.

In summary, baroreceptor-mediated renin release appears to occur by two mechanisms: 1) physical changes in the afferent arteriole and 2) changes in the synthesis of renal prostaglandins. According to most of the available data, the release of renin is inversely related to the "stretch" of the afferent arteriole as proposed by Tobian (1096). The "stretch" of the afferent arteriole may be described by wall tension (circumferential stress) or volume strain. The most important determinant of these physical parameters, however, appears to be changes in intraluminal pressure or the transmural pressure gradient since increments or decrements in these pressures can override an opposing change in afferent arteriolar radius.

Prostaglandins seem to mediate a large portion of the baroreceptor-mediated renin release within the autoregulatory range. Since physical distortion of tissues stimulates prostaglandin synthesis (908, 1080), it is tempting to speculate that renal prostaglandins are a chemical link between changes in wall tension or volume strain and the release of renin within the autoregulatory range of RBF. Such a conclusion, however, must await experimental confirmation.

B. Autonomic Nervous System

1. Anatomical considerations. Before discussing the role of the autonomic nervous system, primarily the sympathetic nervous system, in the control of renin release, it is important to consider the innervation of the renal arterioles and the JG apparatus. In 1952, De Muylder (266) identified nerves traveling to the afferent renal arterioles in the region of the granular JG cells. A decade later, Barajas (50) examined the innervation of the JG apparatus by electron microscopy and found that nonmyelinated nerve fibers containing dense-core vesicles, indicative of noradrenergic nerves (1233), were associated with the afferent and efferent arterioles in monkeys and rats. In the ensuing years, other researchers (81, 801, 1169) have confirmed that the JG cells of rats, dogs, and humans are innervated by sympathetic fibers. Wagermark et al. (1169) combined fluorohistochemical identification of biogenic amines and specific stains for the granules of the JG apparatus to demonstrate the presence of noradrenergic nerve terminals in the afferent arteriolar walls near the granular JG cells. These nerve terminals are now known to be separated from the granular JG cells by a distance of approximately 1200 to 2000 Å with a basement membrane intervening between the two structures (50, 52, 54). These noradrenergic nerves have been shown to consist of axons and varicosities that are partially or completely surrounded by Schwann cells (52). Taken collectively, these studies (50, 52, 54, 81, 266, 801, 1169, 1233) provide the morphologic evidence for a functional relationship between the sympathetic nervous system and renin release. See Barajas (51, 51a) for a more extensive discussion of these anatomical relationships.

In addition to pharmacologic evidence for the existence of beta-adrenergic receptors on the granular JG cells, Atlas et al. (32) have observed that the fluorescent beta-adrenergic antagonist 9-amino-acridin propranolol, when given i.v. to rats, aggregated in the vascular poles of the glomeruli in association with the preglomerular afferent arteriole. This binding was greatly reduced by pretreatment with *d,l*- and *l*-propranolol but was less affected by *d*-propranolol.

While the noradrenergic innervation of the renal arterioles and the JG apparatus is well-established, the cholinergic innervation of these structures is not as well-defined. McKenna and Angelakos (718) found that the afferent arterioles received cholinergic innervation from ganglion cells in the hilus of the canine kidney. These acetylcholinesterase-containing fibers were not affected by ablation of the nerves traveling with the renal vessels even though this treatment removed all traces of cortical noradrenergic nerve fibers. They concluded that the cholinergic innervation of the kidney was completely independent of the noradrenergic nerve supply. However, Barajas (51a) found that the distribution and density of the renal nerves containing acetylcholinesterase in the rat were very similar to those of the noradrenergic fibers. Furthermore, treatment with the neurotoxin 6-hydroxydopamine, which destroys catecholamine-containing neurons, caused the complete disappearance of norepinephrine and acetylcholinesterase from the nerves innervating the glomerular arteries. Therefore, the possible cholinergic innervation of the granular JG cells is still a subject of controversy.

2. Sympathetic nervous system. A. DIRECT AND INDIRECT STIMULATION OF THE RENAL NERVES. Vander (1115) was the first to demonstrate that electrical stimulation of the renal artery and its encompassing sympathetic nerves released renin into the circulation of anesthetized dogs. However, GFR, RPF, and sodium excretion were decreased by renal nerve stimulation and, since the prior induction of osmotic diuresis with mannitol prevented the nerve-stimulated release of renin, it was possible that the decrease in sodium excretion precipitated by nerve stimulation elevated renin release by a macula densa mechanism. Assaykeen and Ganong (30) reported that stimulation of the renal nerves in anesthetized dogs led to a 2-fold increase in PRA that was blocked completely by pretreatment with propranolol, a beta-adrenergic receptor antagonist. Changes in renal function were not mentioned. These authors (30) hypothesized that the norepinephrine released by stimulation of the renal nerves increased renin release by one or more of the following mechanisms: 1) by decreasing the stretch on the granular JG cells as a result of constriction of the afferent arterioles; 2) by decreasing the GFR and thus the amount of sodium reaching the macula densa; and 3) by a direct beta-adrenergic action on the granular JG cells. Because some doubt existed as to the specificity of the nerve stimulation in Vander's work (1115), Johnson et al. (535) isolated and stimulated the renal nerves in anesthetized dogs with a single nonfiltering kidney. Direct renal nerve stimulation caused a 3-fold increase in renin secretion and a 20% decrease in RBF. However, the prior intrarenal infusion of papaverine prevented the decrement in RBF, but not the increment in renin secretion, caused by nerve stimulation. Since sympathetic nerve stimulation increased renin release in the absence of a functional macula densa or any change in RBF, a direct action on the granular JG cells was indicated.

Additional pharmacologic characterization of the renin release caused by sympathetic excitation was provided by Loeffler et al. (667). Upon stimulation of the renal artery and the accompanying nerves in anesthetized dogs,

PRA was increased 2- to 4-fold, a response completely abolished by propranolol. Pretreatment with phenoxybenzamine, an alpha-adrenergic antagonist, elevated basal PRA by 3-fold and lowered MAP by 30%, but failed to alter the increment in PRA attendant to nerve stimulation. Simultaneous pretreatment with propranolol and phenoxybenzamine did not affect the hypotension caused by phenoxybenzamine but completely prevented the increment in PRA caused by phenoxybenzamine. Also, the nerve-stimulated increase in PRA was blocked. The data indicated that both nerve-stimulated and alpha-adrenergic antagonist-induced renin release occurred via beta-adrenergic receptors. (Changes in renal function were not reported.) Coote et al. (231) studied the effects of alpha- and beta-adrenergic blockade on the renin release caused by stimulation of the severed distal ends of the renal nerves in unilaterally nephrectomized, anesthetized cats, and they came to a different conclusion. Nerve stimulation resulted in a 9-fold increase in PRA associated with a 30% drop in RBF. Phentolamine, an alpha-adrenergic antagonist, blocked both the increase in PRA and the decrease in RBF. When the renal artery was constricted to produce decrements in RBF similar to those caused by nerve stimulation, PRA increased 3-fold; however, this increase was not affected by phentolamine. Propranolol prevented the renin release elicited by nerve stimulation but did not mitigate the decrement in RBF. Based on these observations, they concluded that nerve-stimulated renin release was primarily mediated by changes in RBF and that the propranolol-sensitive step in this excitation-secretion process was distal to the effects of norepinephrine on vascular smooth muscle. However, in later studies (528) these same investigators found that *d*-propranolol, which possesses only 1/100 of the beta-adrenergic receptor blocking activity of *l*-propranolol, had no effect on nerve-stimulated renin release whereas a racemic mixture of *d,l*-propranolol completely prevented the increase in PRA. Stimulation-induced vasoconstriction of the renal vasculature was increased to the same extent after *d*-, or *d,l*-propranolol. Changes in renal salt metabolism were not measured. As with phentolamine (231), *d,l*-propranolol did not alter the rise in PRA caused by constriction of the renal artery. Therefore, nerve-stimulated renin release appeared to be the result of a direct action of norepinephrine on the beta-adrenergic receptors of the granular JG cells and was not attributable to changes in RBF. This conclusion is consistent with the observation that renin release induced by non-adrenergic mechanisms, i.e. renal artery stenosis, was not affected by propranolol. The authors did not reconcile this conclusion with the earlier observations (231) that phentolamine blocked nerve-stimulated renin release.

In perhaps the most complete study of nerve-stimulated renin release, Taher et al. (1072) stimulated the renal nerves of anesthetized dogs at a frequency that consistently increased renin secretion 5- to 10-fold without altering RBF, GFR, or sodium excretion. The increase in renin secretion after nerve stimulation was blocked completely by *l*- and *d,l*-propranolol but not by *d*-propranolol. Because no significant change in MAP, RBF, GFR, or urinary electrolyte excretion occurred in any of these experiments, the increase in renin secretion caused by stimulation of the renal nerves could not have occurred via the renal baroreceptor or macula densa mechanisms. Again, the stereospecific blockade of nerve-stimulated renin secretion by propranolol emphasized that the norepinephrine released by the renal nerves impinged on beta-adrenergic receptors located on the granular JG cells.

Because physiologic stimulation of the renal nerves originates within the central nervous system, several groups of researchers (100, 875, 876, 933, 1106, 1110, 1268) have determined the effect of electrical stimulation of central nerve tracts on renin release and RBF. Ueda et al. (1110) stimulated the mesencephalic pressor area (dorsal part of the central gray stratum and adjacent areas) and observed a 5- to 9-fold increase in renal venous PRA, a drop in RBF, and a marked increase in MAP. Because renal denervation prevented the increase in PRA and slightly attenuated the decrement in RBF, the elevated renin release was considered to be due to an acceleration of sympathetic nerve activity in the kidney; however, sympathetic-nervous-system-induced changes in renal salt metabolism could not be excluded. Stimulation of the pressor area of the medulla oblongata in anesthetized dogs also has been shown to elevate renin release by 3-fold, despite the fact that MAP rose by 70% (876). This rise in PRA was blocked by renal denervation. Furthermore, this stimulation of renin release was impaired by propranolol but not by phenoxybenzamine (875). Unfortunately, RBF and sodium excretion were not measured (875, 876).

Zehr and Feigl (1268) found that intermittent stimulation of the hypothalamus of *conscious* dogs lowered MAP and increased heart rate without changing RBF. Sixty minutes after stimulation had began, PRA was lowered by 50% in dogs consuming a low or normal sodium diet. After propranolol pretreatment, which lowered basal PRA values, hypothalamic stimulation failed to cause a further decrement in renin release. In addition, renal denervation, which resulted in a 50% drop in basal PRA, also prevented the decrement in PRA elicited by hypothalamic stimulation in both normal and sodium-depleted dogs. They concluded that the sympathetic nervous system has a "tonic" stimulatory effect on renin secretion that could be inhibited by the activation of fiber tracts originating in the hypothalamus. In similar studies in anesthetized cats, Richardson et al. (933) found that excitation of the dorsolateral pons elevated MAP by 40%, decreased RBF by 28%, and increased renin secretion by 100%. Unilateral renal denervation before pontine stimulation prevented the increase in renin secretion and the decrement in RBF in the denervated, but not in the intact, kidney. Furthermore, a unilateral renal arterial

infusion of phenoxybenzamine increased the basal rate of renin secretion, potentiated the renin release elicited by pontine stimulation, and prevented the decrement in RBF during central stimulation. These effects of phenoxybenzamine were restricted to the infused kidney. Intravenously administered propranolol completely blocked the 4-fold increment in renin secretion and enhanced the renal vasoconstriction caused by pontine stimulation (933). An increase in PRA, which was blocked by renal denervation, has been described when the supramammillary portion of the hypothalamus was stimulated in anesthetized rats (786). In addition, electrical stimulation of the defense area near the superior colliculus has been shown to increase PRA, MAP, and heart rate in anesthetized dogs (100).

Therefore, it is apparent that renin release can be elevated or suppressed by higher centers in the central nervous system via changes in the level of renal nerve activity. These nerve-induced alterations of renin release are mediated via intrarenal beta-adrenergic receptors and are independent of changes in RBF. More importantly, the renal nerve-mediated alterations of renin release caused by stimulation of the central nervous system are not affected by the increments and decrements in MAP that occurred during central stimulation. Ueda (1106) has reviewed the anatomical relationships of the areas of the central nervous system mentioned above (100, 875, 876, 933, 1110).

Because renal sympathetic nerve activity has been shown to be inversely related to carotid sinus pressure (579, 802), the effect of bilateral occlusion of the carotid arteries below the carotid sinus on renin release has been studied (136, 164). Initially, Skinner et al. (1023) found that bilateral carotid occlusion failed to change PRA in vagotomized, anesthetized dogs, but later (164) they discovered that this maneuver did indeed elevate renin release if renal perfusion pressure was maintained at control levels. About this same time, it was reported that plasma AII levels were increased during bilateral carotid occlusion in anesthetized dogs (485). This maneuver also increased PRA in normal and sodium-depleted dogs, and this increase was accentuated if renal perfusion pressure was controlled (722). However, Brennan et al. (136) could find no correlation between carotid sinus pressure and renin release in vagotomized or intact animals even if renal perfusion pressure was held constant.

In a similar fashion, Brosnihan and Travis (142) failed to find a significant increase in PRC during bilateral carotid occlusion in anesthetized cats whose basal rates of renin release had been suppressed by saline infusion. In contrast, Cunningham et al. (244) demonstrated that carotid sinus hypotension resulted in a rapid, sustained, reflex increase in PRA in sodium-depleted, vagotomized, anesthetized dogs whose aortic pressures were held constant by the use of an external pressurized reservoir connected to the arterial system. When carotid sinus pressure was lowered from 115 to 79 mm Hg, PRA increased by 60% and heart rate was unchanged. If carotid sinus pressure was lowered to 15 mm Hg, PRA and heart rate increased by 75% and 17%, respectively. Thus, the magnitude of the increase in PRA did not appear to be related to the magnitude of the decrease in carotid sinus pressure. Denervation of the carotid sinuses prevented the rise in PRA elicited by bilateral carotid occlusion, but the efferent pathway (probably the renal sympathetic nerves) was not identified. Cunningham et al. (244) felt that the failure of some investigators to observe an increase in renin release during carotid sinus hypotension was due to volume expansion with saline or failure to control both aortic pressure and afferent vagal baroreceptor input.

Other neural pathways may operate to modify renin release with the stimulus originating in one or more of the peripheral cardiopulmonary receptors (21, 484, 689–691, 1081, 1083, 1084, 1269). With a cardiac autotransplantation technique that left the atrial receptors innervated and the ventricular receptors denervated, Thames et al. (1084) noted that the usual increase in PRA during nonhypotensive hemorrhage in anesthetized dogs was greatly attenuated. Several years later, cardiopulmonary receptors in the atria, ventricles, and lungs were found to suppress the firing rate of the adrenergic nerves that innervate the peripheral vascular beds, including the kidney (689). Prompted by these earlier studies, Mancia et al. (690) discovered the existence of vagally-innervated receptors in the cardiopulmonary region that continuously inhibited renin release. In anesthetized dogs whose aortic nerves had been severed and whose carotid sinuses had been vascularly isolated in order to maintain intrasinus pressure at control levels, interruption of afferent vagal impulses by bilateral cooling of the cervical vagi caused a 5-fold increment in PRA that was associated with a 7% fall in RBF. Because the changes in PRA and RBF observed during vagal cooling were prevented by prior renal denervation, the authors felt that vagal afferents from the heart and lungs exerted a tonic restraint on renin release by suppressing efferent renal nerve activity. Similarly, an increase in right atrial stretch suppressed PRA in anesthetized dogs, an effect prevented by bilateral cervical vagotomy (21). Progressive distension of the superior vena cava-right atrial junction resulted in graded decrements (1 to 2 mm Hg) in right atrial pressure in sodium-depleted, anesthetized dogs (141). Renin secretion progressively increased to four times the control value, whereas MAP and RBF were unchanged. Thus, a decrement in atrial pressure of less than 1 mm Hg was capable of initiating reflex stimulation of renin secretion (141). Mechanical distention of the left atrial-pulmonary region of sodium-depleted, anesthetized dogs has been shown by Zehr et al. (1269) to suppress the rate of renin secretion by 50% within 5 min after distention had begun. Central venous pressure, MAP, and RBF were unchanged. This rapid suppression of renin secretion was prevented by either renal denervation

or bilateral cervical vagotomy, which indicated that left atrial distention reduced renin secretion via vagal afferent and renal sympathetic efferent nerve pathways. Ventricular receptors with vagal afferents that reflexly suppress renin secretion also have been identified (1081). Nonhypotensive hemorrhage of anesthetized dogs increased renin secretion 3-fold without affecting RBF. The administration of the veratrum alkaloid cryptenamine into the left coronary artery lowered MAP and heart rate and completely ablated the renin response to hemorrhage despite the fact that MAP dropped by 15%. Vagotomy prevented cryptenamine from impairing hemorrhage-induced renin release (1081).

After the afferent and efferent limbs of these cardiopulmonary receptors had been located (21, 690, 1081, 1269), Thames et al. (1083) examined the interactions between the carotid baroreceptors and the cardiopulmonary receptors in the control of renin release. If the aortic nerves of anesthetized dogs were cut, but the carotid sinuses left intact, vagal cold block increased MAP and inhibitory nerve traffic from the carotid baroreceptors but had no effect on renin secretion. However, if the aortic nerves were severed and the carotid sinuses were vascularly isolated to maintain intrasinus pressure at control levels, vagal cold block elevated renin secretion. Furthermore, a nonhypotensive hemorrhage increased renin secretion in intact, but not in vagotomized dogs. Based on these and previous observations (21, 136, 689, 690, 1081, 1084, 1269), Thames et al. (1083) stated that 1) cardiopulmonary receptors with vagal afferent pathways tonically inhibit renin release even in the presence of a normally functioning carotid baroreceptor system, 2) these cardiopulmonary receptors can respond to a decrease in central blood volume that does not activate the arterial baroreceptors, and 3) the normal buffering effects of the arterial baroreceptors can inhibit the increase in renin secretion that normally results from complete interruption of vagal afferent nerve activity originating in the cardiopulmonary receptors. These conclusions are completely consistent with the observation that these same cardiopulmonary receptors actively oppose the renal vasoconstriction resulting from carotid sinus hypotension (691).

The existence of cardiopulmonary-volume receptors that control renin release in humans has been questioned (481, 645). Hesse et al. (481) discovered that an acute 10% reduction in blood volume in humans did not increase PRA even though right atrial pressure was decreased. Mean arterial pressure did not change in these experiments. Previous investigators (147, 160, 390, 479) also had reported that the removal of 400 to 600 ml of blood from humans did not increase PRA. Recently, Mark et al. (695) attempted to assess the effects of the low pressure-cardiopulmonary and high pressure-carotid baroreceptors on renin release in man by using graded lower body suction. Lower body suction at −10 and −20 mm Hg decreased central venous pressure without affecting arterial pulse pressure. This maneuver produced vasoconstriction in the forearm, but PRA did not change. It was assumed that low-pressure, but not high-pressure baroreceptor inhibition was reduced by this degree of negative pressure. When lower body suction was increased to −40 mm Hg, central venous pressure and arterial pulse pressure were reduced and forearm vascular resistance and heart rate were increased. These changes were thought to indicate a reduction in the inhibition of the sympathetic nervous system by both the low- and high-pressure baroreceptors. In the latter experiments, PRA rose from 2.1 to 7.4 ng of AI/ml/hr, and this increase was blocked by propranolol. Mark et al. concluded that a decrease in cardiopulmonary baroreceptor restraint in humans did not result in an increase in renin release in the presence of tonic inhibition from the carotid baroreceptors (695), which is in accord with the observations made by Thames et al. (1083) in anesthetized dogs. These results also may explain why PRA did not rise in humans subjected to mild hemorrhage (147, 160, 390, 479).

On the other hand, Kiowski and Julius (592) found that renin release was stimulated when the cardiopulmonary mechanoreceptors of healthy volunteers were activated by impeding venous return to the heart with leg tourniquets. The inflation of thigh cuffs decreased right atrial pressure, cardiopulmonary blood volume, and cardiac output, but did not alter intraarterial systolic and diastolic pressure, the pulse pressure, or intraabdominal pressure. The rise in PRA caused by this procedure was blocked by propranolol and was absent in patients with recently transplanted kidneys. Kiowski and Julius (592) suggested that Mark et al. (695) did not observe an increase in PRA with the lower levels of lower body suction, which did not alter the arterial baroreceptors, because intraabdominal pressure decreased and because they sampled blood over too short a time. Thus, the existence of cardiopulmonary-volume receptors that control renin release in humans remains controversial, and Hesse et al. (481) have hypothesized that the differing sensitivity of the low pressure volume receptors in humans and dogs might be related to the fact that the frequent shift from the supine to the upright position in humans probably causes greater pressure/volume reductions in the atria than does nonhypotensive hemorrhage or a small amount of lower body negative pressure.

Since mechanoreceptors in the heart and lungs inhibit renin release by way of afferent vagal and efferent renal sympathetic pathways (21, 136, 689, 690, 1081, 1084, 1269), the effects of bilateral cervical vagotomy on renin release are of interest. As early as 1969, bilateral cervical vagotomy was reported to elevate the plasma concentration of AII (484), but only in recent years has the effect of this denervation on renin release been characterized (142, 1252, 1253, 1260). Bilateral cervical vagotomy has been shown to increase PRC in anesthetized cats even if extracellular fluid volume was markedly increased by the

i.v. infusion of saline (142). This is a significant finding since volume expansion has been demonstrated to decrease renal nerve activity markedly in conscious cats with either intact or denervated baroreceptors (986). It is tempting to speculate that volume expansion suppresses renal sympathetic nerve traffic via the cardiopulmonary receptors mentioned above. Zanchetti (1260) found that cervical vagotomy caused a rapid, but short-lived, elevation of renin secretion in anesthetized cats that was blocked by renal denervation. Other investigators (21) have noted an increase in renin release in anesthetized dogs after bilateral cervical vagotomy. In perhaps the most comprehensive set of studies, Yun et al. (1252, 1253) examined the effect of cervical vagotomy and/or sinoaortic denervation on renin release in anesthetized, sodium-loaded dogs in which renal perfusion pressure was maintained at the control level by means of a suprarenal, aortic snare. Ninety minutes after bilateral cervical vagotomy, PRA was increased 3-fold and MAP was slightly elevated. Sinoaortic denervation alone increased PRA 7-fold and MAP by 28%. Vagotomy after sinoaortic denervation did not affect blood pressure but did result in a further increment in PRA. Propranolol completely prevented the increase in PRA elicited by sinoaortic denervation and vagotomy, but did not block the rise in blood pressure (1252). Later it was found that renal denervation alone blocked about 80% of the increase in renin release observed after sinoaortic denervation and vagotomy, and the residual effect was ablated by prior adrenalectomy (1253). Yun et al. concluded that the increase in PRA after sinoaortic denervation resulted from an increase in sympathetic nerve discharge to the kidneys and nerve-induced release of catecholamines from the adrenal medulla whereas the increase in PRA seen after bilateral cervical vagotomy was due to an elevation of renal nerve activity alone (1252, 1253). These data are consistent with the earlier observations that vagotomy is followed by an increase in renal sympathetic nerve activity (222, 689).

In summary, it is apparent that the renal sympathetic nerves have a profound influence on renin release, and renal nerve activity is, in turn, controlled by several neural reflex arcs. It should be mentioned that accelerated renal sympathetic nerve activity has been implicated as a cause for the increased renin release that accompanies or follows psychosocial stimuli (219), auditory stimuli (1122), intermittent electrical shock (647), and exercise (649) in rats; immobilization stress in rabbits (1101); heat stress (305) and avoidance operant conditioning (101) in baboons; heat stress (607), running exercise (606), the hypnotic suggestion of running (605), mental arithmetic (604), psychosocial stimuli (220), operant conditioning for cardioacceleration (1251), ethanol intoxication and hangover (663), passive-tilt (318, 846), upright posture (224), and high renin hypertension (316) in humans.

B. INCREASED CIRCULATING LEVELS OF CATECHOLAMINES. In 1964, it was discovered that the i.v. infusion of norepinephrine into anesthetized dogs elevated the concentration of AII in the blood, and this increase was potentiated if renal perfusion pressure was held constant by means of a suprarenal, aortic clamp (997). A year later, Vander (1115) found that both norepinephrine and epinephrine stimulated renin release in anesthetized dogs in which renal perfusion pressure was held at the control level. Since this increase in renal venous PRA was accompanied by a decrease in GFR and sodium excretion, and since the induction of osmotic diuresis with mannitol reduced this catecholamine-induced renin release, it was proposed that norepinephrine and epinephrine elevated PRA by activation of the macula densa. However, a direct action of norepinephrine and epinephrine on the granular JG cells could not be excluded. Some years later, Wathen et al. (1177) reported that intrarenal infusions of norepinephrine and epinephrine rapidly increased renin secretion in anesthetized dogs. Sodium excretion was depressed, and MAP did not change. Intravenously administered norepinephrine actually decreased renin secretion as MAP rose; therefore, these authors concluded that intrarenally administered catecholamines stimulated renin secretion by constricting the renal afferent arterioles and this effect could be overridden by an increase in MAP (1177). The renin-releasing effects of norepinephrine in anesthetized dogs were subsequently confirmed, and, in addition, isoproterenol was reported to have no effect on renin release (164). Nash et al. (783) demonstrated that the diminution of renal function precipitated by intrarenally infused norepinephrine did not appear to be the stimulus for norepinephrine-induced renin release since the simultaneous infusion of saline into the canine kidney did not block the renin release caused by high doses of norepinephrine. In subsequent years, Johnson et al. (535) showed that both epinephrine and norepinephrine stimulated renin secretion from the nonfiltering kidneys of anesthetized dogs in association with a large decrement in RBF. Since prior dilatation of the renal afferent arterioles with papaverine prevented the increment in renin secretion caused by epinephrine, but not norepinephrine, it was suggested that epinephrine increased renin secretion by vasoconstrictor activation of the renal baroreceptor whereas norepinephrine increased renin secretion by a direct action on the granular JG cells. Considerably more interest in the subject was aroused when DeChamplain et al. (261) and Gordon et al. (402) showed that i.v. norepinephrine and epinephrine elevated PRA in normal and hypertensive humans in the presence of either a small (261) or large (402) pressor response. Again, this renin release was thought to be due to afferent arteriolar vasoconstriction (402). Isoproterenol was tested again in dogs, but was found to increase PRA only in dogs with chronic renovascular hypertension (37). Normal dogs exhibited little renin response to isoproterenol (37).

Beginning in 1970, research in this area progressed

rapidly, and soon it was established that norepinephrine and epinephrine elevated renin release by direct stimulation of beta-adrenergic receptors on the granular JG cells. In the first thorough pharmacologic analysis of norepinephrine-induced renin release, Ueda et al. (1109) measured changes in the PRA of renal venous blood during the i.v. delivery of norepinephrine into anesthetized dogs. A dose of 10 μg/kg/min of norepinephrine elevated PRA 3-fold as blood pressure rose, and RBF, GFR, and salt excretion dropped. Dibenamine, an alpha-adrenergic antagonist, completely reversed the effects of norepinephrine on RBF, GFR, and salt excretion, but did not alter the ability of norepinephrine to elicit renin release. Propranolol did impair norepinephrine-induced renin release. Furthermore, small doses of isoproterenol elevated PRA but failed to alter RBF, GFR, and salt excretion. This effect of isoproterenol was prevented by propranolol but not by renal denervation. These researchers (1109) concluded that norepinephrine elicited an increase in renin release by a direct action on the granular JG cells. Another group of investigators (29, 856) chose a different, but quite ingenious, method of studying the renin response to increased blood levels of epinephrine. By inducing hypoglycemia with insulin, they were able to increase the release of epinephrine from the adrenal medulla in anesthetized dogs. A 3- to 5-fold increase in the plasma concentration of epinephrine (plasma norepinephrine did not change) led to a 2- to 3-fold elevation of PRA in the absence of any change in blood pressure. The decrement in plasma potassium concentration attendant to insulin treatment may have been a partial stimulus to renin release, but maintenance of plasma potassium at control levels during hypoglycemia did not prevent the increase in PRA. More importantly, unilateral adrenalectomy and denervation of the remaining adrenal gland lowered basal renin release and reduced the renin response to hypoglycemia, whereas renal denervation was without effect. Additional experiments revealed that hypoglycemia-induced renin release was blocked by propranolol and potentiated by phenoxybenzamine. In similarly prepared animals, i.v. infusions of epinephrine sufficient to elevate plasma epinephrine concentrations to those observed during insulin-induced hypoglycemia provoked an increase in PRA that was blocked by propranolol and potentiated by phenoxybenzamine.

Up to this point it appeared that renin release from the kidney was a beta-adrenergically-mediated event. However, this idea was brought into serious doubt when Winer et al. (1227) reported that the increase in renin release caused by the i.v. infusion of norepinephrine into anesthetized dogs was blocked by either propranolol or phentolamine. In addition, the elevation of PRA that resulted from an intrarenal infusion of isoproterenol was prevented by the i.v. infusion of phentolamine, *l*-propranolol, *d*-propranolol, or practolol, but was not affected by lidocaine. The intrarenal administration of cyclic AMP also elicited renin release that was impaired by propranolol or phentolamine. In order to explain these startling results, the authors hypothesized that cyclic AMP was the intracellular mediator of renin release and that the blockade of norepinephrine-, isoproterenol-, and cyclic AMP-induced renin release by propranolol and phentolamine was due to an action of these antagonists at a site distal to cyclic AMP production. Presumably, this site of action was inside the granular JG cells rather than at the sarcolemma. It should be pointed out that the majority of the reports in this area of research do not support the observations with receptor antagonists made by Winer et al. (1227).

For instance, Tanigawa et al. (1078) found that the increments in PRA caused by norepinephrine, epinephrine, and isoproterenol were blocked by propranolol, but not by phenoxybenzamine. Furthermore, the potency ratio between these catecholamines for the stimulation of renin release was isoproterenol > epinephrine > norepinephrine, a rank order that was identical to that reported by Pettinger et al. (890) for the conscious rat. Assaykeen et al. (31) also demonstrated that the increase in PRA caused by isoproterenol in anesthetized dogs was blocked by *d,l*- or *l*-propranolol, but not by *d*-propranolol, phentolamine, or phenoxybenzamine. In addition, the effects of alpha- and beta-adrenergic receptor antagonists on nerve-stimulated renin release (vide supra) and their effects on norepinephrine- and epinephrine-induced renin release in vitro (vide infra) convincingly indicate that norepinephrine and epinephrine elevate renin release by stimulating beta-adrenergic receptors on the granular JG cells.

Early reports indicated that isoproterenol was not capable of eliciting renin release (37, 164), but in subsequent years numerous investigators have found isoproterenol to be a potent agonist for renin release. Isoproterenol-induced renin release has been reported in anesthetized dogs (31, 123, 212, 928, 1078, 1109, 1227), conscious dogs (421, 482a), anesthetized normotensive rats (737, 738, 887), conscious normotensive rats (645, 890, 893), conscious hypertensive rats (893), and both normotensive (252, 619, 646) and hypertensive (619) humans. Furthermore, propranolol has been demonstrated to block or impair isoproterenol-stimulated renin release in anesthetized dogs (31, 212, 1078, 1109, 1227), conscious dogs (482a), anesthetized rats (737, 738), conscious normotensive rats (645), and normotensive humans (646). In 1972, Reid et al. (928) questioned the belief that only intrarenal beta-adrenergic receptors are stimulatory to renin release. They found that i.v. isoproterenol increased both PRA and the rate of renin secretion in anesthetized dogs despite the maintenance of constant renal perfusion pressure by an aortic clamp. In contrast, no significant change in PRA occurred during the direct intrarenal arterial infusion of isoproterenol. Since the effect of i.v.

isoproterenol occurred in the absence of changes in plasma potassium levels, renal perfusion pressure, GFR, RPF, and electrolyte excretion and was not abolished by renal denervation or hypophysectomy, these researchers suggested that the effect of isoproterenol on renin secretion was mediated by some circulating factor of nonpituitary origin. However, this study (928) must be interpreted with caution as careful examination of the data reveals that: 1) due to high levels in two dogs, there was a remarkable amount of variation (the standard error was more than 50% of the mean) in the control renin release values of the animals given isoproterenol intrarenally; 2) a second intrarenal infusion of isoproterenol was given to two dogs even though the control values were two to three times greater than those values seen before the first isoproterenol infusion; and 3) almost twice as many studies were performed with i.v. than with intrarenal administration. More importantly, other investigators have shown that isoproterenol is quite efficacious in elevating PRA when infused directly into the kidneys of anesthetized dogs (31, 123, 212, 1078, 1227), into isolated perfused kidneys (1125, 1135, 1157), or added to renal cortical slices in vitro (1197).

However, it should be pointed out that more recent studies by Johnson et al. (535a, 537a) support the idea that circulating catecholamines may increase PRA by activation of extrarenal beta-adrenergic receptors. The i.v. infusion of epinephrine into conscious uninephrectomized dogs elevated PRA by 3.5-fold, but the infusion of epinephrine into the renal artery did not increase PRA. Mean arterial pressure decreased in the former situation but not in the latter experiment. The renin response to epinephrine was blocked by *l*-propranolol. Intravenously-administered isoproterenol increased PRA more than did epinephrine, but epinephrine was more potent than norepinephrine (537a). Subsequently, it was shown that the rise in PRA caused by i.v. epinephrine in conscious dogs was not blocked or impaired by splenectomy (to prevent the increase in hematocrit caused by epinephrine), renal denervation (to prevent the reflex activation of the renal sympathetic nerves), the maintenance of plasma potassium concentration (to counteract the hypokalemia caused by epinephrine), or indomethacin (to inhibit the synthesis of prostaglandins) (535a). The authors concluded that the intrarenal beta-adrenergic receptors controlling renin release were activated only by increasing neural activity or by concentrations of circulating catecholamines above the physiologic range.

Hypertension caused by pheochromocytoma is associated with increased circulating levels of epinephrine and/or norepinephrine and PRA is often elevated in these patients (483, 502, 687, 1151). Maebashi et al. (687) noted that those patients who had tumors that secreted more norepinephrine than epinephrine had elevated PRA values whereas those patients who secreted more epinephrine than norepinephrine exhibited normal renin values. Conversely, Vetter et al. (1151) reported just the opposite situation. Fray et al. (352) studied the effects of hypersecretion of norepinephrine from a transplantable pheochromocytoma on renin release. The rats possessing this tumor had suppressed PRA values not related to changes in renal renin content. Furthermore, renal baroreceptor-stimulated renin release was suppressed in isolated, perfused kidneys taken from these animals. The exact role of catecholamines in altering renin release in pheochromocytoma is in need of further study.

Concerning the role of dopamine in renin release, it was originally reported that intrarenally administered dopamine increased renin release if given to dogs with chronic hypertension but was without effect in normal dogs (37). Later, i.v. dopamine in doses that resulted in a significant elevation of blood pressure was found to increase PRA in anesthetized dogs (856). Chokshi et al. (212) reported that the administration of dopamine directly into the renal artery of anesthetized dogs resulted in a slight decrement in renal venous PRA and an increment in RBF in both the presence and absence of propranolol. However, Imbs et al. (514) found that renin secretion increased 4-fold when dopamine was infused into the denervated kidneys of anesthetized dogs. Renal blood flow rose, but MAP, urine volume, and sodium excretion were not altered. Furthermore, the dopaminergic antagonist haloperidol, but not propranolol, blocked the increments in renin secretion and RBF caused by dopamine. Thus, dopamine-induced renin release appeared to be due to activation of specific dopamine receptors within the kidney.

Dopamine has not been demonstrated to have a consistent effect on renin release in humans. On the basis of changes in PRA and changes in the ratio of dopamine/norepinephrine in the urine in response to upright posture in normotensive and hypertensive patients, Barbeau (55) postulated that an increase in the ratio of dopamine/norepinephrine at the kidney would inhibit renin release. Horky et al. (502) reported a similar negative correlation between the ratio of urinary dopamine/norepinephrine and PRA, in both the recumbent and upright position, in 71 patients suffering from hypertension of differing causes. However, when dopamine was actually infused into normal humans, PRA either did not change (35, 810a) or was increased (1212). In the latter case (1212), equipressor doses of dopamine and norepinephrine had exactly the opposite effects on renin release. When dopamine was infused i.v. into cirrhotic patients with elevated PRA values and various degrees of renal impairment, PRA decreased in conjunction with an increase in RPF (58). Since MAP and sodium excretion were unchanged, the decrement in PRA probably was due to the increase in afferent arteriolar wall tension that occurred when the renal vasculature was vasodilated at a constant renal perfusion pressure (58). Since dopamine, unlike

norepinephrine or epinephrine, vasodilates the renal vasculature in doses that elevate MAP (712), and since dopamine has become a useful agent in the treatment of cardiogenic shock, the effects of dopamine on renin release in humans need to be better defined.

C. EFFECTS OF CATECHOLAMINES ON RENIN RELEASE IN VITRO. A number of investigators have used renal cortical slices in vitro to examine the direct action of catecholamines on renin release, thereby eliminating hemodynamic, tubular, hormonal, and neurogenic influences. In the first study of this type, Michelakis et al. (744) found that both norepinephrine (2.7×10^{-6} M) and epinephrine (5.4×10^{-6} M) increased the "net production" of renin from canine renal cell suspensions. Several years later, Rosset and Veyrat (961) reported that norepinephrine (10^{-5} M) stimulated renin release from human kidney slices in vitro. Renin release from feline renal cortical cells also was reported to be stimulated by isoproterenol as well as by norepinephrine and epinephrine (526). In the first thorough pharmacologic study, Nolly et al. (805) observed that *l*-norepinephrine elicited a concentration-related increase in renin release whereas *d*-norepinephrine was without effect. In addition, norepinephrine-induced renin release was blocked by *l*-, but not *d*-, propranolol. Neither phentolamine nor phenoxybenzamine affected basal renin release in vitro, but both alpha-adrenergic antagonists potentiated the renin release caused by *l*-norepinephrine (805). When ascorbic acid was added to the incubation media in order to prevent the oxidation of catecholamines, Weinberger et al. (1197) discovered that norepinephrine, epinephrine, and isoproterenol elicited a concentration-related increase in renin release from rat kidney slices at concentrations ranging from 10^{-9} M to 10^{-7} M. Thus, Weinberger et al. (1197) demonstrated that both norepinephrine and epinephrine were capable of elevating renin release in vitro in concentrations that were comparable to those observed in conscious rats in vivo (945). In addition, norepinephrine-, epinephrine-, and isoproterenol-induced renin release was inhibited by *d,l*- and *l*-propranolol but was not affected by *d*-propranolol or phentolamine. Recently, a new technique has been developed whereby renin release from isolated rat glomeruli can be studied (771). When superfused in vitro, these glomeruli, which include fragments of afferent arteriole but are free of renal tubules, increased their rate of renin release when exposed to norepinephrine, epinephrine, or isoproterenol.

Concerning the effect of dopamine on renin release in vitro, Henry et al. (474) found that a significant increase in renin release occurred at dopamine concentrations of 10^{-5} M in the presence of ascorbic acid. However, when tissue monoamine oxidase was inhibited with phenipraZine, as little as 10^{-8} M dopamine elevated renin release. Because dopamine-induced renin release was blocked by *d,l*-propranolol, but was not altered by phentolamine, cocaine, or haloperidol, it was concluded that dopamine stimulated renin release by interacting with beta-adrenergic receptors rather than dopaminergic receptors. These observations are in direct opposition to those of Imbs et al. (514), who stated that dopamine-induced renin release was due to stimulation of specific dopamine receptors within the kidney. As mentioned previously, the effects of dopamine on renin release need to be better characterized.

Catecholamines also increase renin release from the isolated, perfused kidneys of rats (1016, 1125, 1131, 1135), rabbits (1157), and cats (444). In the first studies of this type, Vandongen et al. (1125, 1135) determined that isoproterenol elevated renin release from the Krebs-dextran perfused rat kidney in the absence of any change in perfusion pressure or perfusate flow. The elevation of renin release caused by isoproterenol occurred rapidly and was prevented by *d,l*-propranolol but not by *d*-propranolol or phenoxybenzamine. Norepinephrine increased renin release 4- to 6-fold in association with a 60% increase in renal perfusion pressure and no change in perfusate flow. The increment in renin release elicited by norepinephrine was blocked by *d,l*-propranolol and was greatly potentiated by phenoxybenzamine, which also prevented the rise in renal perfusion pressure. In later studies, these same researchers (1131) found that nonvasconstrictor doses of both norepinephrine and epinephrine stimulated renin release in this system and, as before, this stimulation of enzyme release was prevented by *d,l*-propranolol and accentuated by phenoxybenzamine. Small doses of isoproterenol also have been demonstrated to elevate renin release from the isolated, blood-perfused rabbit kidney in the absence of changes in renal vascular resistance, RPF, or serum potassium levels (1157). Again, isoproterenol-induced renin release was blocked by propranolol (1157). Harada and Rubin (444), in isolated feline kidneys perfused with Locke's solution, found that norepinephrine caused a dose-related increase in renin release in the presence of phenoxybenzamine that was blocked by propranolol.

Related to catecholamine stimulation of renin release, Fishman (339) studied the effect of epinephrine on the membrane potential of granular JG cells in vitro. Mechanically isolated granular JG cells from mice exhibited a resting potential of approximately −70 mV, and epinephrine (10^{-4} M) slightly hyperpolarized the cells. Epinephrine also has been shown to hyperpolarize smooth muscle cells and, as mentioned above, the granular JG cells are modified smooth muscle cells. Thus, at the cellular level, catecholamines may increase renin release from granular JG cells by hyperpolarization and a subsequent alteration of calcium transport.

D. ROLE OF ALPHA-ADRENERGIC RECEPTORS IN RENIN RELEASE. As was seen in the preceding discussion, a wealth of information has accumulated to indicate that the renal sympathetic nerves and circulating norepineph-

rine and epinephrine elicit renin release by the stimulation of intrarenal beta-adrenergic receptors rather than by altering renal hemodynamics or electrolyte excretion. This concept is of cardinal importance when considering the effects of drugs on renin release since most drugs, either directly or indirectly, alter the functional status of the autonomic nervous system. While the stimulatory role of beta-adrenergic receptors in the control of renin release is quite clear, the exact role of renal alpha-adrenergic receptors is a subject of controversy.

Several investigators have hypothesized that alpha-adrenergic receptor stimulation may inhibit renin release. The first suggestion of such an occurrence was by Pettinger et al. (890), who constructed renin release dose-response curves with norepinephrine, epinephrine, and isoproterenol in conscious rats. Whereas isoproterenol elicited a linear, dose-related increase in PRA, epinephrine stimulated renin release at small doses but depressed PRA values back to the control level as the dose was increased. On the other hand, norepinephrine caused a dose-related decrease in PRA (down to 85% of the control value) at low doses, but renin release was stimulated as the dose of norepinephrine was increased. It was suggested that a dynamic balance existed between beta-adrenergic stimulation and alpha-adrenergic depression of renin release in this model. However, this study was limited by the fact that the patterns of renin release obtained could be explained partly on the basis of the changes in blood pressure caused by these agents. Later Vandongen and Peart (1133) reported that the alpha-adrenergic agonist methoxamine antagonized isoproterenol-induced renin release in the isolated, perfused rat kidney. In addition, methoxamine has been demonstrated to prevent isoproterenol-induced renin release from rat kidney slices in vitro (1197). The fact that alpha-adrenergic antagonists have been shown to potentiate norepinephrine-induced renin release from kidney slices in vitro (805) and from the isolated perfused rat kidney (1125, 1131, 1135) could be interpreted as evidence for alpha-adrenergic receptor-mediated inhibition of renin release.

However, other explanations for these results are possible. For instance, Weinberger et al. (1197) have suggested that the potentiating effect of alpha-adrenergic blocking agents on norepinephrine-induced renin release in vitro was due to the ability of these drugs to block the uptake of norepinephrine and thereby increase the amount of norepinephrine available for beta-adrenergic receptor stimulation. Furthermore, these investigators demonstrated that methoxamine inhibited isoproterenol-induced renin release in vitro by beta-adrenergic blockade rather than by alpha-adrenergic stimulation (1197).

As was pointed out by Adler-Graschinsky and Langer (9), the concentration of norepinephrine required to activate postjunctional alpha-adrenergic receptors is 30 to 100 times higher than that necessary to activate postjunctional beta-adrenergic receptors. This being the case, norepinephrine should stimulate renin release in vitro at small doses and inhibit release at large doses if alpha-adrenergic activation does indeed inhibit renin release. In this respect, Desaulles et al. (272), Capponi and Vallotton (189), and Morris et al. (771a) reported that norepinephrine (10^{-5} M) inhibited renin release from rat kidney slices in vitro. In these studies, isoproterenol was shown to cause a concentration-related increase in renin release that was lessened by *d,l*-propranolol. Furthermore, the inhibitory effect of norepinephrine on renin release was reversed by phentolamine (272, 771a) and phenoxybenzamine (189). In a similar fashion, low concentrations (10^{-12} to 10^{-7} M) of norepinephrine caused a dose-related increase in renin release from renal cortical slices obtained from sodium-depleted rats, but a higher concentration (10^{-4} M) of norepinephrine inhibited renin release (669). In the presence of phentolamine, this high concentration of norepinephrine (10^{-4} M) stimulated renin release (669). These results suggest that there is a bimodal dose-response curve for norepinephrine-induced renin release in vitro. However, other investigators (805) have reported that norepinephrine elevated renin release at the same concentration (10^{-5} M) used by Capponi and Vallotton (189). Morris et al. (771a) also found that epinephrine (10^{-5} M) and methoxamine (10^{-5} M) inhibited renin release, an effect blocked by phentolamine. The alpha-adrenergic agonists phenylephrine, oxymetazoline, and clonidine did not change renin release in vitro. More recently, Meyer and Herrmann (733) reported that tyramine, an indirectly acting sympathomimetic agent, diminished isoproterenol-induced renin release in a dose-dependent fashion in conscious rats. If the dose of isoproterenol was increased, tyramine no longer attenuated the effect of isoproterenol on renin release. Since renal denervation or pretreatment with reserpine or phenoxybenzamine abolished the inhibitory effect of tyramine on isoproterenol-induced renin release, it was concluded that tyramine released catecholamines that acted on inhibitory alpha-adrenergic receptors within the kidney. It is interesting to note that a very small dose of tyramine potentiated the rise in PRC elicited by isoproterenol. The authors (733) suggested that this small dose of tyramine released an amount of norepinephrine that, although too small to activate the inhibitory alpha-adrenergic receptors, was sufficient to activate stimulatory beta-adrenergic receptors. This suggestion is consistent with the greater potency of norepinephrine at beta-adrenergic receptors as compared to alpha-adrenergic receptors (9). It is probable that the inhibitory doses of tyramine released a much greater amount of norepinephrine within the kidney than would be released by even high frequencies of renal nerve stimulation. Therefore, although certain drugs such as clonidine appear to suppress renin release by an action at renal alpha-adrenergic receptors (894), the exact role of these intrarenal alpha-

adrenergic receptors in the endogenous neurogenic control of renin release remains to be resolved. However, it is generally recognized that an increase in sympathetic nerve activity in the kidney will result in an increase, rather than a decrease, in renin release.

3. Parasympathetic nervous system. Acetylcholinesterase-containing fibers have been identified within the kidney (48, 718, 776), and there is physiologic evidence for the existence of renal vasodilatory fibers (621, 1230). More specifically, acetylcholinesterase-containing fibers have been demonstrated to innervate cells of both the proximal and distal tubules (776) as well as the afferent arteriole (718). However, it cannot be stated with absolute certainty that these fibers represent renal cholinergic nerves since renal noradrenergic fibers have also been demonstrated to contain acetylcholinesterase (51a). Intrarenally administered acetylcholine has been shown to increase RPF, urine volume, and sodium and potassium excretion, but had a variable effect on GFR (521, 1114). All of these changes were reversed or prevented by atropine (1114). In addition, Stinson et al. (1043) have presented evidence indicating that the decrease in renal vascular resistance observed during renal arterial hypotension in conscious dogs is mediated, in part, by cholinergic nerves.

Although the influence of the sympathetic nervous system on renin release has been well established, efferent parasympathetic nerves have not been demonstrated to affect renin release. Renin release can be modified by afferent vagal fibers arising in the cardiopulmonary region (21, 136, 689, 690, 1038, 1081, 1084, 1269); however, these afferent sensory fibers cannot be considered cholinergic fibers just because they are found within the vagus. In addition, these vagal fibers actually constitute the afferent limb of a reflex arc that ultimately modifies renin release via efferent sympathetic fibers (1083). Although Brennan et al. (137) showed that right atrial distension, a maneuver that is known to increase parasympathetic activity consistently (375), decreased renin release in anesthetized dogs, this effect was probably due to a reflexly induced decrement in renal sympathetic nerve activity (21, 689, 690, 1801, 1269) rather than to an increase in efferent parasympathetic activity. Therefore, at this time, there is no evidence to suggest that efferent parasympathetic fibers can modify renin release.

It was first reported that intrarenally infused acetylcholine had no effect on renin release in normal anesthetized (164) and conscious (37) dogs, but would increase PRA in conscious dogs with chronic, renovascular hypertension and normal PRA levels (37). Abe et al. (5) have reported that renin secretion failed to change in anesthetized dogs during the intrarenal infusion of acetylcholine at normal renal perfusion pressures, despite the fact that total RBF increased more than 2-fold. Also, an intrarenal infusion of acetylcholine did not alter the increment in renin secretion caused by renal arterial hypotension (5). When Tagawa and Vander (1069) induced renal dilatation with acetylcholine in salt-depleted anesthetized dogs, renal venous PRA was suppressed only in those dogs with an initial high renal vascular resistance. However, since a significant natriuresis occurred in all dogs, the suppression of renin release in these three animals could have occurred via the macula densa. In addition, renal afferent arteriolar vasodilatation at a constant renal perfusion pressure would result in an increase in wall tension that should suppress renin release. In a similar fashion, Osborn et al. (848) found that an intrarenal arterial infusion of acetylcholine into one kidney of anesthetized dogs caused an ipsilateral increase in RBF and sodium excretion but essentially no change in renin secretion. Lastly, acetylcholine had no effect on renin release from the rat renal slice in vitro (276). In conclusion, the effects of exogenously supplied acetylcholine on renin release are poorly defined and are probably of only pharmacologic interest. Acetylcholine does not alter renin release directly, but rather appears to act indirectly by changing sodium excretion (521), vascular tone (5, 521, 1069), or adrenergic neuronal activity (667a).

C. Renal Sodium Metabolism and the Macula Densa Segment of the Distal Tubule

The macula densa region of the distal tubule is composed of a specialized group of columnar or cuboidal cells that are in close contact with the granular JG cells of the glomerulus from which the tubule originates (53, 400). The macula densa is usually found at the boundary of the ascending loop of Henle and the distal tubule (1116). Both light and electron microscopy have revealed that the macula densa and the granular cells of a single nephron are so intimately related that at times only an incomplete basement membrane separates them. Vander (1116) has presented an excellent review of the anatomical and biochemical evidence that suggests a functional relationship between the macula densa cells and the granular cells of the JG apparatus.

Three decades ago, Goormaghtigh (400) recognized this intimate relationship between the granular and the macula densa cells and suggested that GFR was in some way controlled by the ionic composition of the tubular urine at the macula densa via the release of renin by the granular cells. The hypothesis that renin may in some way control single nephron GFR still has its proponents (435, 788, 990, 1090, 1092), but this control mechanism does not require the secretion of renin into the venous blood. Thurau et al. (1090, 1092) have reported results from retrograde microinjection studies that support this hypothesis, but these data provide little insight into the relationship between changes in the composition of the tubular fluid at the macula densa and changes in the rate of renin secretion into the blood. The role of the macula densa as a sensor for renin secretion, as opposed to a role in regulating single nephron GFR, will be discussed here.

In 1963 Brown et al. (143) discovered that sodium depletion in humans elevated PRA and that sodium

loading suppressed PRA. In subsequent years this observation has been corroborated by many researchers in humans (11, 144, 155, 227, 261, 389, 907, 950, 1153), dogs (88, 149, 344, 373, 406, 533, 757), rats (255, 344, 397, 416, 448, 572, 894), rabbits (1037), and sheep (104, 105). Total daily sodium excretion falls to very low levels during sodium depletion due to a decrease in the fractional excretion of the filtered sodium load. Since much of the increase in the efficiency of sodium reabsorption occurs in the proximal tubule (758, 1038), the tubular sodium concentration and sodium load (the product of sodium concentration and tubular fluid flow rate) passing the macula densa segment of the distal tubule will be decreased. Conversely, sodium loading results in an increase in total daily sodium excretion. The fractional reabsorption of sodium decreases in the proximal tubule (277, 281), and the tubular sodium concentration and sodium load passing the macula densa cells is increased. Based on these observations alone, it would be reasonable to conclude that a decrease in sodium transport into the macula densa cells would constitute a stimulus to renin release whereas an increase in sodium transport at the macula densa cells would suppress renin release.

Vander and Miller (1124) conducted the first study designed to determine the relationship between tubular sodium transport and renin release. They noted an inverse correlation between the control sodium excretion and renal venous PRA in anesthetized dogs. There was no correlation between renal venous PRA and MAP, RPF, filtration fraction, or plasma sodium concentration. This same reciprocal relationship was observed during suprarenal aortic constriction sufficient to decrease sodium excretion without changing RPF or GFR. If sodium excretion was restored during renal hypotension by the administration of osmotic diuretics (urea, mannitol, or sodium sulfate), renal venous PRA was suppressed back to prehypotensive levels. Induction of diuresis with urea, mannitol, acetazolamide, or chlorothiazide 40 min before aortic clamping severely blunted the increase in renin release normally elicited by renal arterial hypotension. Based on these observations, Vander and Miller (1124) stated that a decrement in tubular sodium concentration or load in the region of the macula densa stimulated renin secretion. They advanced the following argument. The tubular urine passing the macula densa has a sodium concentration less than that of plasma as a result of sodium reabsorption in the thick ascending limb of the loop of Henle. Thus the sodium concentration at the level of the macula densa will depend on the flow rate from the ascending loop of Henle, which in turn will depend on the flow rate from the proximal tubule. During renal arterial hypotension, the urine flow rate decreases in both segments and sodium reabsorption is increased. As a result, sodium transport at the macula densa also decreases. Diuretics increase the urinary flow rate through the proximal tubule and the loop of Henle and increase the sodium content of tubular urine. The increase in sodium transport at the macula densa then suppresses renin secretion back to control levels.

A definitive test of this macula densa hypothesis would require an analysis of the composition of the tubular fluid in this region of the nephron during conditions of altered sodium transport; however, the macula densa region and the adjacent portion of the ascending limb are not accessible to micropuncture. Although the results of one micropuncture study have been reported (216), most subsequent investigations of this mechanism have involved the use of physiologic or pharmacologic perturbations to alter renal sodium excretion in an attempt to relate the rate of renin release to changes in sodium metabolism. The pharmacologic approach proved to be of limited value since it initially led to the establishment of two schools of thought. One group (90, 230, 740, 1090, 1092) proposed that an increase in renin release resulted from an increase in sodium transport at the macula densa whereas the other (216, 357, 783, 1120, 1124) believed that renin release was inversely related to sodium transport at the macula densa.

Since the "loop" diuretics were known to inhibit sodium reabsorption in the thick ascending limb of the loop of Henle (1002, 1060) and led to a large increment in the sodium content of the tubular urine passing the macula densa, Meyer et al. (740), Cooke et al. (230), and Birbari (90) examined the effects of these drugs on renin release. Meyer et al. (740) found that furosemide caused a rapid 3-fold increase in PRA and a 15-fold increase in sodium excretion when injected i.v. into anesthetized, uninephrectomized rabbits. The rise in plasma renin was attenuated by expansion of the extracellular fluid (ECF) volume with isotonic saline or salt-poor serum albumin. However, it is unlikely that the renin release was due to a decrease in the extracellular fluid volume since similar renin responses were obtained in rabbits with ureteral-vena caval anastomoses. They concluded that furosemide-induced renin release was the result of an increase in tubular sodium concentration, but also suggested that the original Vander hypothesis might be correct if furosemide inhibited sodium transport into the macula densa cells (740). This would account for the inability of furosemide-induced natriuresis to inhibit renin secretion.

Cooke et al. (230) found that ethacrynic acid brought about a 3-fold increase in renin release in anesthetized dogs within 5 min. At this time, urine flow and sodium excretion had increased by 18- and 30-fold, respectively. When volume depletion was prevented by ureteral vena caval anastomosis, the increase in PRA evoked by the drug was not affected. When chlorothiazide was administered in a similar experiment, renal venous PRA was not changed. For further study of the mechanism by which ethacrynic acid elicited renin release, urinary stop-flow studies were conducted. Ureteral occlusion alone increased renal venous PRA by 2-fold, and PRA returned to control levels after release of the clamp. In a second experiment, ureteral clamping again elevated renal ve-

nous PRA; however, administration of ethacrynic acid at this point induced no further increment in PRA values. When urine flow was allowed to resume, PRA remained elevated (four times the control values) at a time (15 min) when sodium-rich urine was passing through the nephron. These researchers suggested that ethacrynic acid increased renin release either by a direct effect on the granular cells of the JG apparatus or by increasing the sodium load or concentration at the macula densa. However, they also suggested that ethacrynic acid might inhibit sodium transport at the macula densa cells. Chlorothiazide supposedly failed to increase renin release because 1) sodium and volume losses were prevented by the infusion of the urine produced, and 2) chlorothiazide would not increase sodium delivery to the distal tubule as much as would ethacrynic acid (230).

Birbari (90) administered ethacrynic acid or mannitol to anesthetized dogs to increase tubular sodium concentration in the region of the macula densa. Ethacrynic acid increased PRA by 2.4-fold at a time when sodium excretion had increased 32-fold. Hypertonic mannitol also induced a natriuresis, but in this instance PRA dropped by 30%. In spite of the data obtained with mannitol, Birbari also concluded that renin secretion was stimulated by an increase in the urinary sodium concentration at the macula densa. It should be pointed out that none of these researchers (90, 230, 740) attempted to relate their findings to the alterations in PRA and renal salt metabolism that were known to occur after sodium depletion or sodium loading.

Although later we will discuss in great detail the mechanism by which furosemide and ethacrynic acid increase renin secretion, the reader should be apprised at this time that both drugs have direct effects on renin release that are not related to their diuretic activity but are probably mediated via the renal baroreceptor mechanism, the renal sympathetic nerves, renal prostaglandins, and/or a direct effect on the granular JG cells of the afferent arteriole (45, 235, 303, 847, 1120). In addition to these direct effects on renin release, furosemide and ethacrynic acid appear to inhibit ion transport at the macula densa cells (989) and thus prevent the macula densa from sensing the increase in sodium concentration and load caused by these drugs. These facts being considered, the aforementioned observations (90, 230, 740) are easily reconciled with the original hypothesis of Vander (1124). Subsequent studies have indeed proved that renin release is inversely related to sodium excretion.

Freeman et al. (357) used ureteral occlusion to study the effects of sodium excretion on renin secretion in anesthetized dogs with a single kidney. As expected, ureteral clamping alone increased renin secretion to five times the control values without changing RBF. Intrarenal infusion of papaverine at this point elevated RBF but caused no further elevation of renin release. After the release of the ureteral clamp, renin secretion fell to below control levels within 5 min and serial urine samples revealed a large increase in sodium excretion. When the same experimental procedure was performed in a second group of dogs receiving ethacrynic acid instead of papaverine, renin secretion declined slowly after restoration of urinary flow despite the fact that the subsequent natriuresis was of the same magnitude as that seen after stop-flow studies with papaverine. Despite the fact that renin secretion decreased during the postocclusion period, it still remained twice as high as the control values. This degree of elevation of renin secretion was the same as that seen when ethacrynic acid was infused into the kidney in the absence of ureteral clamping. Freeman et al. concluded that ethacrynic acid had direct renin-releasing effects and that the rate of renin release was inversely related to the rate of sodium transport at the macula densa. Although Freeman et al. (357) did not mention it, comparison of their data obtained with papaverine and ethacrynic acid strongly support the idea that ethacrynic acid inhibits sodium transport at the macula densa cells.

Fortunately, a great deal of the research in this area has involved physiologic manipulation of sodium excretion that did not involve the administration of diuretics. For instance, Nash et al. (783) studied renin secretion in anesthetized dogs during normonatremic and hyponatremic volume expansion. Volume expansion with an i.v. infusion of isotonic (0.85%) saline increased the fractional excretion of sodium by 30% and suppressed renin secretion. Infusion of hypotonic (0.42%) saline decreased the fractional excretion of sodium by 60% and increased renin secretion to about five times the control values. In addition, volume expansion incurred by the i.v. infusion of hypotonic saline increased renin release from both kidneys, but a unilateral, intrarenal infusion of isotonic saline, which was sufficient to restore sodium excretion back to normal, suppressed renin secretion only in the infused kidney. An intrarenal arterial infusion of isotonic saline also prevented the increment in renin release normally observed during renal arterial hypotension. This saline infusion increased sodium excretion by 60%, compared to prehypotensive values, despite the fact that GFR and renal perfusion pressure were greatly reduced. No relationship between renin release and renal hemodynamics, water balance, or renal vein plasma sodium concentration was detected. These observations indicate that there is a reciprocal relationship between the rate of renin secretion and the filtered sodium load and fractional excretion of sodium.

Churchill et al. (214) studied renin secretion from the kidneys of anesthetized dogs during repeated stop-flow maneuvers. The animals were infused i.v. with 10% mannitol in 0.15 M sodium chloride, and renin release was measured during a sequence of 10-min periods of clearance, ureteral clamping, and clearance. Thirty minutes later these procedures were repeated in half of the dogs. In the remaining dogs, 10% mannitol in 0.1 M sodium sulfate was infused during the second stop-flow sequence.

The ratio of the renin values measured during the second stop-flow period (SF_2) to the renin values during the first stop-flow period (SF_1) was one for the animals infused with mannitol in the sodium chloride solution, indicating that ureteral occlusion reproducibly increased renin secretion. In the dogs that received mannitol in the sodium sulfate solution during SF_2, the ratio of the renin values was 0.5, indicating that replacement of 0.15 M sodium chloride with 0.1 M sodium sulfate reduced by 50% the effect of ureteral occlusion on renin release. Since replacement of sodium chloride with sodium sulfate resulted in a higher distal tubular sodium concentration after SF_2, it was decided that renin release was inversely related to sodium concentration or load.

Humphreys et al. (507) used an ingenious approach to study the role of altered sodium excretion in the control of renin release. Isolated canine kidneys were perfused at a constant pressure with blood circulating from a donor dog, and the effect of changes in sodium excretion on renin release from the perfused kidney was compared with that of changes in the in situ kidney of the donor dog. During intravascular volume expansion with canine blood, GFR, RBF, and sodium excretion increased in the in situ kidney whereas renin release decreased by nearly 90%. None of the parameters changed in the isolated kidney. This volume expansion resulted in a 47% increase in MAP in the donor dog, but of course renal perfusion pressure was held constant in the isolated kidney. Although sodium excretion from the in situ kidney increased by 4-fold, the increase in MAP also could have contributed to the suppression of renin relase. Hemorrhage, sufficient to drop MAP by 35%, did not affect renal function or renin secretion in the perfused kidney. In the in situ kidney, GFR, RBF, and sodium excretion decreased but renin secretion was not changed. The most important observation made by Humphreys et al. (507) occurred during hemodilution without volume expansion. Since GFR was held constant in the perfused kidney as plasma oncotic pressure dropped, sodium excretion was increased 3.4-fold as renin secretion fell by 72%. Hemodilution resulted in a decrease in intravascular volume in the donor dog (a 38% decrease in MAP was recorded), which in turn led to a 40% drop in GFR in the in situ kidney. Sodium excretion in this kidney fell to 48% of the control values and the rate of renin secretion tripled. Restoration of plasma oncotic pressure by the infusion of hyperoncotic albumin reversed the effects of hemodilution on sodium excretion and renin release in the isolated perfused kidney. It is unlikely that the effect of hemodilution on renin release from the in situ kidney resulted from the hypotension since hemorrhage-induced hypotension of the same magnitude did increase renin secretion. Therefore, the results of the hemodilution experiments provide dramatic proof that the rate of renin release is inversely related to sodium excretion.

Recently, Churchill et al. (216) examined the relationship between renin secretion and distal tubular sodium concentration and load in anesthetized rats. These sodium measurements were made in the cortical distal tubules, at approximately 21% of the total length of the distal tubule, of sodium-loaded, control and sodium-depleted rats, at steady states of sodium balance. They found that early distal tubular sodium load, but *not* sodium concentration, was directly related to the dietary intake of sodium, and that the rate of renin secretion was inversely related to dietary sodium intake. More important, when the logarithm of the rate of renin secretion in each individual rat was plotted as a function of the sodium load in the distal tubule, a close inverse relationship was noted. In a more recent study, Churchill et al. (215a) found that both saline- and mannitol-induced diuresis decreased renin secretion and increased sodium load in the early distal tubule of the anesthetized rat. However, the sodium concentration of the tubular fluid was increased by saline and decreased by mannitol. Although the use of conventional micropuncture techniques forced the collection of tubular fluid downstream from the macula densa in only cortical nephrons, this inverse relationship between renin secretion and tubular sodium load is consistent with the hypothesis that changes in dietary sodium intake elicit changes in the sodium load at the macula densa that in turn mediate changes in the rate of renin secretion. In addition, it appears that both the sodium concentration of the tubular fluid at the macula densa and the rate of flow of the fluid in this region of the nephron are important determinants of the control of renin secretion by the macula densa.

In studies designed to determine whether glomerular filtration was necessary for sodium to inhibit renin release, Shade et al. (1008) measured renin secretion in anesthetized, thoracic caval-constricted dogs with either a single filtering or nonfiltering kidney. Intrarenal infusions of hypertonic saline sufficient to increase renal venous plasma sodium concentration from 141 to 158 mEq/l in dogs with a filtering kidney resulted in a 70% decrease in renin release and a 13-fold increment in sodium excretion. A similar infusion into dogs with a nonfiltering kidney had no effect on renin release even though the plasma sodium concentration of renal venous blood rose from 139 to 156 mEq/l. These data indicated that the inhibition of renin release by sodium chloride was mediated by a renal tubular mechanism and eliminated the possibility of a vascular action or a direct effect of sodium chloride on the granular cells of the JG apparatus.

When the data of all of these researchers (90, 214, 216, 230, 357, 507, 740, 1008, 1124) are considered collectively, it is apparent that renin secretion, as controlled by the macula densa, is inversely related to tubular sodium load. This relationship, as established in animal experiments, is consistent with the observations made during sodium depletion and sodium loading in humans. Even though earlier reports (90, 230, 740) suggested that renin release

was directly related to sodium transport at the macula densa cells, we now know that the use of diuretics that block sodium transport at the macula densa in these experiments led to conclusions that conflicted with other reports.

Concerning the macula densa mechanism controlling renin release, four other topics need to be considered. They are: 1) the effect of acute changes in the osmolarity or oncotic pressure of renal arterial blood on renin release; 2) the role of ECF volume expansion per se in suppressing PRA during saline infusion; 3) whether it is sodium or chloride ion that is sensed by the macula densa cells; and 4) whether sodium ion has a direct effect on the granular JG cells to suppress renin release.

The effect of osmotic changes on renin release was investigated by Young and Rostorfer (1250). They infused hypertonic solutions of sodium chloride, dextrose, and urea intrarenally for 30 to 60 sec in pentobarbital-anesthetized dogs. These infusions increased renal arterial plasma osmolarity by an average of 45 mOsm/l and consistently increased renin secretion approximately 4-fold. Both RBF and GFR were elevated by the infusions. These investigators felt that the hyperosmolarity of the arterial blood had a direct effect on the volume of the granular cells of the JG apparatus that caused them to increase their rate of renin secretion. However, it should be pointed out that the release of renin from isolated rat renal glomeruli in vitro was inhibited when the superfusate osmolality was increased by 30 mOsm/l (354). Although hyperosmolar solutions infused into the renal artery eventually induced a natriuresis that suppressed renin release via the macula densa, determination of the exact mechanism by which an increase in renal arterial plasma osmolarity elicits an initial increase in renin release will require additional study.

On the other hand, the mechanism by which intrarenal arterial infusion of hyperoncotic solutions stimulate renin secretion has been identified with reasonable certainty. Hall and Guyton (434) elevated the oncotic pressure of plasma entering the kidney by infusing dextran or human serum albumin into the renal arteries of anesthetized dogs. Renal venous colloid osmotic pressure increased 7 to 10 mm Hg during the infusion of dextran or albumin, and renin secretion rose 3-fold. RBF was consistently increased, urine flow and sodium excretion were decreased, and GFR was unchanged or slightly decreased. The elevated renin secretion was compatible with activation of the macula densa mechanism that regulates renin release. The urinary flow rate was reduced probably as a result of enhanced tubular reabsorption of sodium in response to increased plasma oncotic pressure in the peritubular capillaries (1034). This increased reabsorption led to a decrease in sodium excretion (434) that was sensed by the macula densa cells. It is noteworthy that Humphreys et al. (507) found that at a constant renal perfusion pressure a decrease in renal plasma oncotic pressure had exactly the opposite effect, i.e. renin release fell as sodium excretion increased. It is important to remember that the molecular and ionic constitutents of the hyperosmolar solutions used by Young and Rostorfer (1250) are freely filtered whereas dextran and human serum albumin (434), because of their high molecular weight, are not filtered at the glomerulus. As a result, the initial increase in renin secretion induced by hyperosmolar and hyperoncotic solutions may be due to activation of different intrarenal mechanisms.

Another important point to consider when discussing the macula densa and its ability to regulate renin release is whether the volume expansion per se that accompanies i.v. saline infusion contributes to the suppression of PRA. Since saline infusion reduces the proximal tubular reabsorption of sodium, probably by raising glomerular capillary pressure and reducing oncotic pressure in the peritubular capillaries (587), the delivery of sodium to the distal tubule rises and suppresses renin release via the macula densa. However, the expansion of ECF volume could conceivably depress renin release via the renal baroreceptor or by reflexly decreasing renal sympathetic nerve activity (986). Several groups of investigators have approached this problem in different ways.

In a very comprehensive study, Blair-West et al. (103) restricted the water intake of sheep for 10 to 17 days. During this time, PRC increased 2- to 3-fold. When the animals were then offered solutions containing 20, 35, 50, 70, or 141 mM sodium chloride, the sheep usually drank a volume of fluid approximately equal to what they had lost during dehydration. Plasma protein concentration declined to the same extent in every animal, regardless of the sodium content of the solution consumed, which indicated that there had been a uniform increase in plasma volume in each group of sheep. Ingestion of 20 or 35 mM salt solutions precipitated a decrement in plasma sodium concentration and sodium excretion whereas PRC rose or did not change. As the sodium content of the drinking solutions increased, sodium excretion was increased and PRC was suppressed. Suppression of PRC after drinking showed a significant inverse correlation with the amount of sodium consumed, the amount of sodium excreted, and the plasma sodium concentration. Blair-West et al. concluded that changes in PRC after rehydration were related to the amount of sodium consumed rather than to the alteration of plasma volume.

Anderson et al. (20) decreased intravascular and ECF volumes and increased PRA in conscious dogs by salt deprivation. In separate experiments, total ECF volume was restored with (Ringer's solution) or without (5% dextrose in water) sodium repletion, plasma volume alone was expanded (5% dextran in 5% dextrose in water), or plasma volume was increased as ECF volume decreased (20% dextran in 5% dextrose in water). Only the infusion of sodium-containing Ringer's solution significantly suppressed PRA even though all four infusions increased plasma volume and MAP to the same extent. Tuck et al. (1102) performed a similar study in normotensive hu-

mans who had been salt depleted for 6 days. Plasma renin activity was measured during the infusion of isotonic saline, 5% dextrose in water, or 40,000 molecular weight dextran in 5% dextrose in water. During saline infusion PRA was depressed by 25% and 50% at 10 and 60 min, respectively; however, the infusion of dextran did not significantly suppress PRA despite the fact that the increase in intravascular volume, as reflected in changes in hematocrit, was the same as that seen during saline infusion. In addition, PRA was not altered by the infusion of 5% dextrose in water. If activation of the renal baroreceptor and/or withdrawal of renal sympathetic tone during ECF volume expansion had contributed to the suppression of renin release, then each of these infusions should have suppressed PRA equally since intravascular volume was increased to the same extent in every case. Thus, these observations strongly support the idea that saline suppression of renin release results from a specific effect of sodium rather than volume expansion per se.

A similar conclusion was reached by Bull et al. (160) from studies with normotensive volunteers undergoing volume depletion with furosemide and sodium restriction. After 2 weeks, both blood and plasma volumes were decreased, the net sodium loss was 290 mEq, and PRA had increased from 1.3 to 5 ng of AI/ml/hr. At this point, positive sodium balance was induced by the oral administration of 185 mEq of sodium a day for 6 days while blood volume was maintained constant by serial plasmapheresis and/or phlebotomy. As sodium balance became positive (+33 mEq) and sodium excretion increased, PRA decreased to 2.2 ng of AI/ml/hr despite the fact that the mean blood volume was further decreased. The authors felt that these observations were best explained in terms of changes in tubular sodium transport during sodium depletion and repletion.

Stitzer and Martinez-Maldonado (1044) demonstrated that glomerular filtration was necessary for isotonic ECF volume expansion to depress PRA in anesthetized dogs. After PRA had been elevated from 15 to 42 ng of AI/ml/hr by bilateral ureteral clamping, rapid expansion of ECF volume with isotonic saline did not affect this stimulated renin release. Similarly, if this sequence were reversed, isotonic saline lowered basal PRA from 16.8 to 4.8 ng of AI/ml/hr and bilateral ureteral obstruction at this point returned PRA to control levels. Although ureteral occlusion still caused a 3-fold (PRA 4.8 to 14 ng of AI/ml/hr) increment in renin release after isotonic volume expansion, the absolute values obtained were much less than those observed after ureteral occlusion alone. The authors concluded that glomerular filtration was a prerequisite for isotonic ECF volume expansion to suppress PRA since this suppression appeared to depend on the delivery of fluid or solute to the distal nephron. However, Leenen et al. (644) noted that the administration of normal saline to dialysis patients with chronic renal failure suppressed PRA by 40% as blood pressure and plasma volume increased. Thus it would appear that the renal baroreceptor and the renal sympathetic nerves modulate the renin release in these functional anephric patients infused with normal saline. Taken collectively, these reports (20, 103, 160, 1044, 1102) indicate that saline suppression of renin release is due primarily to the effects of increased sodium transport in the renal tubules rather than volume expansion per se.

Until recent times, it was generally believed that the ion sensed by the macula densa cells was sodium and that changes in tubular sodium metabolism signaled a change in renin release. However, in 1976 Kotchen et al. (608) presented convincing evidence that chloride was more important than sodium in altering renin release via the macula densa. Plasma renin activity was elevated in rats by placing them on a low sodium chloride diet. After 1 week of dietary alteration, the animals were divided into three groups that received one of the following drinking solutions: deionized water (control group), isotonic sodium bicarbonate, or isotonic sodium chloride. Similar positive changes in sodium balance occurred in the sodium chloride- and sodium bicarbonate-treated groups. Plasma renin activity decreased in the rats drinking sodium chloride, but remained elevated in those animals drinking distilled water or sodium bicarbonate. Chloride balance was negative in the control and sodium bicarbonate-treated rats, but was positive in the animals drinking isotonic saline. Similar experiments were carried out in sodium-depleted rats given solutions of potassium bicarbonate or potassium chloride. Treatment with potassium chloride suppressed PRA in association with a positive chloride balance whereas potassium bicarbonate-treated animals exhibited a negative chloride balance and elevated PRA values. Potassium and sodium balances were positive in both groups. Thus, the suppression of renin release in these experiments correlated with net chloride balance rather than net sodium balance. In addition, acute volume expansion of anesthetized rats with isotonic sodium chloride or sodium bicarbonate revealed that, despite similar increments in plasma volume in the two groups of animals, sodium chloride lowered PRA to a much greater extent than did sodium bicarbonate. Since the chloride delivery, as determined by micropuncture, after ECF volume expansion with isotonic sodium chloride was greater than after expansion with isotonic sodium bicarbonate, these authors concluded that sodium bicarbonate and potassium bicarbonate failed to suppress PRA because they did not increase the distal tubular delivery of chloride to the macula densa. Furthermore, these same researchers soon reported that sodium iodide, unlike sodium chloride, failed to lower PRA in sodium-depleted rats despite similar sodium, potassium, or total halide (chloride + iodide) balances (370). These data support that idea that the inhibition of renin release by sodium chloride is mediated by the co-transport of sodium and chloride ions into the cells of the macula densa.

To elucidate the role of chloride ion in the suppression

of renin release further, Kotchen et al. (610) measured PRA in sodium-depleted rats that had been given drinking solutions containing one of several sodium or choline salts. Plasma volume and the cumulative sodium and potassium balances of animals treated with sodium chloride, sodium bromide, sodium acetate, sodium nitrate, and sodium thiocyanate were not different. Of the sodium salts tested, only sodium chloride and sodium bromide lowered PRA, with sodium bromide causing a greater suppression than sodium chloride. When similar studies were conducted with choline salts, choline chloride, unlike choline bicarbonate, suppressed PRA by 97%. This remarkable degree of suppression elicited by choline chloride occurred despite the fact that these animals exhibited a marked negative sodium balance. Therefore, in the rat, chloride appears to be the ion involved in the regulation of renin release by the macula densa (370, 608, 610).

However, Stephens et al. (1041) found that renin secretion was suppressed when either sodium or potassium lactate was infused intrarenally into anesthetized, thoracic caval-constricted dogs. They noted that sodium excretion was elevated in both cases, but chloride excretion decreased during sodium lactate infusion and increased during potassium lactate treatment. Thus, the lowering of renin secretion by potassium lactate could be the result of the increased concentrations of sodium or chloride in the tubular fluid, but the data obtained with sodium lactate were more consistent with sodium as mediating the decrease in renin secretion. Therefore, it appears that further experimentation will be required to delineate the role of chloride ion in the control of renin release in the dog.

1. Sodium. Concerning the direct effects of sodium ion on renin release from the granular JG cells, Shade et al. (1008) found that intrarenal arterial infusions of sodium chloride suppressed renin release from filtering, but not from nonfiltering, kidneys in anesthetized dogs. They concluded that the inhibition of renin release by sodium chloride required an intact tubular system and glomerular filtration and that sodium chloride did not act via a direct action on the renal baroreceptor. Furthermore, it was suggested that sodium must be present on the luminal side of the distal tubule in order to suppress the release of renin.

A number of other investigators have examined the effect of sodium ion on renin release in vitro. Renal cortical slices (25, 131, 189, 234, 439, 681, 682, 742, 823, 982, 1201), renal cortical cell suspensions (681), and superfused glomeruli (107, 354, 494) were used in these experiments in order to eliminate the influences of glomerular filtration and the tubular transport of ions on renin release. Oelkers et al. (823) were among the first to examine the effects of varying the sodium concentration of the incubation medium on renin release from rat renal cortical slices. They observed that increasing the sodium concentration from 80 to 160 mEq/l caused a 3- to 4-fold increase in renin release; however, when the sodium concentration was increased and the osmolality of the incubation medium was kept constant, a similar increase in the sodium concentration caused only a 1.5-fold increase in renin release. Weinberger and co-workers (25, 1201) also failed to find an increase in renin release from rat renal cortical slices when the sodium concentration was increased and the osmolality of the medium was kept constant. Braverman et al. (131) noted a 30% increase in the release of renin from rat renal cortical slices when the sodium concentration of the medium was elevated from 20 to 100 mEq/l at a constant osmolality; however, when the sodium concentration was further increased to 160 mEq/l, no further increment in renin release was observed. Similar changes were observed in kidney slices obtained from normal and sodium-depleted rats. Performing the reverse experiment, Capponi and Vallotton (189) found a similar direct relationship between sodium concentration and renin release in vitro. When the sodium concentration was decreased from 140 to 30 mEq/l, renin release was suppressed by 25% when the osmolality was maintained constant and by 44% when the osmolality was allowed to decrease. In contrast to the above reports, Michelakis (742) found that stepwise increments in the sodium concentration from 50 to 300 mEq/l suppressed the release of renin from renal cortical slices by over 50%. Osmolality was maintained constant in these studies. Saruta and Matsuki (982) also reported a slight suppression of renin release with increasing sodium concentrations; however, osmolality also was allowed to increase.

In perhaps the most complete studies, Lyons and Churchill (681, 682) determined the effect of sodium concentration on renin release from both rat renal cortical slices and cell suspension. With kidney slices, they found that increasing the sodium concentration from 50 to 100 mEq/l caused an 8- to 10-fold increase in renin secretion while further increments in sodium content up to 150 mEq/l caused little additional stimulation of renin secretion. The intracellular sodium concentration and the total sodium content of the tissue were found to increase progressively as the sodium concentration of the medium was increased, and these values were positively correlated with the increased rate of renin secretion. When ouabain was added to the incubation medium, raising the sodium concentration from 50 to 100 mEq/l now suppressed the secretion of renin by 54% even though the intracellular and total tissue sodium concentrations increased to an extent similar to that in the absence of ouabain. In contrast to these findings, Lyons and Churchill discovered that increasing the sodium concentration of the medium in a stepwise fashion from 50 to 144 mEq/l suppressed renin secretion from renal cortical cell suspensions by approximately 50% and that the addition of ouabain to the incubation medium did not alter this reciprocal relationship between sodium concentration and renin release. Thus, changes in sodium con-

centration had opposite effects on renin secretion from renal cortical slices and cell suspensions. The authors suggested that this discrepancy may be due to a difference in the composition of the tubular fluid and incubation media as a result of the continued transcellular transport of ions in the renal slices. Furthermore, they suggested that whenever changes in the sodium content of the medium parallel the sodium concentration at the luminal membrane of the distal tubule, as in vivo and in ouabain-treated slices, a negative relationship will exist between medium sodium concentration and renin secretion. This suggestion is consistent with the macula densa hypothesis; however, it fails to explain the stimulatory effect of sodium on renin secretion from renal slices in vitro (681, 682).

In isolated superfused glomeruli, Blendstrup et al. (107) observed that increasing the superfusate sodium concentration from 110 to 135 mEq/l, without altering the osmolality, caused a 2.4-fold increase in renin release, which was sustained for 3 hr. In a subsequent study, the same group (354) reported that elevating the osmolality of the solution reversed the renin-releasing effects of an increase in superfusate sodium concentration. As a result, they concluded that sodium chloride had no direct ionic effects on renin release but rather elicited renin release by virtue of its osmotic effects on water movement. In addition, they proposed that the rate of renin release in vitro was related directly to the volume of the granular JG cell. In contrast to these findings, Holdsworth et al. (494), with the same type of preparation, reported that decreasing the sodium concentration from 140 to 110 mEq/l, without altering osmolality, caused a transient 2.7-fold increase in renin release. The reasons for these disparate results (107, 354, 494) are not apparent.

In summary, a direct effect of sodium ion on renin release from granular JG cells has not been clearly demonstrated since increments in sodium concentration have been shown to increase, decrease, or have no effect on renin release depending on the experimental conditions employed. However, if one considers only the range of sodium concentrations that are observed in vivo, i.e. 100 to 160 mEq/l, changes in sodium concentration had only slight effects on renin release in vivo in dogs with nonfiltering kidneys and in vitro in rat renal cortical slices or cell suspensions. In superfused glomeruli, alterations in sodium within this range will change the rate of renin release; however, this appears to be related to alterations in water movement that may affect granular JG cell volume. Thus, if sodium does exert a direct effect on the granular JG cells, its contribution to the control of renin secretion must be slight.

In conclusion, experiments have firmly established an effect of renal sodium metabolism on renin release. Renin release is inversely related to the sodium load sensed by the macula densa cells of the distal tubule.

2. Potassium. Since potassium was known to increase the excretion of sodium (126, 546, 954), and since the rate of release of renin from the kidney was known to be inversely related to sodium excretion (vide supra), it is not surprising that a number of researchers have examined the effects of potassium on renin release. Vander (1119), in the first study of this type, determined the effects of intrarenal infusions of potassium chloride on renin release in anesthetized dogs. Potassium, in doses of 0.2 and 0.4 mEq/min, suppressed renal venous PRA in eight of ten dogs without altering RPF, GFR, or MAP. The urinary excretion of sodium and potassium was increased from the infused kidney, and similar results were observed in sodium-depleted dogs. Vander (1119) concluded that elevations in plasma potassium concentration caused a reversible inhibition of renin release that was mediated either through a direct action of potassium on the granular JG cells or through an alteration in sodium excretion. Furthermore, he suggested that this phenomenon might be of physiologic importance since renin release was suppressed by elevations in plasma potassium content of less than 0.5 mEq/l. These findings (1119) in anesthetized dogs were subsequently confirmed by a number of investigators (340, 988, 1008, 1041). Flamenbaum et al. (340), for example, observed a 29% decrease in PRA and a 77% decrease in renin secretion in anesthetized dogs after an intrarenal infusion of potassium chloride in a dose that raised the renal arterial plasma potassium concentration by 2.2 mEq/l. No change in MAP, GFR, RBF, or the intrarenal distribution of RBF was observed. Interestingly, plasma aldosterone levels were increased 2-fold by these intrarenal infusions of potassium. Since an increase in the excretion of sodium accompanied the suppression of renin release, potassium was thought to suppress renin release through an intrarenal mechanism most likely related to the increased sodium load presented to the macula densa.

Shade et al. (1008) studied the effects of intrarenal infusions of potassium chloride on renin release in anesthetized, thoracic caval-constricted dogs with filtering and nonfiltering kidneys. It should be pointed out that basal renin secretion is elevated in dogs with a partial constriction of the thoracic vena cava. In dogs with filtering kidneys, an infusion of potassium chloride, sufficient to increase the renal venous plasma potassium concentration by 2 mEq/l, suppressed renin secretion by 78% without altering RBF or MAP. In contrast, similar doses of potassium failed to alter the secretion of renin in dogs with a single, nonfiltering kidney. These findings indicated that glomerular filtration and an intact renal tubular system were necessary for potassium to suppress the release of renin. Furthermore, it appeared that potassium suppressed renin release by an action on the macula densa rather than by a direct action on the granular JG cells. The inability of increased potassium concentration to alter renin release from rat renal cortical slices (25, 982) and isolated glomeruli (354) in vitro supports this conclusion.

In an attempt to determine the effect of the accom-

panying anion on potassium suppression of renin release, Stephens et al. (1041) infused potassium lactate intrarenally into anesthetized, thoracic caval-constricted dogs. They found that potassium lactate, in doses that increased renal venous plasma potassium content by 2.1 mEq/l, suppressed renin secretion by 50% and increased the excretion of sodium, potassium, and chloride. Intrarenal infusions of potassium sulfate suppressed renin secretion by 68% in association with an increase in renal venous plasma potassium concentration of 1 mEq/l. Since potassium lactate and sulfate suppressed renin release in a fashion similar to potassium chloride (1008), it was concluded that potassium, rather than its accompanying anion, suppressed renin release (1041).

In another revealing study, Schneider et al. (988) simultaneously measured the proximal reabsorption of sodium (by micropuncture methods) and renin release during the intrarenal infusion of potassium chloride in anesthetized dogs. During the infusion of potassium, which reduced renin secretion by 50%, the urinary excretion of potassium and sodium increased 3- and 2.5-fold, respectively; however, the proximal reabsorption of sodium was not changed. Since sodium excretion increased in the absence of a change in proximal tubular sodium reabsorption, Schneider et al. suggested that potassium inhibited the reabsorption of sodium in the ascending limb of the loop of Henle and thus increased the delivery of sodium to the macula densa. This increase in sodium load at the macula densa then suppressed the release of renin.

A number of investigators have examined the effects of potassium on renin release in conscious dogs (1, 708, 1249) and observed results similar to those obtained in anesthetized dogs (340, 988, 1008, 1041, 1119). When McCaa et al. (708) infused potassium chloride i.v. into conscious dogs for 15 days, they observed a 0.8 mEq/l increase in serum potassium concentration and a 48% suppression of PRA. In a subsequent study, the same group of researchers (1249) infused potassium chloride i.v. into conscious dogs for 15 days and observed a 0.8 mEq/l increase in serum potassium, a 5-fold increase in potassium excretion, and a 56% increase in sodium excretion. In contrast to their previous studies, potassium loading failed to alter PRA in a consistent fashion. Although the reason for this discrepancy was not clear, it should be pointed out that the control PRA values in the second study were 50% lower than those encountered in the first study. Thus, the low basal release of renin combined with the continued loss of sodium may have prevented the suppression of renin release by potassium. When these studies were repeated in adrenalectomized dogs maintained on a constant dose of mineralocorticoid, a similar rise in plasma potassium concentration increased PRA and caused an even greater increase in sodium excretion when compared with intact animals. However, this increase in PRA was accompanied by a 23 mm Hg decrease in MAP that may have activated the sympathetic nervous system or the renal baroreceptor.

Abbrecht and Vander (1) tested the effects of chronic potassium depletion on renin release in conscious dogs. After the dogs had ingested a potassium-deficient diet for 5 to 7 weeks, plasma potassium concentration fell by approximately 2 mEq/l whereas plasma sodium content was unchanged. Plasma renin activity was increased by 3- to 4-fold in each of the five dogs studied, and, interestingly, the maximal stimulation of renin release occurred when the dogs were in a positive sodium balance of between 20 to 60 mEq. After potassium repletion, PRA returned to the values seen before dietary potassium restriction. Because these investigators found that a reduction in plasma potassium concentration increased renin release, whereas an increase in plasma potassium decreased renin release (1119), they suggested that plasma potassium concentration exerted a tonic influence on the release of renin. In addition, the authors (1) suggested that potassium depletion stimulated renin release by: 1) a direct action on the granular JG cells, 2) by decreasing the delivery of sodium ion to the macula densa secondary to a reduction in GFR or an increase in the proximal reabsorption of sodium, and/or, 3) a reduction in renal vascular resistance. Galvez et al. (371) obtained similar results when they measured PRA in dogs that had been depleted of potassium by a combination of hemodialysis and a reduction in dietary potassium intake. Serum potassium decreased from 4.5 to 1.8 mEq/l, urinary potassium excretion decreased from 40 to 5 mEq/day, and the cumulative sodium balance increased to $^{+}$374 mEq. No change in MAP, GFR, or RPF was discerned. Plasma renin activity increased from 0.4 to 17.2 ng of AI/ml/hr, and this increase was accompanied by a 5-fold increase in the urinary excretion of PGE. When the synthesis of renal prostaglandins was inhibited by indomethacin, PRA was reduced by 96% even though sodium and potassium balance did not change. It was concluded that potassium depletion stimulated the release of renin through a prostaglandin-dependent mechanism that did not involve the transport or delivery of sodium to the macula densa unless sodium transport at these cells was controlled in some way by renal prostaglandins.

When Sealy et al. (999) examined the effects of alterations in dietary sodium and potassium on renin release in conscious rats, they observed an inverse relationship between potassium intake and PRA. In addition, when a low sodium-high potassium diet was provided, the increase in potassium intake blocked the usual rise in PRA observed during sodium depletion. Since both sodium and potassium excretion increased when the animals ingested this low sodium-high potassium diet, the authors suggested that potassium altered the release of renin either by changing the sodium load reaching the macula densa or by a direct action of potassium on the granular

JG cells. This inverse relationship between renin release and potassium balance in the conscious rat was subsequently confirmed by Kotchen et al. (608) and Campbell and Schmitz (186). Conversely, Corvol et al. (236) reported that an acute oral potassium load increased PRC in anesthetized rats in association with a marked natriuresis. However, this disparate finding may have resulted from the use of anesthetics and acute potassium loading (236).

Since chloride ion alone had been found to inhibit renin release (610), Kotchen et al. (608) examined the effects of potassium chloride and potassium bicarbonate on PRA in sodium-depleted, conscious rats. The oral ingestion of potassium chloride for 8 days suppressed PRA by 75% whereas potassium bicarbonate did not alter PRA. Both groups of rats exhibited a positive potassium balance; however, the plasma potassium levels were 1 mEq/l higher in the potassium chloride-treated group as compared to the animals receiving potassium bicarbonate. The authors concluded that the signal ultimately produced by potassium at the macula densa was modified substantially by the anion delivered with potassium. Thus, although the accompanying anion does not appear to affect the ability of potassium to suppress renin release in dogs (1041), the same inverse relationship between potassium and renin release has been observed in dogs (1, 340, 371, 708, 988, 1008, 1041, 1119, 1249) and rats (186, 608, 999).

Maebashi et al. (686) were the first to explore the effects of potassium administration on renin release in humans. Although the oral administration of potassium chloride for 5 days did not alter PRA in normal humans ingesting a normal sodium diet, it did suppress renin release in normal subjects and patients in whom renin levels were stimulated with hydrochlorothiazide or a low sodium diet and in patients with renovascular hypertension. In a more complete study, Dluhy et al. (283) reported that raising potassium intake from 40 to 200 mEq/day for 5 to 7 days decreased PRA by 36% in normal subjects on a low sodium diet. This fall in PRA was accompanied by a 4-fold increase in urinary potassium excretion and a 0.5 mEq/l increment in serum potassium concentration but no change in sodium excretion. Since changes in potassium concentration did not affect the renin-renin substrate reaction in vitro, and since sodium excretion was unaltered, the authors (283) suggested that the chronic administration of potassium suppressed renin release 1) by a direct action of potassium on the granular JG cells, 2) by altering the neural control of renin release, and/or 3) by alterations in extracellular fluid volume. In a later study, the same investigators (482) found no change in PRA when small amounts of potassium chloride were infused into sodium-depleted, normal subjects for 2 hr even though the subsequent rise in serum potassium content was similar to that seen after 1 week of potassium loading (283). However, when an infusion of sodium chloride was superimposed onto the potassium chloride infusion in these sodium-depleted subjects, the suppression of renin release was greater than that observed during the infusion of sodium chloride alone (282). Serum potassium levels were the same before and after the addition of sodium chloride to the infusate. Thus, the presence of sodium ion appeared to be a prerequisite for potassium to suppress renin release acutely in sodium-depleted humans.

Unlike Maebashi et al. (686), Brunner et al. (150) found that potassium loading with potassium chloride for 5 to 7 days decreased PRA by 44% in 18 of 21 normotensive and hypertensive patients on an ad libitum sodium diet. Potassium administration was accompanied by a natriuresis whether PRA was suppressed or not. Also, whereas potassium loading decreased PRA, potassium repletion failed to affect renin release. Changes in PRA were found to be inversely correlated with change in plasma potassium and the urinary excretion of potassium and to be independent of changes in sodium balance. When normal humans were given a high sodium diet supplemented with either 40 or 200 mEq/day of potassium for 5 to 6 days, PRA was 36% lower in patients ingesting the high-potassium diet (497). Serum potassium content, urinary sodium excretion, and MAP were not changed during potassium loading, but RBF was increased by 32%. The elevation of RBF was thought to be the result of a decrease in the intrarenal production of AII (497). It is not known whether the increase in afferent arteriolar wall tension that should occur when the renal vasculature is vasodilated at a constant renal perfusion pressure played a part in the suppression of renin release during potassium loading.

In order to examine the possibility that potassium suppressed renin release by virtue of its aldosterone-releasing properties, Miller et al. (753) studied the effects of potassium loading on renin release in adrenalectomized patients and patients with primary adrenal insufficiency. All of the patients were on a fixed daily dose of mineralocorticoids. When the patients' potassium intake was increased from 60 to 300 mEq/day, a marked natriuresis, an increase in serum potassium concentration, and a decrease in body weight were noted. In three patients in whom sodium losses were not replaced, PRA was found to increase even though serum potassium was elevated and the patients were in a positive potassium balance. However, when sodium losses were replaced, PRA was found to remain unchanged despite a similar rise in serum potassium and a similar positive potassium balance. Thus, in Addisonian patients, potassium loading induced a negative sodium balance that was associated with an increase in PRA; however, when sodium balance was maintained, potassium loading failed to alter PRA. Since potassium loading had been shown to suppress renin release in normal subjects (150, 497), but had no effect on PRA in these patients, the authors (753) hy-

pothesized that high circulating levels of mineralocorticoids were the missing component in these patients and that mineralocorticoids were necessary, by some unknown mechanism, for potassium to suppress renin release. In like fashion, Young et al. (1249) found that potassium infusions increased PRA from 0.08 to 0.29 ng of AI/ml/hr in conscious adrenalectomized dogs maintained on a fixed daily dose of aldosterone. However, this increase in renin release was associated with a marked natriuresis and a 23 mm Hg decrement in MAP.

Although these findings are consistent with a role for mineralocorticoid in potassium-induced renin suppression, such a mechanism is not consistent with observations made by other researchers or the known actions of the mineralocorticoids. For example, Vander (1119) observed a significant decrease in renin release within 10 min of beginning an intrarenal infusion of potassium into anesthetized dogs, and Shade et al. (1008) observed a decrease within 15 min. Unfortunately, aldosterone levels were not measured in these studies. Flamenbaum et al. (340) observed a 77% decrease in renin secretion and a 2-fold increase in urinary aldosterone excretion within 15 min of beginning an infusion of potassium into the renal arteries of anesthetized dogs. Even though aldosterone excretion was found to increase in the latter study, it is difficult to believe that this increase in aldosterone could suppress renin release within 15 min since a 20- to 30-min delay has been observed between the time that aldosterone is administered and the onset of antinatriuresis. Furthermore, aldosterone acts on the late distal tubule and collecting tubule, sites distal to the macula densa. Since mineralocorticoids might alter potassium suppression of renin release by a mechanism other than their classical effects on the collecting tubule, it would be of interest to know the effects of potassium on renin release in animals or humans treated with the aldosterone antagonist spironolactone.

The effects of potassium deprivation on renin release also have been examined in man. Brunner et al. (150) observed that potassium depletion increased PRA in normotensive and hypertensive subjects, and this elevation of PRA was associated with sodium retention, a decrease in plasma potassium content, and a decrease in potassium excretion. Himathongkam et al. (482) found that acutely lowering serum potassium concentration by 0.3 mEq/l, by the ingestion of glucose, resulted in a 2-fold increase in PRA in normal humans. A similar rise in PRA was observed by Henrich et al. (473) when serum potassium was reduced by 1.4 mEq/l by the hypokalemic dialysis of patients with renal failure. In patients with hypokalemia due to psychogenic vomiting, Radfar et al. (922) found a 91% decrease in PRA when the serum potassium level was increased from 2.3 to 3.5 mEq/l. No change in blood pressure was observed. It also should be mentioned that hypokalemia and hyperreninemia are found in association with Bartter's syndrome (287, 1148). Although both the hypokalemia and hyperreninemia are mitigated by administering inhibitors of prostaglandin synthesis to these patients (287, 1148), the exact role of hypokalemia in stimulating renin release in this case is not known.

In summary, small changes in serum potassium concentration have been shown to exert profound effects on the release of renin, and this control mechanism may be of physiologic significance. In addition, an inverse relationship between potassium balance and renin release has been demonstrated in dogs, rats, and humans. The mechanism by which potassium suppresses renin release appears to involve an increase in the delivery of sodium to the macula densa since potassium had no inhibitory effects in dogs with a single, nonfiltering kidney or in rat renal slices in vitro. Although it is unclear whether potassium inhibits the proximal tubular reabsorption of sodium, the intrarenal administration of potassium consistently induced a natriuresis. Since it is this increase in sodium excretion that appears to suppress renin release, potassium must inhibit sodium reabsorption at some point proximal to the macula densa, possibly in the proximal tubule or the ascending limb of the loop of Henle. On the other hand, the suppression of PRA in humans by chronic potassium loading appears to be independent of whether this dietary alteration induces a natriuresis. Although studies in adrenalectomized animals and Addisonian patients suggest that an increased circulating level of mineralocorticoid is required for potassium to exert its effect on renin release, further studies are necessary to clarify this point. Since inhibitors of prostaglandin synthesis have been found to inhibit the renin release caused by potassium depletion in dogs and the hypokalemia and hyperreninemia in patients with Bartter's syndrome, a role for renal prostaglandins also must be considered in the control of renin release by potassium.

D. Calcium

The presence of calcium ion in secretory and smooth muscle cells is an important requirement for stimulus-secretion coupling (965) and excitation-contraction coupling (1202), respectively. Since the granular JG cells are both secretory cells and modified smooth muscle cells, it is not surprising that a number of investigators have directed their attention to the role of calcium in the release of renin. These studies, however, have been complicated by the observations that, in addition to the possible direct effects of calcium on renin release, calcium can inhibit sodium reabsorption (356, 1059), alter catecholamine release (965), and affect blood pressure (1195). For these reasons, it has been difficult to assess the role of calcium in the renin release process.

Kotchen et al. (613) infused calcium chloride intrarenally into anesthetized dogs and observed a 71% suppression of renal venous PRA. This fall in renin release was accompanied by a rise in serum calcium from 4 to 6 mEq/l, a 9-fold increase in the fractional excretion of

calcium, and a 4-fold increase in the fractional excretion of sodium. Blood pressure, GFR, and RBF were unchanged. Because calcium ion failed to affect plasma angiotensinase activity or the velocity of the renin-renin substrate reaction in vitro, the authors (613) concluded that calcium ion inhibited the release of renin through a macula densa-mediated mechanism related to the increase in sodium excretion.

To investigate the possibility that the chloride anion might have contributed to the suppression of renin release by calcium chloride, Kotchen et al. (612) performed similar experiments in anesthetized dogs in which calcium gluconate was infused intrarenally. Calcium gluconate suppressed renal venous PRA by 69% without changing blood pressure, RBF, or GFR. Since the decrease in renal venous PRA correlated with the increase in the fractional excretion of sodium, Kotchen et al. (612) again concluded that the effect of calcium on renin release was mediated by sodium and/or chloride transport at the macula densa cells.

Watkins et al. (1178) conducted similar experiments in which calcium chloride and calcium gluconate were infused intrarenally into sodium-depleted, anesthetized dogs. Calcium chloride decreased renin secretion by 65% and increased the excretion of calcium and chloride; however, in contrast to previous studies (613), RBF was decreased by 25% and sodium excretion was unchanged (1178). In like fashion, calcium gluconate suppressed the rate of renin secretion by 72%, decreased RBF by 60%, increased the excretion of calcium, and did not alter the excretion of sodium or chloride. In sodium-depleted dogs with a single nonfiltering kidney, calcium chloride again suppressed the rate of renin secretion by 63% and RBF by 40%. From these studies, it was concluded that calcium ion per se was responsible for the suppression of renin secretion in sodium-depleted dogs. Inhibition of renin release was thought to occur via a direct action of calcium on the granular JG cells. It is unlikely that calcium inhibited renin release via an action on the renal nerves or the renal baroreceptor. That is, increased calcium would be expected to facilitate the liberation of norepinephrine, thus stimulating renin release, and a decrease in afferent arteriolar radius at a constant renal perfusion pressure would lead to a decrease in circumferential stress, also a stimulus to renin release.

Along these lines, Iwao et al. (522) found that intrarenal infusions of calcium chloride increased renin secretion from 1.7 to 38.1 ng of AI per g of kidney weight/min in anesthetized dogs with denervated kidneys. Renal blood flow was found to increase from 2.8 to 3.2 ml/g of kidney/min, and urine flow also increased. In a subsequent study, the same group of researchers (1242) observed a variable but consistent increase in renal venous PRA when calcium chloride was infused intrarenally into anesthetized dogs. The effect of calcium on renin secretion in these studies (522, 1242) was exactly the opposite of that observed in the studies mentioned above (612, 613). The reason for obtaining such disparate results is unknown unless it can be attributed to the presence (612, 613) or absence (512, 1242) of the renal sympathetic nerves.

In rats, Kotchen et al. (609, 613) found that chronic calcium loading, produced by giving the animals 1% calcium chloride to drink, did not alter PRA, renal renin content; serum calcium, sodium, and potassium concentration; or the urinary excretion of sodium and potassium. The urinary excretion of calcium was, however, greatly increased. In rats on a low sodium diet ingesting 1% calcium gluconate, similar results were obtained. However, in sodium-depleted rats ingesting 1% calcium chloride, PRA was suppressed by 36% and renal renin content was decreased by 56% relative to the sodium-depleted control animals. The concentrations of serum electrolytes were unchanged. These investigators (609, 613) concluded that the ability of calcium salts to decrease the release of renin was due to the accompanying chloride anion. Also, since calcium loading suppressed the release of renin only in sodium-depleted rats, they suggested that calcium may not have a primary role in the regulation of renin release but rather may modify the release of renin caused by other stimuli.

Weidmann et al. (1195) examined the renin response to calcium chloride and calcium gluconate infusions in six patients with chronic renal failure. A calcium chloride infusion, sufficient to raise the serum calcium levels by approximately 2 mEq/l, did not change PRA but did increase blood pressure in all of the patients studied. Similarly, when calcium gluconate, in quantities sufficient to elevate the serum calcium levels by 2.2 to 5.5 mEq/l, was infused into normal subjects on a normal sodium intake, PRA remained constant (310, 415). In contrast, Kisch et al. (594) noted that an infusion of calcium chloride suppressed PRA by 29% in normal subjects on a low sodium diet. Calcium chloride failed to alter the urinary excretion or plasma levels of sodium or potassium, and the infusion of an equal amount of sodium chloride produced an equal fall in PRA. Changes in blood pressure were not reported. Thus, it would appear that calcium does suppress renin release in normal, sodium-depleted humans but not in normal humans on a normal sodium intake or in patients with renal failure. These findings in humans are consistent with those of Kotchen et al. (609, 613) in rats and suggest that serum calcium concentration is a modified rather than a primary regulator of renin release.

Brinton et al. (139) reported elevated PRA values in four of seven hypertensive patients with primary hyperparathyroidism. After parathyroidectomy, PRA, plasma calcium concentration, and blood pressure returned to within the normal range. In contrast, PRA levels were not elevated in normotensive, primary hyperparathyroid patients; normotensive patients with secondary hyperparathyroidism; or normotensive patients with hypercalcemia of other etiologies. The authors (139) concluded

that the increase in PRA was not the result of the hypercalcemia per se since normal PRA values were observed in normal subjects infused with calcium gluconate and since normal PRA levels were observed in the normotensive, primary hyperparathyroid patients. Similarly, elevated parathyroid hormone levels did not appear to be involved since normal PRA levels were observed in the patients with secondary hyperparathyroidism. Along these lines, infusions of parathyroid hormone had no effect on PRA in dogs (710) and normal humans (310). Thus, the mechanism that stimulates renin release in hypertensive, primary hyperparathyroid patients is unclear.

Llach et al. (665) examined the effects of acute and chronic hypocalcemia on PRA in normal subjects and patients with hypoparathyroidism. Infusion of the chelating agent ethylenediaminetetraacetate (EDTA) decreased the serum calcium concentration by 1.5 mEq/l but did not alter the supine and upright PRA values when compared to the control responses obtained during 5% dextrose infusions. Orthostatic hypotension was observed in the EDTA-infused subjects. In the patients with pseudohypoparathyroidism and hypoparathyroidism, values for supine and standing PRA were not different from those obtained in normal subjects. Furthermore, when these hypoparathyroid patients were infused with calcium gluconate in amounts that would produce hypercalcemia, the supine and standing PRA values remained within the normal range. Thus, it would appear that the release of renin in humans is not affected by acute or chronic hypocalcemia.

In an attempt to explore the effects of calcium on renin release without the influences of changes in systemic hemodynamics, renal nerve activity, or circulating hormones, several investigators have used the isolated perfused kidney (351, 352a, 668, 883) or renal cortical slices (25, 63, 209, 213a, 742, 769, 873, 1242). Fray (351), with the isolated rat kidney perfused with a Krebs-Henseleit solution, observed a 5-fold increase in perfusate renin concentration when kidneys obtained from sodium-loaded and sodium-depleted rats were perfused with a calcium-free medium. When calcium was added back to the perfusate, a concentration-dependent inhibition of perfusate renin concentration occurred. Perfusion pressure and perfusate flow were not influenced by changes in perfusate calcium concentration. If, however, renal perfusion pressure was reduced from 110 to 50 mm Hg after renin release was maximally stimulated by perfusion with a calcium-free medium, no further increment in renin release was observed. In later studies with the same system, Fray and Park (352a) found that a decrease in renal perfusion pressure was more effective in stimulating renin release if the calcium concentration of the perfusate was lowered from 5 to 0 mM. In addition, an increase in renal perfusion pressure increased, rather than decreased, renin release when the perfusate was free of calcium. Either raising the potassium concentration or lowering the sodium concentration of the perfusate partially inhibited the renin release elicited by acute calcium deprivation. In similar studies with the perfused rat kidney, Logan et al. (668) observed a significant increase in renal venous renin concentration after the removal of calcium from the perfusate; however, addition of lanthanum, an antagonist of calcium, to the perfusate suppressed this rise in renin release by 97%. Furthermore, the addition of EDTA to the perfusate increase the renin concentration in the venous effluent by 9-fold, and the addition of lanthanum to the perfusate at this point suppressed the elevated renin levels by 56%. In subsequent studies, the same group of investigators (883) reported that the perfusion of rat kidneys with a calcium-free solution containing EDTA caused a transient rise in perfusion pressure followed by a gradual 4-fold increase in renal venous renin concentration. This increase in renin release was not blocked by propranolol, phenoxybenzamine, or the removal of magnesium from the perfusate. If ethylene-glycol-aminoethyl-tetraacetate (EGTA), which has a greater affinity for calcium than for magnesium, was added to the perfusate, a transient but less pronounced rise in perfusion pressure occurred, and an immediate 2-fold increase in renal venous renin concentration was noted. These findings led to the suggestion that an increased influx or rise in intracellular calcium ion inhibited the release of renin. Fray and Park (352a) suggested that the events that lead to a change in cytoplasmic calcium concentration might depend on the membrane potential of the granular JG cells and/or the sodium-calcium exchange at the cellular membrane.

In contrast, Michelakis (742) found that increasing the calcium concentration from 0 to 2.5 mM caused approximately a 2-fold increase in the renin released into the incubation medium when canine renal cortical slices were studied. Similar findings were reported by Morimoto et al. (769). Yamamoto et al. (1242) found that a similar increase in calcium concentration caused a 2-fold increase in renin release, but no change in the release of protein or acid phosphatase, from canine renal cortical slices in vitro. In rat renal cortical slices, however, increasing the calcium concentration in the incubation medium did not change renin release (25, 209). If the slices were first pretreated with a calcium-free medium, the introduction of calcium caused an immediate 4- to 5-fold increase in the release of renin (209). Since a similar stimulation of renin release by calcium occurred when the incubation solution contained choline chloride rather than sodium chloride, it was concluded that calcium stimulated renin release by a direct mechanism unrelated to the transport of sodium (209).

Park and Malvin (873) studied the effects of calcium on renin release from ovine renal cortical slices in vitro and observed changes similar to those reported in studies conducted in vivo and in isolated perfused kidneys. When the calcium concentration of the incubation medium was increased from 0 to 5 mM, the release of renin decreased

by 38%. If the renal slices were incubated in 59 mM rather than 5.9 mM potassium, an identical increase in calcium concentration caused an 83% suppression of renin release. Furthermore, ouabain was found to suppress renin release by 70% in a calcium-containing medium but did not alter renin release in a calcium-free medium. Because a high potassium concentration and ouabain have been found to increase intracellular calcium concentration in vascular smooth muscle, Park and Malvin (873) proposed that an increase in intracellular calcium decreased the release of renin. As further support for this point, the chelation of extracellular calcium with EDTA or EGTA and the subsequent depletion of intracellular calcium caused a 9-fold and 5-fold increase in renin release, respectively. Churchill (213a) also found the inhibition by ouabain of renin release from rat renal cortical slices in vitro to be dependent on the availability of extracellular calcium. Churchill (213a) proposed that an increase in the intracellular concentration of sodium, resulting from the inhibition of the sodium-potassium ATPase by ouabain, led to an increase in the intracellular concentration of calcium via a sodium-calcium exchange mechanism similar to that found in vascular smooth muscle.

Baumbach and Leyssac (63) also assessed the effects of calcium on the release of renin from isolated, superfused rat glomeruli. When the calcium concentration of the superfusate was decreased from 2 mM to 0 mM, a 3-fold increase in renin release occurred. The addition of EGTA to the superfusate caused no further stimulation of renin release. The calcium ionophore A23187, which increases the influx of calcium into cells, decreased renin release from glomeruli superfused with 2 mM calcium and blocked the rise in renin release associated with superfusion with a calcium-free medium, but failed to block the increase in renin release due to superfusion with a calcium-free EGTA-containing medium. Thus, it would appear that the release of renin is inversely related to the intracellular concentration of calcium in the granular JG cells. Interestingly, the calcium antagonist lanthanum decreased renin release in the presence and absence of calcium in the medium. This suppression of renin release by lanthanum was blocked by the addition of EGTA to the superfusate. Logan et al. (668) reported a similar suppression of renin release by lanthanum in the isolated perfused kidney. The mechanism of this inhibition of renin release by lanthanum is unclear, but it may be related to the ability of lanthanum to inhibit the passive efflux of calcium from cells as has been demonstrated in vascular smooth muscle (274). From these findings, these researchers (63) proposed that renin release was not an exocytotic process since an increase in intracellular calcium was associated with a decrease in renin release. Consequently, it was suggested that changes in intracellular calcium modify renin release by regulating the volume of the granular JG cells. According to this hypothesis, increased intracellular calcium reduces cell volume and suppresses the release of renin whereas a decrease in intracellular calcium increases cell volume and stimulates the release of renin.

Although most of the studies have concentrated on the effect of calcium on the basal rate of renin release, several investigators (444, 652, 1134) have examined the role of calcium in stimulated renin release. Vandongen and Peart (1134) found, with the isolated perfused rat kidney, that reducing the perfusate calcium concentration from 3.7 to 0.32 mM completely blocked AII-induced vasoconstriction. However, even in the presence of a low calcium concentration, AII suppressed basal PRC by 72% and isoproterenol-induced renin release by 92%. When the perfusion medium contained no calcium or no calcium and EDTA, the inhibition of basal and isoproterenol-induced renin release by AII was prevented. These findings indicate that the contraction of vascular smooth muscle and the inhibition of renin release by AII depend on the level of extracellular calcium. In addition, the observation that lowering extracellular calcium inhibited renal vasoconstriction without altering the suppression of renin release by AII indicates the greater sensitivity of the vasoconstrictor process to changes in extracellular calcium.

The role of calcium in sympathetically-mediated renin release has been studied extensively. Viskoper et al. observed in the isolated perfused rabbit kidney that isoproterenol increased renal venous renin concentration by 17% without changing renal vascular resistance (1158). When EGTA was added to the blood perfusing the kidney, a similar increase in renin release was caused by isoproterenol. Fray and Park (352a) found isoproterenol to be more potent in increasing renin release from the isolated perfused rat kidney as the calcium concentration of the perfusate was decreased. Lester and Rubin (652) observed a biphasic increase in renin release following isoproterenol in isolated perfused cat kidneys, i.e. an initial rapid rise in renin release that was followed by a secondary transient increase. Perfusion of the kidney with calcium-free media or an infusion of the calcium antagonist D-600 did not change the initial rise in renin secretion but blocked the secondary increase in renin secretion seen with isoproterenol. These same interventions also failed to alter furosemide- and glucagon-induced renin release. Thus, in keeping with previous observations, it appears that extracellular calcium is not required for the initial stimulation of renin release brought about by isoproterenol, furosemide or glucagon. Lester and Rubin (652) suggested that the secondary rise in renin release, which appeared to be dependent on the extracellular concentration of calcium, involved the synthesis and/or mobilization of the secretory product.

Harada and Rubin (444) examined the effects of norepinephrine and renal nerve stimulation on renin release and calcium efflux in the isolated, perfused cat kidney. Phenoxybenzamine was added to the perfusate to block adrenergic vasoconstrictor responses. Norepinephrine

caused a dose-related increase in renin release. When the kidneys were perfused with a calcium-free solution or a calcium-free solution containing EDTA, norepinephrine produced a similar increase in renin release; therefore, extracellular calcium was not required for norepinephrine-induced renin release. In kidneys in which the intracellular stores of calcium had been labelled with radioactive calcium, norepinephrine produced a dose-related increase in renin release and calcium efflux. Both of these responses were blocked by an infusion of the beta-adrenergic antagonist propranolol. In like fashion, renal nerve stimulation increased both the release of renin and the efflux of calcium. From these findings, it was suggested that norepinephrine, released by nerve stimulation or from extrarenal sources, acts directly on the granular JG cells to mobilize intracellularly bound calcium. The cellular efflux of calcium and the subsequent fall in intracellular calcium content then caused the increase in the release of renin.

In summary, when considering the role of calcium in renin release, it is apparent that intracellular, rather than extracellular, calcium is the most important determinant. According to these studies, if intracellular calcium levels are decreased by beta-adrenergic stimuli, calcium chelators such as EDTA or EGTA, or the absence of extracellular calcium, renin release is stimulated. In contrast, if the intracellular levels of calcium are elevated by decreasing the efflux of calcium with lanthanum or by increasing calcium influx with high potassium, ouabain, AII, or calcium ionophores, renin release is inhibited. As indicated by Baumbach and Leyssac (63), this reciprocal relationship between intracellular calcium content and renin release suggests that a mechanism other than exocytosis may be involved in the release of renin from the granular JG cells.

E. Magnesium

Several investigators have examined the effects of magnesium on the release of renin in vivo (211, 217, 594) and in vitro (63, 318a, 351, 769). When Churchill and Lyons (217) infused magnesium chloride intrarenally into anesthetized dogs, they observed a 2-fold increase in renin secretion. This stimulation of renin secretion was accompanied by a 4-fold increase in the magnesium concentration of renal venous plasma, a 2-fold increase in sodium excretion and urine volume, a 9 mm Hg decrease in MAP, and no change in RPF or GFR. Since the increase in sodium excretion would be expected to suppress renin release, and since RPF and MAP did not change significantly, magnesium appeared to increase renin secretion either through a direct action on the granular JG cells or through an alteration in the activity of the sympathetic nerves innervating these cells.

Wilcox (1211) studied the effects of magnesium chloride on renin release from denervated, autotransplanted kidneys in anesthetized dogs. An i.v. infusion of magnesium chloride, which increased the plasma magnesium levels by 0.05 to 1 mEq/l, caused an 9-fold increase in renin secretion and a 13% increase in RPF. GFR, MAP, and sodium excretion were unchanged. When calcium chloride was infused along with magnesium chloride, the increments in renin secretion and RPF caused by magnesium were decreased by approximately 75%. Since the renal nerves were severed, and since renin secretion did not correlate with changes in RPF or sodium excretion, but rather with changes in plasma magnesium concentration, Wilcox (1211) concluded that magnesium elicited renin secretion by a direct action on the granular JG cells. Furthermore, since calcium chloride blocked the renin-releasing effects of magnesium chloride, it was suggested that magnesium might stimulate renin release by antagonizing the flux of calcium across the cell membrane of the granular JG cells.

In contrast to the reports (217, 1211) cited above, the i.v. infusion of magnesium sulfate into normal human subjects on a low sodium diet failed to change PRA (594) even though equimolar amounts of calcium chloride and sodium chloride lowered PRA. The i.v. infusion of magnesium sulfate did not affect the urinary excretion of sodium or potassium. The plasma concentration of magnesium increased by 1.3 mEq/l.

With isolated perfused kidneys from sodium-depleted rats, Fray (351) found that increasing the magnesium concentration of the perfusate in a stepwise fashion from 1.2 to 10 and then to 20 mM caused a 1.7- and 6-fold increase in the cumulative perfusate renin concentration, respectively, without altering renal perfusate flow. Since changes in the sodium concentration of the perfusate did not affect renin release in this system, it is unlikely that magnesium stimulated renin release via the macula densa. Similarly, since renal perfusion pressure and perfusate flow were not changed by magnesium, activation of the intrarenal baroreceptor appears unlikely. However, perfusion of the kidneys with calcium-free medium elevated renin release, and the addition of 20 mM magnesium to the perfusate did not produce a further increase in the release of renin. Thus, as previously suggested (1211), magnesium appears to increase renin release by antagonizing the inhibitory effects of calcium on renin release (351). In later studies, Ettienne and Fray (318a) found that increasing the potassium concentration of the perfusate or elevating renal perfusion pressure inhibited magnesium-induced renin release in the isolated perfused rat kidney. The increase in renin release elicited by a decrease in renal perfusion pressure or isoproterenol was not affected by 20 mM magnesium in the perfusate. Based on these data (318a, 351), it was suggested that hyperpolarization of the granular JG cells by magnesium led to a decrease in the cytoplasmic concentration of calcium and thus renin release.

Morimoto et al. (769) observed a slight decrease in the release of renin from canine renal cortical slices in vitro when the magnesium sulfate concentration of the incubation medium was decreased from 1.2 to 0 mM. When

both calcium and magnesium were removed from the incubation medium, a further decrement in renin release occurred. In contrast, Baumbach and Leyssac (63), with isolated superfused rat glomeruli, did not observe a significant or consistent change in renin release when the concentration of magnesium in the superfusate was reduced from 1.2 to 0.12 to 0 mM.

From the available data, it appears that an increase in plasma magnesium levels stimulates the release of renin whereas a decrease in plasma magnesium concentration lowers renin release. Although the mechanism by which magnesium effects these changes is unclear, much of the evidence points to a direct effect of magnesium on the granular JG cells. In this respect, magnesium may elevate renin release by inhibiting the movement of calcium across the membrane of the granular JG cell. The physiologic, pharmacologic, and pathophysiologic importance of magnesium in the control of renin release remains to be determined.

F. Angiotensin

In 1965, Vander and Geelhoed (1121) proposed a pressure-independent mechanism by which circulating levels of AII inhibited renin release by a direct, intrarenal action. They observed that i.v. AII suppressed basal renin release in anesthetized dogs even when renal arterial pressure was held at control levels by means of a suprarenal aortic clamp. Furthermore, AII decreased renin release in the face of two powerful stimuli to renin release, viz. renal arterial hypotension and elevation of ureteral pressure. In both cases, sodium excretion was markedly reduced, a situation that would be expected to elevate PRA, and yet AII suppressed renin release. This effect of AII was not attributable to its vasoconstrictor activity since an equipressor dose of norepinephrine (with renal perfusion pressure controlled) caused an increase in renin release and since subpressor doses of AII also lowered renal venous PRA. Based on these observations, it was proposed that AII had a direct inhibitory effect on renin release.

Within a short time, DeChamplain et al. (261) noted that both pressor and subpressor doses of AII (infused over a 3-hr period) suppressed PRA in normal and hypertensive humans whose basal rates of renin release had been elevated by sodium depletion. This effect of AII was not mediated via increased aldosterone secretion since a 3-hr infusion of aldosterone did not lower PRA.

In the ensuing years, numerous investigators have conducted animal studies to determine the exact mechanism by which AII suppresses renin release. Bunag et al. (165) observed that AII decreased PRA in anesthetized dogs, even when the basal rate of renin release was elevated by sodium-depletion or a decrease in renal perfusion pressure. Angiotensin II diamide or 8-Ala-AII were without effect and, again, renin suppression by AII was independent of any change in total RBF or renal perfusion pressure produced by the peptide. Other researchers also concluded that renin release from ischemic kidneys was suppressed by circulating AII (1076). It was further shown by Blair-West et al. (105) that physiologic concentrations of exogenously supplied AII prevented the increase in PRC normally observed during the onset of sodium depletion in conscious sheep. Infusion of 3 ng/hr of AII into the renal artery caused no change in systemic blood pressure, urinary sodium excretion, blood AII concentration, or plasma potassium concentration, and yet this dose of AII blocked the increase in renin release usually seen during sodium depletion. Based on these observations, it was suggested that renin release was modulated continuously by feedback from variations in the plasma concentration of AII (105). It has also been reported that rabbits immunized against AII exhibited an increase in PRA in association with the appearance of anti-AII antibodies (1047) and that the i.v. infusion of AII into conscious rats lowered basal PRC by 70% (784a).

Shade et al. (1007) found that AII-mediated suppression of renin secretion did not depend on the presence of a functional macula densa. Renin secretion in anesthetized dogs with a single nonfiltering kidney dropped by 50% within 15 min of beginning an intrarenal infusion of AII. Mean arterial pressure did not change and total RBF was decreased in only two or five dogs. The susceptibility of the renin-suppressing action of AII to specific receptor blockade was studied by McDonald et al. (711) in anesthetized dogs. Intravenous AII increased MAP (renal arterial pressure was controlled with an aortic clamp) and lowered PRA (a 67% decrease), GFR, and RBF. All of these effects were blocked by an i.v. infusion of the AII antagonist 1-Sar-8-Gly-AII. During the i.v. infusion of AII, a unilateral intrarenal infusion of the angiotensin antagonist increased the release of renin from the infused kidney without antagonizing the suppression of GFR and sodium excretion caused by AII. This increase in renin release occurred even when the infused kidney was denervated. Thus, the angiotensin receptor antagonist blocked both the vascular and renin-suppressing actions of AII, but the latter effect was more susceptible to inhibition (711). When either AII or AIII, at doses calculated to increase their concentration in the renal blood by 70 pg/ml, was infused into the renal arteries of anesthetized dogs on a normal or low sodium diet, renin secretion was decreased by 50% to 60% (359). No significant alteration of MAP, GFR, RBF, or sodium excretion was noted in these experiments. Therefore, it appeared that both AII and AIII had a similar effect on renin secretion in both the basal and stimulated states (359). Beckerhoff et al. (69a) also found an equal suppression of PRA when equimolar doses of AII and AIII were given i.v. to anesthetized dogs.

Angiotensin II also suppressed the renin release elicited by other physiologic and pharmacologic stimuli (112, 637, 732). For instance, Meyer et al. (732) reported that isoproterenol elevated PRC approximately 20-fold in conscious rats whereas only a 4-fold increment in PRC was

observed when isoproterenol and AII were infused simultaneously. In this case, AII also prevented the hypotension and tachycardia caused by isoproterenol. Angiotensin II prevented furosemide-induced renin release in conscious rats even though the diuresis caused by furosemide was not altered (637). As before (732), basal PRC values were suppressed by the infusion of AII (637). Finally, PRC was elevated about 10-fold whereas MAP was decreased by 16% within 48 hours of unilateral adrenalectomy in rats (112). An i.v. infusion of AII at this point elevated MAP to 30% above the sham-operated control values and lowered PRC values by 90%. In each of these studies, the authors (112, 637, 732) concluded that the suppression of stimualted renin release by AII was due to: 1) the increase in MAP, 2) afferent arteriolar vasoconstriction, and/or 3) a direct effect on the granular JG cells.

It should be pointed out that intracerebroventricularly administered AII has been reported to lower PRA by 60% in conscious goats (314) and anesthetized cats (668a). It is unclear whether the decrement in PRA was caused by the observed increase in MAP, sodium excretion, or ADH release, but the renal nerves do appear to play an important part in this suppression of renin release (668a). Later, Malayan et al. (688) reported that centrally administered AII appeared to inhibit renin release in anesthetized dogs by stimulation of the release of AVP. Arginine vasopressin has been found to inhibit the secretory function of the granular JG cells directly (1007). Whether circulating AII may affect renin release via the central nervous system is not known at this time.

Other workers (540, 794, 1217) have confirmed and extended the original observations of DeChamplain et al. (261) in humans. For instance, Johnston et al. (540) found that subpressor infusions of AII suppressed PRA in both normotensive and hypertensive humans whether the subjects were on a normal or low sodium diet. More recently, Williams et al. (1217) discovered that infusions of AII caused a dose-related decrease in PRA in normal humans, but were without effect in patients with normal-renin and high-renin hypertension. Therefore, the negative-feedback effect of AII on renin release may not operate in hypertensive patients. Carey et al. (191a) compared the effects of AII and AIII on PRA in normal subjects. Both peptides reduced PRA to an equal extent when similar doses were infused into subjects on a normal or low sodium diet.

Several research groups have described the ability of AII to inhibit renin release from renal cortical slices in vitro (188, 263, 743, 771, 782, 961, 1154, 1225) and from the isolated perfused rat kidney (491, 1134, 1136). In 1969, both Michelakis (743) and deJong (263) reported that AII lowered renin release from renal cortical slices in vitro. In the latter case, renin release from rat renal slices was suppressed in a concentration-dependent fashion. Subsequently, Rosset and Veyrat (961, 1154) found that 10^{-6} M AII inhibited renin release from human kidney slices by 60% to 70%. Wilton (1225) also noted that AII lowered renin release from rat renal slices, but Morris et al. (771) failed to detect any change in renin release from isolated rat glomeruli superfused with an angiotensin-containing solution. However, Capponi et al. (188) determined that AII (10^{-6} M) not only suppressed basal renin release from rat renal slices, but also inhibited isoproterenol-induced renin release in a concentration-dependent fashion. In either case, the inhibition by AII was completely reversed by equimolar concentrations of 1-Sar-8-Ala-AII, a specific angiotensin receptor blocking agent.

Perhaps the most thorough in vitro study of AII suppression of renin release is that of Naftilan and Oparil (782). With rat renal cortical slices, they found that both AII (5×10^{-9} M to 5×10^{-7} M) and AIII (1×10^{-5} M to 1.5×10^{-4} M) caused a concentration-related decrease in renin release. As before (188), 1-Sar-8-Ala-AII completely blocked AII inhibition of renin release but had no effect on basal renin release (782). In addition, it was discovered that the (3-8), 4-8), and (5-8) peptides of AII inhibited renin release, but their potency dropped off sharply as their amino-terminal amino acids were removed. The carboxy-terminal amino acids appeared to be of importance in the inhibition of renin release since the (1-5) peptide of AII exhibited no activity.

When the renal stores of norepinephrine were reduced by 99% by pretreatment with reserpine in vivo, AII still suppressed basal renin release in vitro and isoproterenol still elicited an increase in renin release but, as expected, tyramine was without effect. Lastly, when papaverine was added to block any portion of the renal baroreceptor mechanism remaining in the tissue slice, AII still was able to suppress renin release. Therefore, the inhibition of renin release by AII was concluded to be a direct effect on the granular JG cells, independent of adrenergic or vascular influences. Furthermore, since AII was much more potent than AIII in suppressing renin release, Naftilan and Oparil (782) felt that the AII receptors of the granular JG cells were similar to the vascular receptors and different from the adrenal receptors. It should be pointed out that AIII is more potent than AII in stimulating aldosterone production from adrenal tissue in vivo (177) and in vitro (880), but AIII is only about 20% as potent as AII in causing vasoconstriction in vivo (184) and in vitro (764). Whereas Naftilan and Oparil (782) found AII to be more potent than AIII in suppressing renin release, Freeman et al. (359) found them to be equipotent. However, in the latter studies (359) dose-response curves were not constructed so it is possible that the doses of AII and AIII exceeded those needed for maximal inhibition.

The effects of AII on renin release from the isolated, perfused rat kidney also have been characterized (491, 1134, 1136). When AII was introduced into the isolated rat kidney perfused with an electrolyte solution containing protein and washed bovine red blood cells, renin release was inhibited at doses of AII that did not alter

RPF, GRF, or salt excretion (491). Suppression of renin release was rapidly reversed when AII was removed from the perfusate (491). Vandongen et al. (1136) found that AII inhibited both isoproterenol- and glucagon-induced renin release in the isolated rat kidney perfused with a Krebs-saline solution. As would be expected, AII increased and isoproterenol decreased perfusion pressure, but the inhibitory effects of AII on isoproterenol-induced renin release occurred even though the combination of the two drugs returned perfusion pressure to control levels. Angiotensin III also inhibited isoproterenol-induced renin release. In contrast to more recent studies (782), Vandogen et al. (1136) found that the (3-8) and (4-8) peptides of AII were not active; however, these peptides may be degraded faster in the perfused kidney (1136) than in the renal slice preparations (782). Vandongen et al. (1136), the first investigators to propose a cellular mechanism for AII suppression of renin release, suggested that both isoproterenol and glucagon might stimulate renin release by elevating the intracellular concentration of cyclic AMP and that AII may inhibit the production of cyclic AMP. In this respect, AII had previously been demonstrated to inhibit the stimulation of adenylate cyclase by epinephrine in the isolated rat aorta (1161) and rat uterus (248).

Vandongen and Peart (1134) studied the calcium dependence of AII suppression of renin release. Angiotensin II inhibited both basal and isoproterenol-stimulated renin release from the isolated rat kidney perfused with a solution containing 3.7 mM calcium. In this case, AII reversed the drop in perfusion pressure caused by isoproterenol. However, if the calcium concentration of the perfusate was reduced to 0.32 mM, AII still decreased isoproterenol-induced renin release even though the peptide no longer suppressed basal renin release or elicited vasoconstriction. When a calcium-free perfusate was used, AII failed to lower either basal or isoproterenol-stimulated renin release. Therefore, AII appeared to inhibit basal and stimulated renin release not by renal vasoconstriction, but rather by a mechanism dependent on extracellular calcium.

In conclusion, it is apparent that AII inhibits renin release by a direct action on the granular JG cells. This negative feedback inhibition is referred to as the "short loop" mechanism (572) to distinguish it from the indirect inhibitory effect of increased levels of aldosterone. In the latter case, called the "long loop" mechanism, AII stimulates the secretion of aldosterone, and the resultant retention of sodium and ECF volume expansion eventually suppresses renin release. Thus, the "short loop" effects of AII provide immediate modulation of renin release, whereas the "long loop" mechanism provides feedback control over longer periods of time.

G. Antidiuretic Hormone (Arginine Vasopressin)

Since antidiuretic hormone, or arginine vasopressin (AVP), causes renal vasoconstriction, increases blood pressure, inhibits water excretion, and increases sodium excretion, it is not surprising that this hormone alters renin release. Bunag et al. (165) were the first to examine the effects of AVP on renin release. When renin release was elevated in anesthetized dogs by constriction of the thoracic aorta, an i.v. infusion of AVP decreased renin release in 17 of 21 animals. This decrease was not associated with a consistent change in either MAP or RBF. Oxytocin had no effect on PRA when infused in the same concentration as AVP; however, at 10 times the dose of AVP employed, oxytocin inhibited renin release in three of four dogs. An intrarenal infusion of AVP in two of the animals decreased renin release and RBF and increased MAP slightly.

In a similar type of study, Vander (1118) compared the renal effects of vasotocin and AVP in anesthetized dogs. Vasotocin reduced renal venous PRA both in normal dogs and in dogs whose basal PRA values were elevated by ureteral occlusion. Renal blood flow and MAP were not changed by vasotocin. In like fashion, AVP suppressed renin release without modifying systemic or renal hemodynamics in animals with ureteral obstruction. Vander (1118) concluded that these peptides inhibited renin release either by increasing the sodium load reaching the macula densa or by a direct effect on the granular JG cells. Tagawa et al. (1071) found that small doses of AVP lowered PRA in conscious, sodium-depleted dogs. This suppression of secretory function was dose-related and reversible. Furthermore, at the doses given, AVP did not affect plasma osmolality, plasma sodium concentration, MAP, or heart rate. Because a 1 μU/ml increase in plasma AVP concentration decreased PRA by 25%, it was suggested that AVP played a role in the physiologic control of renin release.

Johnson et al. (536) also examined the effects of small doses of AVP and its 1-desamino-8-arginine derivative (DDAVP) on renin release in conscious, uninephrectomized dogs ingesting a low salt diet. The i.v. administration of these two peptides caused similar changes in urine volume and urinary osmolality; however, only AVP increased sodium excretion, potassium excretion, and MAP. In addition, AVP decreased PRA by 40% whereas DDAVP was without effect. An intrarenal infusion of AVP suppressed PRA by 34% without changing blood pressure or heart rate but the administration of DDAVP by the same route did not affect PRA. Johnson et al. (536) concluded that AVP increased electrolyte excretion and reduced PRA via selective activation of renal vascular receptors and this action was not shared by DDAVP. In keeping with these findings, Shade et al. (1007) provided the best evidence to date for a direct effect of AVP on renin release. In anesthetized, sodium-depleted dogs with a single, nonfiltering kidney, they observed in two separate groups of experiments a 50% and 80% inhibition of the rate of renin secretion after the intrarenal infusion of AVP. Renal blood flow and MAP were not affected when AVP was given by this route.

Because AVP inhibited renin secretion in the absence of a functional macula densa and changes in renal hemodynamics, the authors proposed that AVP acted directly on the granular JG cells.

Recent reports indicate that AVP also may mediate the changes in renin release caused by other stimuli. Schrier et al. (993), in anesthetized dogs, noted a 60% decrease in the rate of renin secretion after the i.v. injection of AVP. This suppression of renin secretion was accompanied by a decrease in RBF, an increase in MAP and urinary osmolality, and no change in sodium excretion. A similar change in renin secretion and urinary osmolality was seen after bilateral, cervical vagotomy. However, if the dogs were hypophysectomized prior to cervical vagotomy, the latter intervention did not inhibit renin secretion or increase urinary osmolality. Therefore, the authors suggested the existence of a neurohumoral reflex whereby a decrease in parasympathetic tone increased the release of AVP that in turn suppressed renin release. However, it should be pointed out that many other investigators (21, 142, 484, 1252, 1253, 1260) have found that bilateral, cervical vagotomy actually causes an increase in renin release, which is mediated via the renal sympathetic nerves, so the existence of such a neurohumoral reflex is doubtful. On the other hand, Malayan et al. (688) found that an intracerebroventricular injection of AII reduced PRA by 20% and doubled the concentration of AVP in the plasma of anesthetized dogs. After hypophysectomy to remove the source of AVP, centrally administered AII did not alter PRA despite the fact that MAP rose to the same extent as it had in intact dogs treated with AII. It was concluded that the central administration of AII inhibited renin release by stimulating the release of AVP rather than by increasing systemic blood pressure.

Arginine vasopressin also has been found to reduce PRA in normal, anesthetized rats (215, 422, 424, 469) and rats (Brattleboro strain) with hereditary, hypothalamic diabetes insipidus (49, 422, 424, 888). In other studies in rats, AVP and 2-Phe-8-Lys vasopressin (octapressin) did not affect basal PRA but did inhibit isoproterenol-induced renin release in normal rats and rats with a single, nonfiltering kidney (732, 735). Octapressin also was found to prevent furosemide-elicited renin release in rats (637). A similar suppression of isoproterenol- and furosemide-induced renin release was, however, observed with other vasoconstrictor agents such as AII and phenylephrine. Thus, the effect of octapressin on stimulated renin release did not appear to result from a specific action of this compound.

Gutman and Benzakein (422, 424) were the first researchers to compare renin values in heterozygous Brattleboro rats (animals that synthesize AVP) and homozygous Brattleboro rats (animals that do not synthetize AVP) with diabetes insipidus (DI). A 2-fold elevation of PRC was measured in anesthetized, male rats with DI when compared to the normal, heterozygous animals. No such difference was detected when the female rats of the two groups were compared. However, exogenously administered AVP reduced PRC significantly in all four groups of Brattleboro rats. The concentration of plasma renin substrate was similar in the control (heterozygous) animals and the rats with DI when both sexes were compared. The surgical removal of the testes or ovaries did not alter PRC in rats with DI.

Balment and colleagues (49, 469) subsequently studied the effects of AVP on renin release in Brattleboro rats, but different results were obtained. In ether-anesthetized rats, PRA was elevated 2-fold in female and 4-fold in male rats with DI when compared to the appropriate sex of heterozygous Brattleboro rats. Interestingly, the treatment of male rats with DI with AVP reduced PRA to within the normal range encountered in heterozygous animals. The suppression of renin release by AVP in these animals was blocked by prior castration but not by hypophysectomy. In contrast, AVP tended to increase PRA in intact female rats with DI and yet suppressed renin release in hypophysectomized females with DI. Although it is unclear how gonadal and hypophyseal hormones modify the effects of AVP on renin release, it is apparent from these studies (49, 469) that sex may be an important determinant of the effects of AVP on renin release. Other investigators have confirmed the increased PRA values in rats with DI (417, 637). In addition, Gross et al. (417) found that homozygous Brattleboro rats had a lower blood pressure, a higher serum sodium concentration, and a higher level of renin substrate in the blood than did heterozygous Brattleboro animals, but it is not known whether these factors may have contributed to the elevated PRA values observed in the homozygous rats with DI.

The effects of AVP on renin release also have been assessed in vitro with rat renal cortical slices (276) and in the isolated, perfused rat kidney (603, 1126). DeVito et al. (276) found AVP to have no effect on renin release from rat renal cortical slices in vitro; however, unlike other researchers (vide supra), they observed that AII, norepinephrine, and epinephrine were also without effect. When Vandongen (1126) infused AVP into the isolated, perfused rat kidney, perfusion pressure rose but renin secretion remained constant. In contrast, isoproterenol decreased renal perfusion pressure and increased renin secretion by 7-fold, and pretreatment with AVP prevented both of the effects of isoproterenol. After the kidney was perfused with a calcium-free medium containing EDTA, AVP did not change perfusion pressure or renin secretion but still suppressed isoproterenol-induced renin secretion. Based on these findings, Vandongen (1126) felt that AVP inhibited stimulated renin secretion by a change in renal hemodynamics that was dependent on calcium. In other studies, Konrads et al. (603) reported a decrease in RBF and urinary volume with AVP in the isolated, perfused rat kidney, but DDAVP diminished only urinary volume. Neither pep-

tide altered the basal rate of renin secretion. In this system, isoproterenol increased RBF and urinary volume slightly and caused a 7-fold rise in renin secretion, and all of these changes were reversed by AVP. An infusion of DDAVP into kidneys that had previously received isoproterenol did not affect RBF but did reduce urinary flow and renin secretion the same amount as did AVP. Thus, Konrads et al. (603), unlike Vandongen (1126), believed that the inhibitory action of AVP on renin secretion was independent of its vasoconstrictor action.

Newsome and Bartter (790) were the first clinicians to explore the effects of AVP on renin release in humans. The administration of AVP, combined with an increase in water intake, reduced PRA by 70%. It is not clear from these studies, however, whether the reduction in PRA was due to an increase in extracellular fluid volume, as indicated by the accompanying increase in body weight and decrease in serum sodium content, or was due to a direct effect of AVP in the kidney. In a later study, Goodwin et al. (399) gauged the long-term effects of AVP on renin release in normal subjects in the presence and absence of overhydration. In the absence of the expansion of the fluid volume of the body, AVP tended to decrease PRA in two of six people. In like fashion, PRA fell in two of three subjects previously given a water load; however, the changes in PRA were slight and "unimpressive." Incidentally, oxytocin also caused no change in PRA in the two cases in which it was tested. It was concluded that AVP had no specific inhibitory action on renin release in the absence of expansion of the plasma volume.

In a study of the short-term effects of AVP on renin release in humans, an infusion of AVP caused a progressive fall in PRA (21). When plasma AVP levels increased from 1.6 μU/ml to 9.7 and 14.5 μU/ml, PRA was lowered by 45% and 65%, respectively. Plasma osmolality, plasma sodium concentration, and MAP were not changed, but plasma protein concentration and peripheral venous packed cell volume decreased progressively after the infusion of AVP. Since the decrease in plasma protein concentration paralleled the fall in PRA, it was proposed (21), in agreement with other studies (399), that AVP, in physiologically relevant concentrations, suppressed the rate of renin secretion indirectly by increasing plasma volume at the expense of extracellular fluid volume. In an almost identical study in cardiac patients maintained on diuretic drugs, Hesse and Nielsen (478) reported a 40% reduction in PRA during the infusion of AVP; however, blood pressure, plasma colloid osmotic pressure, and venous packed cell volume remained constant. Because no apparent change in plasma volume occurred, it was concluded that AVP inhibited renin release by a direct, presumably intrarenal, action. This conclusion and these results are at variance with those of previous investigators (399, 582) and may be due to the use of normal subjects on one hand (399, 582) and diuretic-treated patients on the other (478). Because AVP is believed to prevent diuretic-induced renin release in the rat by a renovascular effect (637), AVP may suppress renin release in diuretic-treated patients by an intrarenal action but lower PRA in normal humans by increasing plasma volume.

Joppich and Weber (541) found that PRA was reduced by 67% in infants and children given an infusion of DDAVP. This suppression of renin release was accompanied by a 3-fold increase in sodium excretion and a 45% decrease in urinary volume.

Fichman et al. (334) have compared the PRA values of normal subjects given AVP by infusion and those of patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). As in the studies cited above, exogenously administered AVP suppressed PRA by about 50% when the normal subjects were in the supine position, and PRA increased only slightly upon the assumption of upright posture. Similarly, in patients with SIADH, in which the endogenous levels of AVP are greatly increased, PRA values were low or undetectable, with a mean reduction of 70% in the supine position when compared with normal, supine humans. Upon standing, PRA rose only slightly in the presence of SIADH, and five days of salt restriction caused little change in PRA in these patients. These observations are consistent with the idea that an elevation in the concentration of AVP in the plasma results in a decrease in renin release.

Lastly, the relationship between changes in PRA and plasma AVP levels have been examined after an upright tilting of 85° (249, 251). After this maneuver, both PRA and the circulating levels of AVP increased and reached a plateau at 30 min. Plasma volume fell during this interval. At the end of this 30-min period, the concentration of AVP in the plasma increased further whereas PRA declined, and Davies et al. (249, 251) suggested that the secondary rise in AVP was the cause of the fall in PRA.

In summary, AVP has been found to suppress the release of renin in rats, dogs, and humans. Although AVP has been noted to have variable effects on basal renin release, it has been shown to inhibit stimulated renin release consistently whether the stimulus was sodium depletion, a decrease in renal perfusion pressure, isoproterenol, diuretic agents, ureteral occlusion, or anesthesia. Endogenously synthesized AVP appears to have a similar effect on PRA since PRA is elevated in rats with hereditary diabetes insipidus and suppressed in patients with the syndrome of inappropriate secretion of AVP. In the dog, this peptide appears to inhibit renin secretion by a direct action on the granular JG cells, but in humans, it is unclear whether this inhibition of renin release is due to a direct action on the granular JG cells or to the expansion of the plasma volume. Despite this uncertainty concerning the mechanism of action of AVP, variations in the concentration of AVP in the pathologic range, and most likely in the physiologic range also, are involved in the control of renin release.

H. Prostaglandins

In recent years considerable attention has focused on the role of renal prostaglandins in the control of renin release (14, 30). These investigations have involved two types of experimental approaches: those using prostaglandins or prostaglandin precursors and those using inhibitors of prostaglandin synthesis. The former group of studies will be discussed in this section.

Vander (1117) was the first investigator to explore the relationship between prostaglandins and renin release. He infused PGE_1 and PGE_2 into the renal arteries of anesthetized dogs and observed a 3- to 4-fold increase in urine volume and sodium excretion and a 15% increase in RBF. In the seven dogs in which renal venous PRA was determined, the prostaglandin infusions produced an increase in one dog, a decrease in one dog, and no change in the remainder of the animals. However, since the data from all experimental doses of PGE_1 and PGE_2 were pooled, it is not clear if the doses of the prostaglandins that did not alter renin release might also have failed to alter renal hemodynamics or renal function. A year later, a similar inconsistent effect was observed when PGE_1 was infused i.v. into human subjects: PRA increased in two patients but did not change in two others (193).

In contrast to these earlier findings, Werning et al. (1205) consistently observed a 2- to 3-fold increase in PRA when a bolus of 25 μg of PGE_1 was injected into the aorta above the origin of the renal arteries in anesthetized dogs. Systemic blood pressure decreased by 10 to 20 mm Hg, and heart rate increased by 40 beats/min. Since, however, the increase in PRA was accompanied by a concomitant 2- to 3-fold increase in urine volume, sodium excretion, and potassium excretion, and since the urinary losses were not replaced, the authors concluded that the stimulation of renin release by PGE_1 was due to the loss of salt and water rather than to a direct action of the hormone on the granular JG cells. However, it is possible that the increase in renin release resulted from the fall in blood pressure and/or reflex activation of the sympathetic nervous system. The ability of PGE_1 to stimulate renin release was subsequently confirmed by Riley (935). Intrarenal infusions of 50 ng/kg/min of PGE_1 in anesthetized dogs increased RBF from 170 to 300 ml/min without altering systemic blood pressure. The excretion of sodium and chloride increased 6-fold and potassium excretion increased 3-fold. Despite the fact that these urinary losses were replaced every 5 min by an infusion of an equal amount of normal saline, the rate of renin secretion increased 3- to 4-fold. The stimulation of renin release by PGE_1 occurred in the absence of volume depletion thus indicating that another mechanism(s) must have been involved.

In a series of studies in anesthetized dogs, infusions of PGE_1 or PGE_2 into the renal artery increased renin secretion, RBF, urine volume, and sodium excretion (110, 111, 383, 1256). Unfortunately, urinary losses of salt and water were not replaced in any of these studies. For example, Bolger et al. (111) observed a 2-fold increase in RBF and a 3-fold increase in both urine volume and sodium excretion after intrarenal infusions of PGE_2. Renal venous PRA was doubled by the hormone. In a subsequent study, the same authors (110) observed the same qualitative effects on renin release and renal function when PGE_2 was infused in one-tenth the dose previously reported. Although the experimental data were not presented, the authors also stated that the infusion of small doses of PGE_2 stimulated the release of renin in dogs with a single nonfiltering kidney. This led them to conclude that PGE_2 elevated renin release either by means of hemodynamic changes within the kidney or by a direct action on the granular JG cells (110, 111).

Yun et al. (1256) also examined the effects of intrarenal arterial infusions of PGE_1 and PGE_2 on renin release in anesthetized dogs. In sodium-depleted dogs, in which the endogenous production of prostaglandins had been suppressed by pretreatment with indomethacin, infusions of PGE_2 caused a 3- to 4-fold increase in urine volume, sodium excretion, RBF, and renal venous PRA. Since PGE_2 also caused a slight decrease in MAP, these studies were repeated in dogs in which the renal perfusion pressure was maintained constant by the use of a suprarenal aortic clamp. As in the previous series of experiments, PGE_2 infusions caused a 3- to 4-fold increase in urine volume, RBF, and the rate of renin secretion. Thus, in agreement with the previous investigators (110, 111), Yun et al. (1256) concluded that the stimulation of renin release by PGE_2 must be due to either a direct action of the hormone on the granular JG cells or changes in renal hemodynamics that activated the intrarenal baroreceptor.

In probably the most revealing study to date, Gerber et al. (383) infused PGE_2 into the renal arteries of dogs with a single nonfiltering kidney in which the influences of the sympathetic nervous system had been ablated by renal denervation and an infusion of propranolol, a beta-adrenergic blocking drug. In addition, the dogs were pretreated with indomethacin to eliminate the influence of endogenous prostaglandins on renin secretion. The intrarenal infusion of 10 ng/kg/min of PGE_2 increased RBF from 159 to 232 ml/min and the rate of renin secretion from 281 to 819 ng of AI per min while 100 ng/kg/min of PGE_2 further increased RBF to 314 ml/min and the rate of renin secretion to 1910 ng of AI per min. Systemic blood pressure was not affected. Since these changes in renin secretion occurred in a setting in which neither the macula densa nor the sympathetic nervous system could influence renin release, this study provided convincing evidence that PGE_2 stimulated renin release by activation of the renal baroreceptor and/or a direct effect on the granular JG cells. Regarding activation of the renal baroreceptor, since changes in wall tension or volume strain are thought to mediate baroreceptor-stimulated renin release (vide supra), the increase in afferent

arteriolar radius resulting from PGE_2-induced vasodilatation would be expected to increase wall tension and volume strain (since renal perfusion remained at the control levels) and thus decrease, rather than increase, the release of renin. However, during renal micropuncture studies in anesthetized dogs, Strandhoy et al. (1054) found that PGE_1 and PGE_2 caused a 3-fold increase in renal interstitial pressure while peritubular capillary pressure increased only slightly. Similarly, Sinclair et al. (1017) found that PGE_2 infusions significantly increased renal subcapsular pressure and capsular lymph pressure. These effects appear to be due to the fact that PGE_2 increases RBF and decreases prevenous resistance without altering venous resistance. With these reports in mind, it may be suggested that PGE stimulates the release of renin by increasing renal interstitial pressure and thereby decreasing the transmural pressure gradient. In those circumstances in which the decrease in the transmural pressure gradient is great enough to override the influences of an increase in afferent arteriolar radius, as occurs during ureteral occlusion (393), wall tension would decrease and thereby stimulate the release of renin. In support of this hypothesis, some investigators have reported that PGE_1 and PGE_2 did not stimulate renin secretion from rat and rabbit renal cortical slices in vitro (234, 1188, 1189, 1208) and failed to stimulate renin release in dogs in which interstitial pressure was increased by ureteral occlusion (95). In conclusion, the release of renin by PGE appears to be due to an indirect action, most likely related to the renal baroreceptor, but the exact mechanism cannot be stated with any certainty.

In a series of studies in humans (194, 332, 333, 393, 615, 1276), the effects of i.v. infusions of PGA_1 on renin release have been studied. It should be mentioned at this point that PGA_1 may not be a naturally occurring compound but rather an artifact originating from the dehydration of PGE in vitro (365a). Fichman et al. (333) found that PGA_1, which caused a 4-fold increase in sodium excretion but did not alter systemic blood pressure, produced only modest increments in PRA in six of 10 subjects. Carr (194) reported a similar absence of change in PRA during the infusion of PGA_1 into hypertensive subjects on low and high sodium intakes. In the latter studies, urinary fluid losses were replaced by the oral administration of water. In contrast, Krakoff et al. (615) found that PGA_1 did not change PRA in subjects on a normal sodium diet but increased PRA 3-fold in subjects that had been sodium- and volume-depleted with furosemide. The ability of PGA_1 to elevate PRA in sodium-depleted subjects did not appear to be related to changes in hemodynamic parameters or renal function since the fall in blood pressure, the increase in RPF, and the increase in salt and water excretion caused by PGA_1 were more pronounced in the subjects on the normal sodium diet. Also, the rise in PRA was most evident in those subjects with the highest initial PRA values. Golub et al. (393) reported that nonhypotensive doses of PGA_1 increased PRA in a dose-related manner with the highest dose causing a 5-fold elevation of PRA. Because a similar increment in PRA was observed after the subjects were volume expanded with saline, these investigators suggested that PGA_1 stimulated renin release by a mechanism that was independent of its effects on renal function. Zusman et al. (1276) studied the relationship between plasma PGA, PGE, and PGF concentrations and PRA in normal subjects on a low, ad libitum, and high sodium intake. Plasma PGA concentrations increased from 1.6 ng/ml on an ad libitum diet to 2.1 ng/ml during sodium depletion. Sodium depletion elicited a 5-fold increase in PRA. In contrast, PGA concentrations decreased to 0.8 ng/ml when the subjects ingested a high sodium diet that suppressed PRA by 50%. Plasma PGE and PGF concentrations were not changed by alterations in dietary sodium. These investigators suggested that there might be a cause and effect relationship between changes in the plasma concentration of PGA and renin release in this situation.

While the mechanism by which PGA_1 stimulates renin release requires further study, the possibility that the hypotensive effects of the hormone reflexly activate the sympathetic nervous system should be considered since PGA_1 failed to increase PRA in a patient receiving the adrenergic blocking drugs propranolol and guanethidine (1025). Along these lines, Frisina et al. (363), in anesthetized dogs, found that i.v. PGA_1 caused a 3-fold increase in PRA without altering renal arterial pressure. Propranolol pretreatment completely blocked this PGA_1-induced renin release. Parenthetically, it should be mentioned that two reports have indicated that high concentrations of PGA_1 and PGA_2 reduce the velocity of the renin reaction in vitro (300, 611), but the physiologic significance of this observation is unknown.

The effects of $PGF_{2\alpha}$ on renin release have not been studied extensively. Weber et al. (1188, 1189) found that $PGF_{2\alpha}$ caused a dose-related decrease in renin secretion from rabbit renal cortical slices in vitro. In these studies, 10^{-6} M $PGF_{2\alpha}$ inhibited renin secretion by 40% to 50%. Along these same lines, PRA was found to be suppressed by 41% in women receiving 50 mg of $PGF_{2\alpha}$ intraamniotically for the induction of abortion (1032). In later studies, Weber et al. (1190) found that the in vitro activity of renal PGE_2-9-ketoreductase, the enzyme that converts PGE_2 to $PGF_{2\alpha}$, was increased in rats ingesting a high salt intake when compared with rats on a low salt intake. This increase in enzyme activity resulted in a 5-fold increase in the urinary excretion of $PGF_{2\alpha}$ relative to PGE_2. Since the high salt intake also suppressed PRA by 86%, the authors advanced the hypothesis that the activity of PGE_2-9-ketoreductase was involved in adjusting the activity of the renin-angiotensin system during states of altered salt intake. In contrast, Campbell et al. (178) found that alterations in the dietary salt intake of normotensive and hypertensive humans failed to alter the relative excretory rates of urinary PGE_2 and $PGF_{2\alpha}$. Also,

it should be pointed out that Zusman et al. (1276) observed no change in the plasma concentrations of PGE and PGF when renin release was increased or decreased by altering sodium intake in normal subjects. In addition, Terragno et al. (1080), in conscious dogs, found that changes in renal venous PRA correlated (r = .81) with changes in renal venous PGE concentration rather than with renal venous PGF concentration. However, it may be that only those prostaglandins produced within certain compartments of the kidney, as opposed to those found in the circulation, have the potential to affect renin release. In this respect it is important to recall that almost all of the PGE_2 and $PGF_{2\alpha}$ found in the urine have their origin in renal tissue.

Although infusions of PGE and PGA have produced variable changes in renin release, the intrarenal infusion of arachidonic acid, the fatty acid precursor of the prostaglandins, has been shown to cause a consistent increase in renin release in anesthetized rats, rabbits, and dogs (109, 246, 634, 1187). When Weber et al. (1187) infused arachidonic acid into the aorta above the origin of the renal arteries in anesthetized rats, a 3-fold increase in PRA was observed. Even after volume expansion with saline, PRA was doubled by arachidonic acid. Since these infusions did not affect sodium excretion, urine volume, or MAP, it appeared that arachidonate-induced renin release was not mediated by the macula densa or reflex activation of the renal sympathetic nerves. This contention was supported by the studies of Bolger et al. (109), who examined the effects of intrarenally-infused arachidonic acid on renin release in salt-loaded, anesthetized dogs in which the urinary losses of salt and water were replaced by an i.v. infusion of saline. Arachidonic acid caused a 40% increase in RBF and urine volume, a 70% increase in sodium excretion, and a 5-fold increase in the rate of renin secretion. Each of these effects was inhibited by pretreatment with indomethacin, a drug that inhibits prostaglandin synthetase. More importantly, arachidonic acid was demonstrated to cause a 3-fold increment in renal venous PRA when infused intrarenally in anesthetized dogs with a single denervated, nonfiltering kidney (246). No alteration in renin release was observed when 11,14,17-eicosatrienoic acid, a fatty acid that is not a substrate for prostaglandin synthetase, was infused into similarly prepared dogs. While the authors failed to report changes in RBF and MAP, data from their previous studies (207) indicate that the dose of arachidonic acid necessary to stimulate the renin release would also increase RBF without altering systemic blood pressure. Since the increase in renal venous PRA (246) caused by arachidonic acid was blocked by indomethacin, the authors concluded that one of the prostaglandin metabolites of arachidonic acid elevated the release of renin by a direct action on the granular JG cells and/or by activation of the intrarenal baroreceptor. Although both mechanisms may increase renin release from the kidney in situ, it has been reported that arachidonic acid stimulated renin secretion from rabbit renal cortical slices in vitro. Weber et al. (1188, 1189) and Whorton et al. (1208) found a 2- to 3-fold increase in renin secretion with 3×10^{-6} M and 2.5×10^{-3} M arachidonic acid, respectively. Inhibition of prostaglandin synthetase with indomethacin or 5,8,11,14-eicosatetraynoic acid blocked the increase in renin release caused by arachidonic acid in these in vitro studies. These findings favor a direct stimulatory action on the granular JG cells of a prostaglandin derived from arachidonic acid.

These studies with arachidonic acid have raised two important questions. First, since the synthesis of prostaglandins from arachidonic acid occurs in the renal medulla, how do the prostaglandins so formed reach the granular JG cells of the renal cortex? Some investigators have suggested that prostaglandins are transported from the medulla to the cortex in the renal tubular fluid (207, 1218), while others have hypothesized a countercurrent transport of prostaglandins between the renal arcuate vein and artery analogous to the transport of prostaglandins that occurs between the uterine vein and artery (709). Subsequently, it was found that the renal cortex could synthesize a variety of prostaglandins; however, the capacity of the cortical synthesizing system was estimated to be one-tenth to one-third of the medulla (633, 859, 911, 1209, 1270). The renal cortex was found to synthesize $PGF_{2\alpha}$ PGI_2, PGE_2, PGD_2, and thromboxane A_2 from arachidonic acid and the prostaglandin cyclic endoperoxides, PGG_2 and PGH_2. Therefore, it appears that prostaglandins synthesized in both the renal medulla and the renal cortex have access to the granular JG cells.

Secondly, since arachidonic acid can be metabolized to a number of prostaglandins, which one of these compounds is responsible for arachidonate-induced renin release? Weber et al. (1188, 1189) found that the prostaglandin cyclic endoperoxides stimulated renin secretion from rabbit renal cortical slices in vitro. This cyclic endoperoxide-induced renin release was not of the same magnitude as that observed with equimolar concentrations of arachidonic acid and also was inhibited by indomethacin. Since the prostaglandins known at that time, PGE_2 and $PGF_{2\alpha}$, did not stimulate renin release in vitro, the authors concluded that PGG_2 and PGH_2 exerted a direct action on the granular JG cells that caused them to secrete renin. However, in subsequent studies by Whorton et al. (1207a), PGE_1 and PGE_2 significantly increased renin release from rabbit renal cortical slices in vitro.

In recent years, however, two additional prostaglandins, PGD_2 and PGI_2, have been identified as being formed in the renal cortex from the cyclic endoperoxides and arachidonic acid (1209, 1270), and their effects on renin release have been investigated. Bolger et al. (111) infused PGD_2 intrarenally into anesthetized dogs and observed a 2-fold increase in RBF and a 2- to 3-fold increase in renal venous PRA, an increase in PRA similar to that elicited by PGE_2. Interestingly, PGD_2 caused no

change in urine volume or sodium excretion. In a subsequent study, the same investigators (110) reported a doubling of renal venous PRA when one-tenth the previously used dose of PGD_2 was tested in the same system. As before, stimulation of renin release by PGD_2 was associated with an increase in RBF and no change in sodium excretion. Gerber et al. (383) observed that intrarenal arterial infusions of PGD_2 stimulated renin secretion in anesthetized dogs with a single, denervated nonfiltering kidney. This 2.5-fold increase in the rate of renin secretion caused by PGD_2 was associated with a 2-fold increase in RBF. When PGE_2, at a concentration equimolar to that of PGD_2, was tested in the same series of experiments, it was found that the increment in renin secretion caused by PGD_2 was only 40% of that caused by PGE_2. Both PGD_2 and PGE_2 increased RBF to the same extent. From these studies (111, 383), it would appear that PGD_2 stimulates the release of renin either by a direct action on the granular JG cells or by activation of the intrarenal baroreceptor. However, it subsequently was shown that PGD_2 does not alter renin secretion from renal cortical slices in vitro (1207a); therefore, the renin secretion caused by PGD_2 in vivo appears to be mediated by the renal baroreceptor.

The effects of prostacyclin (PGI_2) on renin release also have been studied (110, 383). Bolger et al. (110) examined the effects of intrarenal infusions of PGI_2 on renin release in anesthetized dogs. They found that PGI_2 produced a 50% increase in RBF and a 2-fold increase in urine volume and sodium excretion in doses that increased renal venous PRA by 25%. Gerber et al. (383) infused PGI_2 intrarenally into anesthetized dogs with a single denervated nonfiltering kidney, after pretreating the dogs with indomethacin to remove the influences of endogenously synthesized prostaglandins, and observed a dose-related increase in renin secretion and RBF. An intrarenal infusion of 1 ng/kg/min of PGI_2 elevated RBF from 121 and 132 ml/min and increased the rate of renin secretion from 538 to 744 ng of AI per min. Increasing the dose at PGI_2 to 10 ng/kg/min further increased RBF to 163 ml/min, and renin secretion rose to 1518 ng of AI per min. Systemic blood pressure was not changed. Thus, when compared with PGE_2 and PGD_2, PGI_2 is the most potent stimulator of renin release. Using rabbit renal cortical slices, Whorton et al. (1208) found that PGI_2 caused a dose-related increase in renin secretion in vitro. In a subsequent study, the same investigators found that 9,11-azoprosta-5,13-denoic acid inhibited the synthesis of PGI_2 by renal cortical slices without altering the synthesis of PGE_2 or $PGF_{2\alpha}$ (1207a). Furthermore, this prostacyclin synthetase inhibitor reduced basal and arachidonic acid-stimulated renin release by 24% and 60%, respectively. Thus, PGI_2, like arachidonic acid, appears to stimulate the release of renin by a direct action on the granular JG cells.

The renal synthesis of prostaglandins may affect the renin-angiotensin system in another way. The first step in the synthesis of prostaglandins involves the release, by a phospholipase, of a fatty acid precursor of prostaglandins and a lysophospholipid (505, 519, 755, 1275). Sen and co-workers and others (857, 1004, 1026) have identified a lysophospholipid released from the kidney which inhibits renin enzyme, and although the physiologic significance of this lipid remains to be determined, it does raise the interesting possibility that a byproduct of the reaction involved in the synthesis of renal prostaglandins may be an intrarenal inhibitor of renin (716).

In summary, PGE_1, PGE_2, PGA_1, PGD_2, PGI_2, PGG_2, PGH_2, and arachidonic acid stimulate the release of renin whereas $PGF_{2\alpha}$ inhibits renin release. Since the renin release elicited by PGE_2, PGD_2, PGI_2, and arachidonic acid is associated with a concomitant elevation of RBF, but no change in salt or water excretion, it appears that this increase in renin release may occur via activation of the intrarenal baroreceptor. Since arachidonic acid and PGI_2 stimulate the release of renin from renal cortical slices in vitro, these compounds seem to possess an additional direct effect on the granular JG cells. On the basis of these findings, and the ability of the prostacyclin synthetase inhibitor, 9,11-azoprosta-5,13-dienoic acid, to inhibit arachidonic acid-induced renin release, we feel that PGI_2 is the most likely candidate for the renin-releasing metabolite of arachidonic acid. However, further studies are required. Does renal PGI_2 production correlate with renin release? What are the effects of thromboxane A_2 on renin release in vivo and in vitro? Do the prostaglandins have direct effects on ion transport at the macula densa?

I. Serotonin

The effects of serotonin (5-hydroxytryptamine) on renin release have not been studied extensively. Originally, an intrarenal arterial infusion of serotonin was reported to have no effect on renin release in anesthetized dogs (164), but later Meyer et al. (731) noted that serotonin elevated PRA in rats. When blood for the determination of PRC was collected after ether anesthesia, an i.m. injection of serotonin produced a rapid, 5-fold increase in PRC that had dissipated by 4 hr after the injection. The renin response to serotonin was completely blocked by the serotonin receptor antagonist methysergide, which had no effect on PRC by itself. Pretreatment with propranolol or camphidonium, a ganglionic blocker that does not enter the brain, attenuated serotonin-induced renin release by 50% and 40%, respectively. Although Meyer et al. (731) did not measure blood pressure in their experiments, the latter observation is consistent with the fact that serotonin causes a long-lasting vasodepression in conscious rats (232), which would serve to activate the sympathetic nervous system reflexly. The portion of serotonin-induced renin release that remained after propranolol may have been the result of hypotensive activation of the renal baroreceptor or a direct action of serotonin on the granular JG cells.

More recently, Ganong et al. (374b) determined the effects of two precursors of serotonin, tryptophan and 5-hydroxytryptophan, on renin release in anesthetized dogs. The i.v. injection of tryptophan caused a dose-related increase in PRA that was not affected by the peripheral inhibition of L-aromatic amino acid decarboxylase with carbidopa. The central inhibition of L-aromatic amino acid decarboxylase with benserazide blunted and renal denervation abolished the rise in PRA caused by tryptophan. It was concluded that the increased conversion of tryptophan to serotonin in the brain led to the stimulation of central serotonergic receptors, which increased sympathetic outflow to the kidney. In other studies, the immediate precursor of serotonin, 5-hydroxytryptophan, caused a modest rise (25%) in PRA that was potentiated by carbidopa and blocked by benserazide. Metergoline, a specific serotonin receptor antagonist, also blocked the ability of 5-hydroxytryptophan to elevate renin release. These data pointed to a central site of action of 5-hydroxytryptophan.

The oral administration of tryptophan, which has been shown to elevate the synthesis of serotonin in the brain (298), to supine humans resulted in a 90% increase in PRA in nine of 11 cases (756). The continuous measurement of blood pressure in five of these volunteers did not reveal any relationship between changes in PRA and blood pressure. Whereas Meyer et al. (731) attributed the rise in PRC after serotonin to a peripheral action of the compound, the elevation of PRA caused by tryptophan was attributed to a central site of action (756).

Lastly, the serotonergic antagonist cyproheptadine significantly lessened furosemide-induced renin release in supine, normotensive humans (308). Because cyproheptadine also has antihistaminic and anticholinergic activity, and because the exact mechanism by which furosemide elicits renin release is not known, the exact significance of these data (308) cannot be stated with any certainty.

In short, the role of serotonin, both peripherally and centrally, in the control of renin release needs further clarification.

J. Cyclic Adenosine 3′,5′-monophosphate

Numerous investigators have delineated the role of the sympathetic nervous system and renal beta-adrenergic receptors in the control of renin release (vide supra). Since stimulation of beta-adrenergic receptors activates adenyl cyclase in many tissues, and since this activation leads to an increase in the intracellular concentration of cyclic adenosine 3′,5′-monophosphate (cyclic AMP) (942), it is not surprising that the role of cyclic AMP in renin release has been studied.

The initial studies concerning the effects of cyclic AMP on renin release involved the infusion of this nucleotide to determine whether the renin response mimicked beta-adrenergic stimulation of renin release. Tagawa and Vander (1070) were among the first investigators to examine the effects of adenosine compounds on renin release in vivo. In anesthetized, sodium-depleted dogs, the infusion of large doses of cyclic AMP (1 to 5 mg/min) directly into the renal artery caused a 6% increase in RBF, a 13% decrease in efferent arteriolar resistance, an 11% decrease in GFR, a 12% decrease in sodium excretion, and a 5 mm Hg decrease in MAP. These minor changes were associated with a marked fall in renal venous PRA in four of the five dogs studied. Lower doses of cyclic AMP (0.05 to 0.2 mg/min) failed to alter renal venous PRA and had essentially no effect on renal hemodynamics and function. Qualitatively similar results were observed when adenosine, adenosine triphosphate, and 5′-adenosine monophosphate were tested. Since efferent arteriolar resistance, MAP, and sodium excretion were decreased by cyclic AMP, the authors were unable to explain the suppression of renin release by a known mechanism, i.e. the renal baroreceptor or macula densa, so they proposed a direct inhibitory effect of adenosine compounds on the granular JG cells.

In contrast, Winer et al. (1227) observed a 4.6-fold increase in renin secretion and a 10% decrease in RBF when cyclic AMP was infused intrarenally (22 μg/kg/min) into anesthetized dogs. Sodium excretion, GFR, and MAP were unchanged. Infusions of equimolar concentrations of adenosine triphosphate, adenosine diphosphate, and 5′-adenosine monophosphate were without effect on renin release or renal function. Of interest was the fact that pretreatment with propranolol or phentolamine abolished the stimulation of renin secretion by cyclic AMP, an observation suggesting that these receptor antagonists acted at a site distal to the site of action of cyclic AMP. The authors (1227) suggested that the discrepancy between their findings and those of Tagawa and Vander (1070) might have been due to the fact that the latter group used sodium-depleted dogs in which the high levels of PRA may have obscured any further increment in PRA caused by cyclic AMP.

In perhaps the most complete study, Allison et al. (13) tested the ability of intrarenal infusions of 5′-adenosine monophosphate, cyclic AMP, and dibutyryl cyclic AMP to alter renin release in anesthetized normal and sodium-depleted dogs. The infusion of 5′-adenosine monophosphate lowered PRA in normal dogs without affecting blood pressure. In normal dogs, cyclic AMP, at doses of 1 and 2.5 mg/min, did not change PRA. However, in three sodium-depleted dogs pretreated with theophylline, cyclic AMP caused a slight increase in PRA when infused at the higher dose. On the other hand, dibutyryl cyclic AMP elicited a 2-fold increase in PRA when infused at 2.5 mg/min and increased PRA in three of four dogs studied with the 1 mg/min dose. A similar rise in PRA was observed when the higher dose of dibutyryl cyclic AMP was given to sodium-restricted dogs pretreated with theophylline. In the latter case, theophylline appeared to raise basal renin release prior to the administration of dibutyryl cyclic AMP. Allison et al. (13) con-

cluded that dibutyryl cyclic AMP stimulated the release of renin by a direct action on the granular JG cells. They explained the greater effectiveness of dibutyryl cyclic AMP in stimulating renin release by its higher lipid solubility and its greater resistance to degradation by phosphodiesterases as compared to cyclic AMP.

These findings with dibutyryl cyclic AMP were confirmed by Okahara et al. (828). In anesthetized dogs with denervated kidneys, an intrarenal infusion of cyclic AMP increased RBF but failed to change renal venous PRA or the rate of renin secretion. In contrast, dibutyryl cyclic AMP caused a 5-fold increase in renal venous PRA and a 40-fold rise in renin secretion. In the latter experiments, this stimulation of renin secretion was accompanied by a 62% increase in RBF and a 3-fold elevation of sodium excretion. Pretreatment with propranolol or sotalol did not affect any of the responses to dibutyryl cyclic AMP. It was concluded that dibutyryl cyclic AMP elicited renin release by a direct action on the granular JG cells rather than by changing renal hemodynamics or electrolyte excretion or by activation of beta-adrenergic receptors.

Hauger-Klevene (452) found that an i.v. infusion of dibutyryl cyclic AMP into anesthetized rats brought about a 5-fold increase in PRA. Pretreatment with dexamethasone inhibited the dibutyryl cyclic AMP-induced renin release by 97%, but blood pressure and heart rate were not measured in these experiments so interpretation of these results is difficult. A similar 5-fold elevation of SRA was observed by Campbell et al. (180) when dibutyryl cyclic AMP was infused intraaortically above the bifurcation of the renal arteries in conscious rats. This infusion did not alter MAP, but heart rate was increased by 20%. Interestingly, indomethacin, an inhibitor of prostaglandin synthesis, completely blocked the increase in SRA, but not the increase in heart rate, caused by dibutyryl cyclic AMP. Thus, we are faced with the intriguing possibility that prostaglandins may mediate the stimulation of renin release caused by cyclic AMP, and, moreover, that prostaglandins may be the final common pathway in beta-adrenergically-mediated renin release. The latter possibility is supported by the fact that isoproterenol-induced renin release in humans and rats has been shown to be blocked by inhibitors of prostaglandin synthesis (180, 365).

Two conflicting reports (489, 882) have appeared concerning the effects of the cyclic nucleotides on renin release in the isolated, perfused rat kidney. On the one hand, Peart et al. (882) failed to observe a change in renin secretion when cyclic AMP or dibutyryl cyclic AMP was infused into rat kidneys in vitro. Cyclic guanosine 3′,5′-monophosphate (cyclic GMP) and 8-bromo-cyclic GMP caused slight increments in renin secretion, but the effect was highly variable and independent of the dose employed. In addition, cyclic AMP and cyclic GMP did not alter renin release or renal perfusion pressure when infused along with theophylline. The authors felt that the lack of stimulation by the cyclic nucleotides in their experiments may have been due to the failure of these hormones to enter the granular JG cells of the kidney. On the other hand, Hofbauer et al. (489) reported that dibutyryl cyclic AMP elicited a dose-related increase in renin secretion, RBF, GFR, and sodium excretion in the perfused rat kidney. The nucleotide 8-bromo-cyclic GMP, in doses equimolar to dibutyryl cyclic AMP, also caused a dose-related rise in RBF, GFR, and sodium excretion, but this derivative of cyclic GMP produced no change in renin secretion. Since the elevation of RBF, GFR, and sodium excretion were comparable with both compounds, it was concluded that dibutyryl cyclic AMP stimulated renin secretion by a direct action on the granular JG cells rather than by an action on the renal baroreceptor or macula densa. Why these two groups of investigators should obtain such divergent results is puzzling. Methodologic differences might account for these contradictory observations since Peart et al. (882) perfused the kidney with a Krebs-Ringer-dextran-saline solution at a constant flow rate whereas Hofbauer et al. (489) used a Krebs-Henseleit-gelatin-saline solution (containing antidiuretic hormone and neomycin sulfate) perfused at a constant pressure.

In 1969, Michelakis et al. (744) first examined the effects of cyclic AMP on renin release from isolated canine renal cortical cells. Cyclic AMP caused a 3-fold increase in the production of renin, and the stimulatory effect was dose-related. Since a similar stimulation of renin production was observed with norepinephrine and epinephrine, the authors suggested that cyclic AMP might function as the intracellular mediator of catecholamine-induced renin release. Yamamoto et al. (1243) observed a 20% increase in renin release from canine renal cortical slices with dibutyryl cyclic AMP, but only a small increase was seen with cyclic AMP. Similarly, Saruta and Matsuki (982) found that renin release increased by only 9% when cyclic AMP was added to the incubation medium of rat renal cortical slices. Thus, although the changes observed were small, in each of these studies (744, 982, 1243) cyclic AMP did appear to stimulate the release of renin from renal cortical tissue in vitro. However, the effects of cyclic AMP and dibutyryl cyclic AMP on renin release were quite weak as compared to those of the catecholamines (805, 1197).

Concerning the link between endogenously produced cyclic AMP and beta-adrenergically-mediated renin release, the studies of Beck et al. (66, 67) have provided the greatest insight. They found that epinephrine increased the cyclic AMP concentration of the renal cortex, outer medulla, and inner medulla by 3-fold, 4-fold, and 2.5-fold, respectively, and this stimulation was inhibited by propranolol (67). Furthermore, the administration of lithium did not alter the basal concentration of cyclic AMP in the cortex and medulla, but this treatment completely blocked the increment in renal cyclic AMP concentration caused by isoproterenol (66). The stimulation of renal cyclic AMP production by parathyroid

hormone and vasopressin was not affected by pretreatment with lithium. Thus, lithium appeared to block beta-adrenergically-mediated cyclic AMP production in the kidney selectively. When isoproterenol was infused i.v. into anesthetized dogs, a 2-fold increase in PRA and a 1.6-fold increase in urinary cyclic AMP occurred (66). Pretreatment of the animals with lithium increased basal PRA from 2.5 to 4.4 ng of AI per ml per hr and decreased the urinary excretion of cyclic AMP by 66%. In these same dogs, isoproterenol caused a 1.7-fold increase in PRA and a 1.3-fold increase in urinary cyclic AMP content. The authors (66, 67) concluded that the increase in PRA after isoproterenol may not be mediated through the beta-adrenergic stimulus-dependent cyclic AMP system in the kidney. However, no other experimental work has been presented to support this belief.

A number of researchers have tried to correlate changes in plasma or urinary cyclic AMP levels with changes in PRA after alterations in sympathetic nerve activity. Since the relationship between plasma or urinary cyclic AMP levels and the intracellular concentration of cyclic AMP in the kidney is not known, studies of this kind must be interpreted with appropriate caution. Lowder and co-workers (438, 670, 671) examined the effects of insulin-induced hypoglycemia on PRA and urinary and plasma levels of cyclic AMP. When insulin was given in a dose that decreased serum glucose levels by greater than 50%, they observed a 4-fold increase in PRA (670) and a 5-fold increase in plasma cyclic AMP concentration (438) in normal subjects. If these people were pretreated with propranolol, a similar decrement in serum glucose concentration after insulin did not alter PRA or the concentration of cyclic AMP in the blood. In addition, insulin caused a 2-fold rise in PRA in adrenalectomized patients but failed to alter the plasma levels of cyclic AMP. A similar dissociation between PRA and plasma cyclic AMP content after insulin was observed in patients with normal-renin hypertension (671) and patients with diabetes mellitus (661).

Because the intrarenal action of parathyroid hormone was known to be responsible for 30% to 50% of the cyclic AMP found in the urine, Weber et al. (1184) studied the effects of sodium restriction on PRA and the urinary excretion of cyclic AMP in patients with hypoparathyroidism. Sodium depletion elevated PRA by 6- to 8-fold and increased the urinary excretion of cyclic AMP by 30%; furthermore, a positive correlation was noted between PRA and urinary cyclic AMP. Propranolol blocked both the increase in PRA and urinary cyclic AMP caused by sodium depletion. It was concluded that renal beta-adrenergic receptors mediated the increase in renin release and renal adenylate cyclase activity during sodium depletion.

In summary, cyclic AMP and dibutyryl cyclic AMP appear to elicit renin release in vivo and in vitro by a direct action on the granular JG cells. Even though this stimulation of renin release by cyclic AMP is believed to mimic beta-adrenergically-mediated renin release, the effects of cyclic AMP and dibutyryl cyclic AMP, even in the presence of phosphodiesterase inhibitors, are quite weak as compared to those of renal nerve stimulation and catecholamines.

K. Adenosine

In recent years, a potential role for endogenous adenosine in the control of renin release, renal hemodynamics, and renal electrolyte metabolism has been recognized (463, 489, 754, 853, 1070). The rate of production of adenosine in the isolated kidney appears to be quite high (355), and numerous stimuli have been shown to elicit further increments in renal adenosine release (355, 754). In addition to renal nerve stimulation, norepinephrine, and AII (355), a decrease in renal perfusion pressure (355, 852) and renal hypoxia (355, 754) have been demonstrated to cause a rapid increase in the release of adenosine from the kidneys of rabbits in vitro (355) and the kidneys of rats, cats, and dogs in vivo (754). The release of adenosine after renal ischemia has been well documented (355, 431, 754, 1111), and it has been hypothesized that adenosine plays an important part in postischemic and hypoxic vasoconstriction in the kidney. Also, the enzyme 5′-nucleotidase, which catalyzes the dephosphorylation of 5′-adenosine monophosphate to yield adenosine, has been found to be located primarily on the external membranes of the cells of the proximal tubule (754). As stated earlier, Tagawa and Vander (1070) found that an intrarenal arterial infusion of adenosine lowered renal venous PRA (by 50%), GFR, sodium excretion, and urinary flow. Renal plasma flow increased slightly. More recently, an infusion of adenosine into the thoracic aorta above the kidneys in salt-depleted, anesthetized rats was shown to decrease renin secretion by 54% (853). Blood pressure was unchanged, but GFR, RBF, sodium excretion, and urinary flow were depressed. Each of these changes was reversed within 3 to 5 min after cessation of the adenosine infusion. When this same experiment was repeated in sodium-loaded anesthetized rats, basal renin secretion was 76% lower than the values measured in the sodium-depleted rats and was not changed by adenosine. As before, sodium excretion, urinary volume, and GFR were decreased, but, paradoxically, RBF increased by 20%. Thus, the sensitivity of the kidney to adenosine appeared to be increased when basal renin secretion was elevated. Adenosine was thought to suppress renin secretion by one of several mechanisms (853). First, adenosine might, by some unknown mechanism, increase the feedback inhibition of renin secretion by intrarenal AII. This possibility is supported by the observation that the renal vasoconstrictor activity of adenosine appears to be directly related to the level of activity of the renin-angiotensin system (851, 853). In addition, AII has been shown to elicit the rapid release of adenosine from the isolated, perfused rat kidney (355). Secondly, adenosine might decrease the rate of renin secretion by inhibiting the

release of norepinephrine from the renal nerves (853). In support, Hedqvist and Fredholm (462) have demonstrated that adenosine caused a reversible, dose-dependent inhibition of nerve-stimulated norepinephrine release in the isolated, perfused rabbit kidney. This prejunctional inhibition of norepinephrine release by adenosine may represent a physiologically active, negative feedback system since renal nerve stimulation enhanced the release of adenosine from the isolated, perfused rabbit kidney (355). If this were the mechanism by which adenosine inhibited renin secretion, then it would have to be assumed that renal nerve activity was decreased greatly in salt-loaded rats (853).

On the other hand, some of the renal effects of adenosine would be expected to increase renin release. For example, since the decrease in urinary sodium excretion after adenosine appeared to result from the large decrease in GFR (853, 854), the sodium load passing the macula densa would be decreased, and this decrease should stimulate renin release. The decrement in GFR after adenosine was much greater than the decrement in RBF (853), and the marked fall in GFR appeared to be due to a 2-fold increase in afferent arteriolar resistance with essentially no change in efferent arteriolar resistance (854). These data (853, 854) are in accord with the earlier findings of Tagawa and Vander (1070), who concluded that adenosine vasoconstricted the afferent arterioles and vasodilated the efferent arterioles in anesthetized dogs. Because a decrease in the afferent arteriolar radius at a constant renal perfusion pressure would result in a decrease in circumferential stress, the renal baroreceptor mechanism controlling renin release should be activated. Thus, the only actions of adenosine that would be expected to lower renin release are the inhibition of norepinephrine release from the renal sympathetic nerves or a direct effect on the granular JG cells.

In summary, adenosine suppresses renin release, and this action is related to the level of activity of the renin-angiotensin system. The only renal actions of adenosine that would account for its ability to inhibit renin release are the attenuation of the release of norepinephrine from the sympathetic neuron or a direct effect on the granular JG cells. Many different stimuli elicit the production of adenosine in the kidney, but the role of endogenous adenosine in the control of renal hemo- and hydrodynamics and renin release is unknown.

III. Pharmacologic Alterations of Renin Release

A. Anesthetics

Because anesthetic agents are used widely in animal experimentation, it is not surprising that a number of studies have focused on the effects of anesthetics on the release of renin. As pointed out in the recent review by Pettinger (889) and as illustrated in table 1, anesthetic drugs, when used in doses that produce a surgical plane of anesthesia, stimulate the release of renin in man and experimental animals.

The mechanisms by which anesthetic agents release renin appear to be as diverse as the pharmacologic properties of the anesthetics themselves. Pentobarbital-induced renin release has received the greatest attention. When administered i.v. to dogs (106, 353, 387, 537, 831, 1257) or rabbits (1174, 1175) or i.p. to rats (903), pentobarbital caused a transient decrease in MAP of 5 to 50 mm Hg and an increase in heart rate. However, blood pressure usually returned to normal within 5 to 10 min whereas PRA remains elevated for up to 4 hr. Warren and Ledingham (1174) found that RBF was decreased by 26% and sodium excretion by 33% 30 min after pentobarbital had been administered to rabbits. At the same time, cardiac output and blood pressure were depressed by 13% and 16%, respectively. In hydrated dogs, Blake (106) observed a decrease in RPF and GFR and an increase in renal vascular resistance after the i.v. administration of pentobarbital, but these parameters returned toward preanesthetic levels during the next 3 hr. Urinary volume and sodium and potassium excretion also were reduced. When these studies were repeated in nonhydrated dogs, no consistent or significant changes were observed. Burger et al. (170) also found that pentobarbital reduced RBF by 37% in dogs without changing MAP. Unfortunately, PRA was not measured in these latter two studies. Based on these observations, pentobarbital may induce renin release by activation of the renal baroreceptor since a decrease in afferent arteriolar radius at a constant renal perfusion pressure would lead to a decrease in circumferential stress (vide supra). In like fashion, if pentobarbital-induced anesthesia decreased the sodium load presented to the macula densa, renin release would be stimulated. From the available data, it is unclear whether the decrease in sodium excretion (106) and the increase in renin release (353, 537, 1257) occur in parallel or have the same temporal relationship. It should be mentioned that pentobarbital *decreased* PRC by 24% in newborn pigs, and this reduction was associated with a 6-fold *increase* in sodium excretion (43).

Ganong (373) examined the effect of beta-adrenergic receptor blockade on pentobarbital-induced renin release in dogs. Propranolol did not affect the 2.5-fold increase in PRA elicited by this barbiturate. In like fashion, Yun et al. (1257) observed that pentobarbital increased PRA by 2-fold in dogs in both the absence and presence of propranolol. In the same study, pentobarbital increased PRA by 2.3-fold in dogs pretreated with the prostaglandin synthesis inhibitor indomethacin. Therefore, pentobarbital must stimulate the release of renin through a mechanism that is independent of the renal sympathetic nerves and the renal prostaglandins. Along these lines, the reader should recall that the macula densa mechanism controlling renin release also operates independently of the renal sympathetic nerves and renally produced prostaglandins.

Tanaka and Pettinger (1077) were the first to study the effects of ketamine on renin release. Twenty minutes

TABLE 1

*The effects of anesthetic agents on renin release**

Anesthetic Agent	Species	Dose	Change in Renin Release (Increase in PRA or PRC)†	Surgical Anesthesia	Comments	Reference
Pentobarbital	Rat	25 mg/kg, s.c.	2-fold	+	Compared with decapitated rats	817
		40 mg/kg, s.c.	4.4-fold	+	Compared with decapitated rats	117
			No change	−	Lightly anesthetized animals that reacted to painful stimuli	117
		35 mg/kg, i.p.	4-fold	+	Peak effect at 10 min, remained elevated 4 hr	199
		35 mg/kg, i.p.	5.7-fold	+	Peak effect at 15 min	643
		30 mg/kg, i.p.	4-fold	+	Peak effect at 20 min	908
		30 mg/kg, i.p.	4.5-fold	−	Normal salt diet	896
		30 mg/kg, i.p.	70-fold	−	Animals treated with DOCA and 0.9% saline drinking fluid	896
	Rabbit	30 mg/kg, i.v.	No change	+	Laparotomy after anesthesia increased PRA 3-fold	719,721
	Dog	30 mg/kg, i.v.	2-fold	+	Reduced by propranolol, not blocked by indomethacin	1254,1257
		30 mg/kg, i.v.	2.5-fold	+	Unaltered by propranolol	373
		30 mg/kg, i.v.	No change	+	Normal sodium diet	353
		30 mg/kg, i.v.	2.4-fold	+	Low sodium diet, peak effect at 25 min	353
		25 mg/kg, i.v.	5-fold	+	Peak effect at 25 min	537
	Pig	20 mg/kg, i.v.	24% decrease	+	Newborn animals	43
Phenobarbital	Humans	3 × 100 mg	1.3-fold	−	Studied in only 3 patients	547
Ketamine	Rat	125 mg/kg, i.m.	1.6-fold	+	Nonsignificant change, measured 1 hr after ketamine in rats on a normal sodium diet	751
		125 mg/kg, i.m.	5.2-fold	+	Measured 1 hr after ketamine in rats on a low sodium diet	748
		40–160 mg/kg, i.p.	1.6–6.5-fold	+	Peak effect observed at 20 min, inhibited 92% by propranolol	1077
		100 mg/kg, i.p.	3.8-fold	+		903
		80 mg/kg, i.p.	4-fold	+	Normotensive Wistar rats	176
			4.5-fold	+	SH rat	176
	Pig	5 mg/kg, i.m.	No change	+	Newborn animals, used in connection with nitrous oxide:oxygen (4:1)	43
	Humans	2 mg/kg, i.v.	No change	+	Premedicated with atropine, PRA measured at 5 and 15 min	750
Urethane	Rat	1250 mg/kg, i.p.	8.4-fold	+	Reached plateau within 15 min and remained elevated up to 240 min	250
		400 mg/kg, i.p.	3-fold	+	Inhibited 90% by propranolol	903
		800 mg/kg, i.p.	21-fold	+	Reached plateau within 15 min and remained elevated up to 100 min, inhibited 45% by propranolol	903
Chloralose	Rat	60 mg/kg, i.p.	No change	−		903
Chloralose + urethane	Rat	50 and 500 mg/kg, i.p.	26-fold	+		903
Morphine	Rat	5 mg/kg	4.3-fold	+		903
	Humans	1 mg/kg	3.5-fold	+	Premedication with morphine and scopolamine prior to nitrous oxide	42
Droperidol Fentanyl (Innovar)	Humans	0.007 and 0.15 mg/kg, i.v.	1.5-fold	+	Premedication with atropine	523
Ether	Rat	50%+	10-fold	+	Rats receiving a normal or high sodium diet	183
		?	11-fold	+	Compared with decapitation	817
		?	3-fold	+	Inhibited 100% by timolol	410
		?	1.5-fold	+		117
		50%+	18-fold	+	Reached plateau within 10 min, remained elevated up to 60 min	199
		?	4.5-fold	+	Reached plateau within 1 min, remained elevated up to 30 min	643
		10%	5.8-fold	+		903

TABLE 1—*Continued*

Anesthetic Agent	Species	Dose	Change in Renin Release (Increase in PRA or PRC)†	Surgical Anesthesia	Comments	Reference
		20%	8.2-fold	+	Reached plateau within 15 min	903
		50%+	6.1-fold	+	Inhibited 96% by propranolol	890
		50%+	4.8-fold	+	Normal salt diet	896
		50%+	8-fold	+	Animals treated with DOCA and 0.9% saline drinking water	896
Halothane	Rat	1.26%	No change	+	Normal sodium diet, PRA measured after 1 hr of continuous administration	751
		1.25%	2.6-fold	+	Low sodium diet, PRA measured after 1 hr of continuous administration	748
		1%	No change	–	Measured after 15 min of administration	903
		2%	1.6-fold	+	Measured after 5 min of administration	903
		4%	8-fold	+	Measured after 5 min of administration	903
	Rabbit	5%	4.8-fold	+	Administered with nitrous oxide and oxygen	981
	Pig	1%	2.3-fold	+	Newborn animals	43
	Humans	?	No change	+	Administered with thiopental, nitrous oxide, and oxygen; premedication with atropine, secobarbital, and meperidine	939
		0.5–1.0%	3.1-fold		Not blocked by practolol; premedication with atropine, thalamonal, and trapanal	1206
		?	1.5-fold	+	Premedication with atropine, meperidine, and promethazine; PRA increased further during surgery	523
Nitrous oxide	Rat	80%	No change	–		903
	Pig	80%	No change	+	Newborn animals	43
	Humans	50%	3.5-fold	+	Combined with morphine (1 mg/kg); premedication with scopolamine and morphine	42
Methoxyflurane	Rat	0.5%	1.7-fold	+	Measured after 5 min of exposure to methoxyflurane	903
		2.5%	2.1-fold	+	Measured after 5 min of exposure to methoxyflurane	903
		?	1.6-fold	–		903
Cyclopropane	Rat	20%	1.4-fold	+	Measured after 5 min of exposure to cyclopropane	903
		50%	2.2-fold	+	Measured after 5 min of exposure to cyclopropane	903
Enflurane	Rat	1.75%	1.8-fold	+	Low sodium diet	748
Fluroxene	Rat	4.55%	1.3-fold	+	Change not significant	751

* In most cases, blood for the determination of control (no anesthesia) PRA and PRC values was drawn from conscious animals or humans via indwelling catheters. However, in many of the studies with rats, control values for PRA or PRC were obtained from blood collected after the decapitation of conscious animals. Surgical anesthesia indicates the absence of a response to painful stimuli.

† Abbreviations used are: PRA, plasma renin activity; PRC, plasma renin concentration; DOCA, deoxycorticosterone acetate.

after the injection of ketamine into rats, SRA was elevated 6-fold. Thereafter, SRA declined and blood pressure and heart rate increased. When the rats were pretreated with propranolol, the ketamine-induced increase in SRA was inhibited by 92%. Propranolol also prevented the increase in blood pressure and heart rate elicited by ketamine. The authors concluded that ketamine released renin through a beta-adrenergic mechanism and that AII mediated the tachycardia and hypertension produced by the drug. In subsequent studies, Miller et al. (748, 751) gauged the effects of ketamine on renin release 1 hr after the induction of anesthesia. In rats ingesting a normal sodium diet, ketamine caused a 1.6-fold (nonsignificant) increase in PRA and a 28 mm Hg decrease in MAP. Basal PRA tripled when rats were placed on a low sodium diet, and ketamine further elevated PRA by 5.2-fold and decreased MAP by 19 mm Hg. Thus, when a stable state of anesthesia was attained with ketamine, PRA was not elevated, even though blood pressure was markedly depressed, unless the animals were sodium-depleted. Although ketamine appears to stimulate renin release by a beta-adrenergic mechanism in the early stages of anesthesia, the role of renal beta-adrenergic receptors in ketamine-stimulated renin release in sodium-depleted rats during the stable phase of anesthesia is unknown.

Pettinger et al. (903) noted that urethane increased SRA by 3-fold and 18-fold after doses of 400 and 800 mg/kg, respectively. The stimulation of renin release peaked

after 10 min and remained elevated up to 100 min. Leenen and deJong (643) also observed a sustained increase in PRA with urethane. Despite the large increase in PRA, heart rate and blood pressure were not changed (903). When the rats were pretreated with propranolol, urethane-induced renin release was inhibited by 88% and 59% at the 400 and 800 mg/kg doses of urethane, respectively. Thus, urethane, like ketamine, also appears to release renin by activation of the beta-adrenergic receptors on the granular JG cells.

Pettinger et al. (890) were among the first to examine the effects of ether anesthesia on renin release. In the rat, ether stimulated renin release by 6-fold, and propranolol inhibited this renin release by 96%. Oates and Stokes (817) subsequently confirmed this finding when they reported that propranolol prevented the 4-fold rise in PRC brought about by ether in rats. Graham et al. (410) found that ether-induced renin release in rats also was inhibited by the beta-adrenergic antagonist timolol. In a later study, Pettinger et al. (903) determined that ether produced not only a dose-related increase in SRA but also a time-related increase in SRA. Thus, as the duration of anesthesia was increased from 5 min to 25 min, SRA was further increased by 4-fold. Other investigators (199, 643) also have found that ether increased renin release and that PRA remains elevated for the duration of the anesthesia. Warren and Ledingham (1174) found that ether did not affect RBF but did suppress sodium excretion by 65% in rabbits. Walsh and Ferrone (1172), in rats, observed a 9% decrease in MAP, a 47% decrease in total peripheral resistance, and a 7% decrease in heart rate. Based on these data, it appears that ether elicits renin release through a beta-adrenergic mechanism, possibly by the reflex activation of the renal sympathetic nerves after systemic vasodilatation.

Wernze et al. (1206) detected a 3-fold increase in PRA during halothane-induced anesthesia in 21 patients undergoing ear surgery. Practolol, a beta-adrenergic antagonist, did not alter the renin response to halothane; therefore, halothane does not appear to release renin by activation of the sympathetic nervous system. A comprehensive study of the mechanism by which halothane releases renin is in order. In addition, the mechanisms by which many other anesthetic drugs, e.g., methoxyflurane, chloralose, enflurane, droperidol, fentanyl, and morphine stimulate renin release have not been studied.

Two other points should be considered concerning anesthesia and renin release. First, several anesthetics, such as ketamine (751, 1077), pentobarbital (903), and halothane and fluorexene (751, 981), stimulate renin release during the induction phase of anesthesia, but in the later stages of anesthesia, the elevated PRA values decline to within the normal range. Thus, as pointed out by Miller et al. (748, 751) and Pettinger (889), the duration of anesthesia has marked effects on renin release, and once the stable anesthetic state is reached, PRA will no longer be increased. The two exceptions to this generalization, ether and urethane (199, 643, 903), increase the release of renin for the duration of the period of anesthesia.

The second point deals with the ability of anesthetic drugs to modify the stimulation or inhibition of renin release elicited by other mechanisms, an event that may occur in both the inductive and stable phases of anesthesia. Pettinger et al. (896) studied the effect of anesthesia on the ability of deoxycorticosterone acetate (DOCA) and sodium chloride to suppress renin release in the rat and found that the treatment of conscious rats for 3 days with DOCA and sodium chloride decreased PRA by 95%. When the study was repeated with ether anesthesia before the collection of blood, DOCA and sodium chloride still suppressed PRA by 88% even though ether increased the control PRA values by 5-fold. However, DOCA and sodium chloride did not alter PRA in rats that had been anesthetized with pentobarbital before obtaining blood for the determination of PRA. In the control rats, pentobarbital increased PRA by 4-fold. In a subsequent study, Campbell and Pettinger (183) reported that the administration of sodium chloride to rats in their drinking water for two days suppressed SRA by 70%. In a similarly treated group of rats, 4 min of exposure to ether before collecting the blood samples increased SRA by 10-fold in the control animals and masked the suppression of renin release usually caused by the ingestion of sodium chloride. Thus, these researchers (183, 896) concluded that the effects of certain anesthetics could override the inhibitory influence of a high salt intake, in both the presence and absence of mineralocorticoid, on renin release.

In addition to masking the suppressant effects of physiologic stimuli on renin release, anesthesia may enhance the elevation on renin release caused by other stimuli. For example, Fray et al. (353) found that pentobarbital had no effect on PRA after its administration to dogs on a normal sodium diet. However, when the dogs were ingesting a low sodium diet, basal PRA was increased by 4-fold in the conscious state and by 10.5-fold in the anesthetized state. In like fashion, Miller et al. (748, 751) saw no change in PRA after the administration of the anesthetics halothane, ketamine, and fluroxene to rats ingesting a normal sodium diet. However, in rats receiving a low sodium diet, PRA tripled in the absence of anesthesia, and halothane, enflurane, and ketamine increased PRA by 2.6-fold, 1.8-fold, and 5.2-fold, respectively. To state these data another way, sodium deprivation increased PRA 3-fold in conscious rats whereas PRA was elevated by 7-fold and 9.5-fold in response to sodium depletion in halothane- and ketamine-anesthetized rats, respectively. Thus, as concluded earlier by Pettinger and coauthors (183, 896), anesthetic agents alter the physiologic response of renin release to changes in sodium intake and visa versa. Oates and Stokes (817) noted that 3 days of water deprivation caused a 7-fold increase in PRC in rats and that anesthesia with ether

elicited a 4-fold elevation of PRC in animals not deprived of water. When water-deprived rats were anesthetized with ether prior to obtaining blood samples, PRC was still increased 7-fold as compared to water-deprived conscious rats. Thus, despite the increase in the basal renin levels in the ether-anesthetized rats, the increments in renin release after water deprivation were similar in these two groups of animals.

McKenzie et al. (719) found that the induction of anesthesia with pentobarbital did not affect basal PRA in rabbits, but did alter the renin response to hemorrhage. In conscious rabbits, hemorrhage increased PRA 2-fold whereas an equal degree of hemorrhage increased PRA 4-fold in anesthetized rabbits. Unfortunately, changes in MAP were not reported for the conscious rabbits after hemorrhage so a comparison of the degree of hypotension in the conscious and anesthetized animals is not possible. In similar studies (537) in the dog, nonhypotensive hemorrhage in the conscious state increased PRA 2-fold without significantly changing heart rate, hematocrit, or the concentration of electrolytes in the plasma. When the dogs were anesthetized with pentobarbital, PRA rose 5-fold, and a subsequent hemorrhage further increased PRA by 3-fold. In the anesthetized dogs, hemorrhage did not change MAP or plasma sodium content, but did significantly increase heart rate, plasma potassium concentration, and the hematocrit. Therefore, although pentobarbital did not affect the threshold of the renin response to hemorrhage, it increased the magnitude of the renin response and altered the physiologic response to hemorrhage when compared to the changes seen in the conscious state.

The effect of anesthesia on the renin release caused by the angiotensin antagonist saralasin was studied by Miller et al. (751). They found that PRA was unchanged 1 hr after the administration of the anesthetics ketamine, halothane, and fluroxene. In conscious animals, saralasin caused a 4-fold increase in PRA whereas PRA was increased by 5-fold, 8.5-fold, and 6-fold after giving saralasin to animals anesthetized with ketamine, halothane, and fluroxene, respectively. After saralasin, MAP decreased by 8 mm Hg in the conscious rats and those anesthetized with ketamine and fluoxene; however, saralasin lowered MAP by 17 mm Hg in halothane-anesthetized rats. Thus, ketamine and fluoxene enhanced the renin-releasing effects of saralasin without affecting the vasodepressor action of saralasin.

Finally, a number of investigators (176, 245, 264, 346, 1005, 1012, 1155) have compared PRA values in normotensive Wistar-Kyoto and spontaneously hypertensive (SH) rats, but the use of anesthetics prior to blood sampling appears to have complicated this comparison. Sen et al. (1005) reported that after ether anesthesia PRA was elevated in young SH rats and reduced in older rats when compared to normotensive Wistar rats. Vincent et al. (1155) confirmed this observation in ether-anesthetized rats. They also noted that ether caused a 2- to 3-fold increase in PRA and increased the variability in the PRA values obtained in both normotensive and SH rats. The effect of ether anesthesia on PRA was determined only at 10 weeks of age, a time at which PRA in the conscious state was identical in both groups. DeJong et al. (264), in conscious rats, found that PRA was identical in 5-week-old normotensive and SH rats but was elevated in SH rats between the ages of 12 and 35 weeks. In contrast to these findings, Czyzewski and Pettinger (245) found no difference in the SRA values obtained from conscious 4-, 8-, 16-, and 40-week-old SH, normotensive Wistar, and normotensive Sprague-Dawley rats. Forman and Mulrow (346) also reported similar PRA values in 3- and 6-month-old conscious SH, Wistar, and Sprague-Dawley rats. In similar studies in conscious rats, Shiono and Sokabe (1012) reported that the PRA values were reduced in 5-, 10-, 20-, and 30-week-old SH rats when compared with normotensive Donryu rats. In the only comparison of SRA values in young conscious and anesthetized normotensive Wistar and SH rats, Campbell (176) found similar SRA values in the two groups when the blood was obtained from age-matched conscious rats; however, when the rats were anesthetized with ketamine, SRA values were 2-fold higher in the SH rats than in the Wistar control rats. Thus, although this subject requires further clarification, at present it appears that anesthesia may elevate renin release more in SH rats than in normotensive rats of the same age. This effect of anesthesia may explain the disparate results obtained in studies examining the role of renin in the pathogenesis of this form of hypertension.

In summary, anesthetics stimulate the release of renin when used in doses that produce surgical anesthesia. Each anesthetic agent appears to alter renin release by a different mechanism, and the chronology of this renin release is different in each case. Additionally, under certain circumstances, the presence of anesthesia will affect the secretory response of the juxtaglomerular cells to physiologic or pathologic stimuli that increase or decrease the release of renin.

B. Drugs Affecting the Autonomic Nervous System

1. Alpha-adrenergic receptor agonists. Several factors have engendered interest in the effects of alpha-adrenergic receptor agonists on renin release. The popularity of the alpha-adrenergic agonists clonidine and alpha-methyldopa as antihypertensive agents and as research tools in cardiovascular studies led researchers to determine the mechanism by which these agents inhibited renin release and the importance of this inhibition in the lowering of blood pressure. In addition, evidence obtained from studies performed in vivo and in vitro led to the idea that alpha-adrenergic receptor stimulation in the kidney suppressed renin release by an action on the granular JG cells. Lastly, the use of alpha-adrenergic receptor agonists and antagonists in the treatment of several pathophysiologic conditions stressed the impor-

tance of knowing how these drugs affected the renin-angiotensin-aldosterone axis.

A. CLONIDINE. The imidazoline compound clonidine exhibits activity at both peripheral and central alpha-adrenergic receptors. For example, the i.v. administration of clonidine to anesthetized dogs has been shown to result in an initial transient increase in blood pressure, associated with a decrease in heart rate and cardiac output and a rise in total peripheral resistance, which is followed by a prolonged period of vasodepression (487). During this prolonged period of vasodepression, heart rate and cardiac output remained suppressed whereas total peripheral resistance returned to the control level. The initial pressor effect of clonidine was shown to be due to a direct effect of clonidine on vascular alpha-adrenergic receptors (595), but the subsequent fall in blood pressure was demonstrated to result from an action of the drug on the vasomotor and cardiac centers of the brain (596). Thus, clonidine still had a pressor effect in spinal animals, but no subsequent fall in blood pressure occurred (595). In like fashion, the central injection of clonidine into anesthetized animals caused an immediate drop in blood pressure and heart rate that was not preceded by a pressor phase (596). The vasodepression was related to the diminution of cardiac output since total peripheral resistance did not decrease relative to the control value. Clonidine, in concentrations that had no direct effect on vascular tone, reversibly reduced nerve-stimulated norepinephrine release from sympathetic neurons (74). This action is known to be due to the activation of prejunctional alpha-adrenergic receptors that are inhibitory to the release of norepinephrine (78), and has been shown to diminish as the frequency of stimulation is increased (433). Clonidine does not cause sympathetic neuronal blockade so sympathetically mediated circulatory reflexes are maintained, albeit at a lower level of activity (843).

Clonidine has been reported to decrease renin release in normotensive (461) and hypertensive (40, 140, 366, 461, 492, 493, 560, 581, 729, 793, 843, 902, 974, 1085, 1180, 1181) humans, conscious (242) and anesthetized (803, 843, 925–927) dogs, and conscious (869, 984) and anesthetized (211, 569, 593, 815, 865) rats. On the other hand, treatment with clonidine also has been reported to cause no change or to elevate PRA in anesthetized rats (201, 957), normotensive humans (1229), and hypertensive humans (278, 366, 560, 793, 1085, 1229), especially in patients with low-renin hypertension (366, 1085).

In the first extensive description of the effects of clonidine on renin release, Onesti et al. (843) noted that clonidine lowered both supine and standing PRA in hypertensive patients ingesting a low sodium diet. After the i.v. administration of clonidine to anesthetized dogs, a 50% decrease in renal venous PRA was observed that did not correlate with any change in MAP, GFR, RBF, urinary sodium excretion, or renal vascular resistance. In fact, the suppression of renin release occurred in the presence of a large decrease in sodium excretion that should have been a stimulus to renin release, and in the presence of an early increase and a later decrease in renal vascular resistance. The introduction of a very small dose of clonidine into the cisterna magna also lowered blood pressure and greatly decreased renal venous PRA. It was concluded that clonidine attenuated orthostatic reflexes in humans, just as it did in monkeys and dogs (229), by decreasing efferent sympathetic nerve activity (432, 843). The fall in PRA was thought to be due to the withdrawal of sympathetic tone, although the authors did not exclude the possibility that clonidine had a direct inhibitory action on the granular JG cells.

In the ensuing years, clinical investigators have studied the antihypertensive effect of clonidine as related to the ability of the drug to alter renin release, catecholamine secretion, and salt balance. Hokfelt et al. (492) found that clonidine lowered blood pressure and PRA in patients with essential and renovascular hypertension and primary aldosteronism but was without effect in patients with pheochromocytoma. In other studies involving multiple dose therapy with clonidine, Fyhrquist et al. (366) noted that patients with initial high PRA values exhibited an initial suppression of renin release but PRA then returned to the control levels. In these patients, clonidine elicited a natriuresis during the early stages of therapy that was followed by sodium retention. In those patients with low pretreatment PRA values, clonidine first decreased sodium excretion but then brought about a progressive natriuresis and rise in PRA. Despite the progressive salt depletion in the latter group of patients, the elevated renin release was thought to result from renal vasodilatation. Blood pressure was lowered in both groups so the hypotensive action of clonidine was not related to the suppression of renin release. In a similar study, patients were classified with regard to their renin status before the administration of clonidine, and the drug was found to suppress PRA from 7.9 to 3 ng of AI/ml/hr in high-renin hypertension and from 0.8 to 0.5 ng of AI/ml/hr in low-renin hypertension (1180). Arterial pressure fell in both groups. In a careful longitudinal study over an 8-week period, clonidine decreased blood pressure to the same extent in normal-renin and low-renin hypertensive patients (1085). However, although renin release was suppressed in the former patients, PRA rose over 6-fold in the latter group of subjects. Sodium and potassium excretion, plasma renin substrate levels, and body weight were unchanged in both groups of patients. Thananopavarn et al. (1085) proposed the following explanation for these observations. In normal-renin hypertension, beta-adrenergic tone predominates in the kidney, and clonidine inhibits renin release by the withdrawal of renal sympathetic tone. Alpha-adrenergic tone, which is inhibitory to renin release, predominates in the kidneys in low-renin hypertension, and clonidine stimulates renin release either by the centrally mediated diminution of renal sympathetic nerve activity or by

acting as an alpha-adrenergic antagonist in the kidney. In either case, patients with low-renin hypertension were presumed to exhibit altered function of their renal alpha-adrenergic receptors.

Other investigators (278) found no change in PRA, even though blood pressure was lowered, in hypertensive patients receiving clonidine for three months. On the other hand, after 1 week of therapy with clonidine, the hypertensive subjects of Niarchos et al. (793) fell into two groups. In the first group, MAP, PRA, and aldosterone excretion fell in concert, but in the second group, none of these parameters changed. All of the nonresponders had some degree of renal insufficiency.

Karlberg et al. (560) reported that the inhibition of renin release by clonidine was highly dose-dependent. That is, 2.25 mg/day of clonidine for 6 months suppressed PRA, but PRA was unchanged at larger doses. They also doubted that the fall in PRA during treatment with small doses of clonidine was due to the withdrawal of sympathetic nerve traffic since heart rate was not decreased. Thus, the hypotensive effect of clonidine does not appear to be related to the suppression of renin release, and long-term treatment with clonidine does not necessarily result in the continued attenuation of renin release.

Single dose or short-term administration of clonidine to hypertensive humans has been shown to produce a more consistent inhibition of renin release (140, 581, 729). For instance, Brod et al. (140) saw that a single i.v. injection of clonidine lowered PRA, renal venous PRA, blood pressure, heart rate, stroke volume, cardiac index, and renal vascular resistance in normotensive and hypertensive subjects. Total peripheral resistance did not change in normotensive subjects but decreased slightly in the hypertensive patients. Neither RBF nor GFR were altered in either group. In agreement with these observations, Meurer et al. (729) found PRA to be depressed by 24% by clonidine at a time when RBF, GFR, and sodium excretion were not affected. The centrally acting, clonidine-like drug ST-600 produced a hemodynamic profile similar to that of clonidine and decreased PRC (581).

Because clonidine appeared to lower PRA, blood pressure, and heart rate by the centrally mediated withdrawal of sympathetic tone, it was only natural for researchers to try to relate changes in these parameters to changes in the metabolism of catecholamines. Hokfelt et al. (492, 493) found that the inhibition of renin release by clonidine was associated with a large decrement in the urinary excretion of norepinephrine, epinephrine, and vanillylmandelic acid. The plasma levels of catecholamines also were decreased. The attainment of upright posture still led to an increase in the plasma concentration of norepinephrine. In addition, the pressor sensitivity to infused norepinephrine and AII was elevated during therapy with clonidine. Hedeland et al. (461) examined the effects of clonidine on insulin-induced renin release in normotensive and hypertensive humans. A good correlation was found between the increase in PRA and the increase in the urinary excretion of catecholamines during insulin-induced hypoglycemia. Clonidine lowered basal PRA and the urinary excretion of norepinephrine and prevented the elevation of PRA and urinary norepinephrine content caused by insulin. A significant elevation of the urinary concentration of epinephrine still occurred. In one patient, clonidine attenuated the ability of infused norepinephrine and epinephrine to elicit renin release. Therefore, clonidine was believed to lower PRA by a centrally mediated decrease in the peripheral release of norepinephrine, but a direct action of the drug at the renal level could not be excluded. The observation that orthostasis-induced norepinephrine release was not accompanied by a rise in PRA during therapy with clonidine also supports the latter hypothesis.

Originally, Onesti et al. (843) reported that clonidine diminished both supine and upright PRA values after the ingestion of low-sodium diet. However, this has not been a consistent finding. For example, Baer et al. (40) and Weber et al. (1180) found that clonidine caused less suppression of renin release in hypertensive patients after dietary salt restriction. In like fashion, Hokfelt et al. (493) observed that salt depletion still elevated PRA during therapy with clonidine, and Karlberg et al. (560) recognized that this drug did not block the increase in renin release elicited by sodium depletion with furosemide. Finally, the rise in PRA that accompanied treatment with the diuretic chlorthalidone was not affected by clonidine but was suppressed by propranolol.

The exact mechanism by which clonidine suppresses renin release has been studied extensively in animals, but researchers have come to different conclusions. Basically, there are two schools of thought. Reid and co-workers (803, 804, 925, 926) have presented evidence that indicates that clonidine suppresses renin release by the centrally mediated withdrawal of renal sympathetic tone. On the other hand, Pettinger et al. (242, 894) and other investigators (211, 1129) believe that clonidine inhibits renin release by stimulating intrarenal alpha-adrenergic receptors, possibly located on the granular JG cells. The role of intrarenal alpha-adrenergic receptors in the control of renin release has been considered previously in the section on the autonomic nervous system.

In 1975, Reid et al. (926) measured blood pressure, heart rate, and PRA in pentobarbital-anesthetized dogs after the injection of clonidine into either the cerebral ventricles or the peripheral circulation. It should be pointed out that in all of the studies of Reid et al. (803, 925, 926), renal arterial pressure was decreased by 30 to 50 mm Hg with a suprarenal aortic clamp during the control period. Thus renin release in these dogs was elevated by hypotensive activation of the renal baroreceptor prior to the injection of the drug to be tested. When clonidine was given centrally, blood pressure and heart rate decreased, but PRA did not decrease unless renal perfusion pressure was maintained at the control

level by means of a suprarenal aortic clamp. Conversely, i.v. clonidine, which lowered blood pressure and heart rate, suppressed renin release whether renal perfusion pressure was or was not held constant. The necessity of maintaining renal perfusion pressure constant in order to demonstrate the renin-suppressing effects of an intracerebroventricular dose of clonidine was thought to result from the fact that blood pressure dropped to a greater extent (−31%) than it did in the animals given clonidine i.v. (−17%). Thus, in the former group, the stimulatory effect of the renal baroreceptor on renin release was thought to override the central inhibitory effects of clonidine. Because a good correlation was detected between the decrease in PRA and the decrease in blood pressure after the central administration of clonidine, with renal perfusion pressure being held constant, the suppression of renin release by this drug was believed to be due to the withdrawal of sympathetic tone. In support of this contention, i.v. clonidine did not suppress renin release from previously denervated kidneys but did suppress the release of renin from the contralateral, innervated kidneys. However, since acute renal denervation per se had caused a 95% decrease in the renal arteriovenous difference in PRA, it is doubtful that clonidine would have caused any further inhibition by any known mechanism. More solid support for a central site of action of clonidine came from the observation that the rate of renin secretion from rat kidney slices in vitro was not depressed by clonidine (10^{-4} M) (804) at concentrations as high as 10^{-3} M (771a, 804).

In later studies, these same investigators (925) reported that clonidine prevented the ability of bilateral carotid occlusion to increase renin release or blood pressure, with renal perfusion pressure held at the control value. In addition, other experiments (803) indicated that ganglionic blockade with pentolinium abolished the suppression of PRA by clonidine in pentobarbital-anesthetized dogs. When renal perfusion pressure was held at the pretreatment level, pentolinium lowered PRA by 45% and decreased blood pressure and heart rate. The subsequent administration of clonidine resulted in the restoration of blood pressure back to the level seen before pentolinium and a transient stimulation of renin release. In a similar animal preparation, oxymetazoline, an imidazoline derivative that does not cross the blood-brain barrier, increased PRA by 2-fold at a time when the vasoconstrictor properties of the compound had dissipated. In more recent studies, Reid et al. (927) reported that the i.v. infusion of a small dose of oxymetazoline lowered PRA in anesthetized dogs, and this inhibitory effect was reversed by phentolamine. Based on these data, the authors (803, 927) again concluded that the inhibition of renin release by clonidine resulted from an action of the drug in the brain rather than the kidney. In addition, they suggested that the stimulation of renin release by clonidine, in the presence of ganglionic blockade, and oxymetazoline resulted from the activation of the renal baroreceptor by renal vasoconstriction. In this respect, afferent arteriolar vasoconstriction at a constant renal perfusion pressure would be expected to decrease the circumferential stress on the arterioles and induce renin release. This contention is supported by the observation that oxymetazoline had no effect on renin secretion from rat renal cortical slices in vitro (771a).

It should be pointed out that Crayton et al. (242) reported that the intrarenal infusion of small doses of clonidine that did not affect MAP or heart rate led to a 47% decrease in PRA in conscious, uninephrectomized dogs. The same doses of the drug given i.v. were without effect; therefore, clonidine was believed to suppress renin release by an intrarenal mechanism in these conscious dogs.

In an extensive pharmacologic study in the conscious rat, Pettinger et al. (894) presented evidence that indicated that clonidine decreased SRA by the stimulation of intrarenal alpha-adrenergic receptors. After first determining that clonidine did not affect the renin-angiotensinogen reaction in vitro, it was shown that clonidine elicited a dose-dependent inhibition of renin release in normal rats. Clonidine suppressed SRA by 85% at 10 min, when MAP was increased by 14%, and by 65% at 100 min, when MAP was decreased by 14%. Kirchertz and Peters (593) observed a non-dose-dependent inhibition of PRC in pentobarbital-anesthetized rats that also was independent of changes in blood pressure. In addition, clonidine blocked beta-adrenergically mediated renin release whether it was elicited by a vasopressor (ketamine) or vasodepressor (hydralazine) agent (894).

When basal SRA values were elevated 8-fold in conscious rats by severe sodium depletion, clonidine lowered SRA by 70% whereas propranolol caused only a 30% fall in SRA (894). Pals (869) reported that a lesser degree of suppression of renin release occurred in sodium-depleted rats; however, the basal PRA values were considerably higher than those reported by Pettinger et al. (894). The inhibitory effect of clonidine on renin release in sodium-deprived rats was not prevented by muscarinic, ganglionic, or peripheral sympathetic neuronal blockade (894). Ganglionic blockade with chlorisondamine greatly potentiated the immediate pressor effects of clonidine in conscious rats, but SRA was still suppressed by 90% at a time when blood pressure had stabilized at the level seen before treatment with chlorisondamine. The alpha-adrenergic antagonist phentolamine blocked the decrease in SRA caused by clonidine in sodium-depleted ganglion-blocked rats. Alpha-adrenergic blockade with phentolamine, phenoxybenzamine, and clozapine blocked the inhibitory effect of clonidine on renin release in both salt-depleted and normal rats. Finally, after sodium depletion, clonidine caused a significantly greater suppression of renin release, in either the presence or absence of ganglionic blockade, than did an equipressor dose of methoxa-

mine. These data, combined with hemodynamic correlates, suggested that clonidine inhibited renin release by activation of an intrarenal alpha-adrenergic receptor.

Chevillard et al. (211) reached the same conclusion when they assessed the effects of intracisternal and i.v. injections of clonidine and naphazoline, another alpha-sympathomimetic agent of the imidazoline series, on renin release in pentobarbital-anesthetized rats. The central administration of clonidine lowered MAP and increased PRC by 57% whereas naphazoline was without effect. After peripheral administration, clonidine still lowered MAP and heart rate, but now caused an inhibition of renin release. Naphazoline, given in an i.v. dose that did not affect blood pressure, also suppressed renin release. Thus, despite its inability to activate the centrally located alpha-adrenergic receptors involved in the modulation of sympathetic outflow, naphazoline suppressed PRC when given peripherally. Chevillard et al. suggested that the rise in PRC seen after intracisternally administered clonidine resulted from the fact that the stimulatory effect of the renal baroreceptor on renin release outweighed the inhibitory effect of decreased sympathetic nerve discharge. This situation is comparable to that seen by Reid et al. (926) after the central administration of clonidine to anesthetized dogs. On the other hand, clonidine lowered MAP to a greater degree when given peripherally to anesthetized rats, but in this case renal baroreceptor stimulation of renin release was prevented by an intrarenal action of clonidine (211). When these same studies were performed with rats anesthetized with urethane, clonidine elevated PRC when given peripherally and had no effect when given centrally (210). Naphazoline was ineffective by either route of injection. These disparate results, which apparently depend on the type of anesthetic agent employed, emphasize the necessity of using conscious animals in experiments of this type.

Further support for a peripheral site of action of clonidine comes from the observation that this drug, in a dose that did not alter renal perfusion pressure, suppressed basal renin release by 62% in the isolated perfused rat kidney (1129). This dose of clonidine did not impair the ability of isoproterenol to elicit renin release; however, a larger dose, which increased renal perfusion pressure and inhibited basal renin release, did blunt the effects of the beta-adrenergic agonist.

It is interesting to note that guanfacine, a centrally acting antihypertensive agent with pharmacologic properties similar to those of clonidine (968), caused a greater degree of suppression of renin release in anesthetized rats than did an equihypotensive dose of clonidine (815).

To summarize briefly, evidence has been presented to support both the central and intrarenal theories regarding the mode of action of clonidine, but the use of anesthetized animals and possibly species differences have confounded the efforts of researchers to come to an agreement. The subject is in need of more intensive study.

B. METHYLDOPA. It has been 20 years since Oates et al. (819) first described the antihypertensive properties of methyldopa, and in the ensuing years, this drug has been demonstrated to lower arterial pressure by an action in the central nervous system. Methyldopa is taken up by noradrenergic nerves in the central nervous system and converted enzymatically to methylnorepinephrine, which then lowers blood pressure by stimulating central alpha-adrenergic receptors (258, 336, 471). Some clinical investigators have noted a correlation between the antihypertensive effects of alpha-methyldopa and a reduction in total peripheral resistance (842, 980) whereas other clinicians have reported the decrement in blood pressure to be associated with a fall in cardiac output and no change in total peripheral resistance (677, 1224). As with clonidine, treatment with methyldopa leads to a decrease in renal vascular resistance in both the supine and tilted position (760), and the decrement in renal vascular resistance is associated with either no change or an increase in RBF (979). Heart rate, in either the supine or upright position, is not altered by methyldopa (651).

In 1969, Mohammed et al. (759) reported that treatment with methyldopa decreased both supine and upright PRA values in one hypertensive and four normotensive humans. Other researchers have noted that methyldopa lowered PRA in hypertensive patients (380, 517, 651, 773, 910, 1194), but this is not a universal observation (672, 969, 1194). For instance, Weidmann et al. (1194) found that methyldopa lowered PRA and blood pressure only in those patients with moderate to severe normal-renin hypertension or hypertension associated with renal failure. The decrement in PRA was felt to be due to a diminution of renal nerve activity. In normotensive subjects, methyldopa did not alter orthostasis-induced renin release and actually amplified the rise in PRA caused by furosemide. Lowder and Liddle (672) also noted that methyldopa did not affect the renin response to furosemide and orthostasis. Gavras et al. (380) detected a correlation between the suppression of renin release and the hypotensive response to this agent in high- and normal-renin hypertension. Plasma renin activity fell by 41% and 15% in these two groups, respectively. However, a comparable vasodepression was seen in patients with low-renin hypertension despite the fact that PRA was unchanged. Finally, Leonetti et al. (651) saw that 1 week of treatment lowered PRA by 50% in patients with low- and normal-renin hypertension but did not attenuate the rise in PRA precipitated by the assumption of upright posture. Propranolol was more efficacious in suppressing upright PRA values than was methyldopa (651), but in another study (910) the drugs had an equal effect on PRA.

Several researchers (348, 436, 919) have investigated the mechanism by which methyldopa inhibits renin

release in anesthetized dogs. Privitera and Mohammed (919) first established that a week of treatment with methyldopa lowered PRA by 44% in conscious dogs and then tested the renin response to renal nerve stimulation in these animals. Even though stimulation of the renal nerves decreased RBF to the same extent in control and treated dogs, the usual rise in renin release caused by increasing nerve activity was not seen in the drug-treated animals. The i.v. infusion of norepinephrine and methylnorepinephrine, with renal perfusion pressure held constant, revealed that norepinephrine was three to four times more potent in eliciting renin release than was alpha-methylnorepinephrine. Moreover, methylnorepinephrine was less potent than norepinephrine in inducing renal vasoconstriction. Based on these data, it was hypothesized that methyldopa lowered renin release by replacing the norepinephrine in the renal nerves with the less potent neurotransmitter methylnorepinephrine. Halushka and Keiser (436) then demonstrated that the renal nerves were indeed necessary for methyldopa to suppress PRA in the anesthetized dog; however, they could not distinguish between a central or peripheral action of methyldopa. The suppression of PRA was more prolonged after the i.v. infusion of methyldopa whereas the hypotensive response was of greater duration after the infusion of the drug into the vertebral artery. The maximal suppression of PRA was greater than 60% by both routes of administration. The fall in MAP was not related to the fall in PRA since acute renal denervation, which prevented the suppression of PRA by methyldopa, actually prolonged the hypotensive response to methyldopa.

In more recent studies, Frankel et al. (348) gauged the ability of methyldopa to lower PRA in the presence and absence of carbidopa, a compound that inhibits L-aromatic amino acid decarboxylase but does not enter the central nervous system. Renal perfusion pressure, which was lowered by 30 to 50 mm Hg with a suprarenal aortic clamp during the control period, was held constant in all of the experiments. Intravenous methyldopa lowered PRA by 47% and decreased blood pressure, but pretreatment with carbidopa attenuated the hypotensive response and completely prevented the fall in PRA caused by methyldopa. When carbidopa was administered centrally and methyldopa was given peripherally, PRA decreased by 45%. Blood pressure also decreased. Furthermore, the intracerebroventricular injection of alpha-methyldopa or methylnorepinephrine lowered MAP but did not change PRA. Therefore, the suppression of renin release by methyldopa appeared to be due to a peripheral action of the drug.

In the only relevant study of methyldopa in conscious dogs, Sweet et al. (1068) found that 3 days of treatment with methyldopa lowered PRA by 43% in renal hypertensive dogs and caused a 56% decrease in PRA when renin release had been elevated 6-fold by chronic therapy with hydrochlorothiazide. Methyldopa also suppressed PRA in normal and water-loaded anesthetized rats (865).

Several questions remain unanswered concerning the suppression of renin release by methyldopa. For example, the coadministration of carbidopa and methyldopa to humans did not alter the decrease in blood pressure caused by the latter compound (578), but it is not known whether carbidopa altered the ability of methyldopa to lower PRA in humans. The effects of methyldopa and methylnorepinephrine on renin release from rat renal cortical slices in vitro are not known.

C. L-DOPA. Although L-dopa per se is not an alpha-adrenergic agonist, it is converted to norepinephrine in the adrenergic neuron. This compound is used most frequently in the treatment of Parkinson's disease, and several researchers have measured PRA during long-term therapy with L-dopa (55, 56, 564, 747, 1062). Barbeau (55, 56) found the PRA values of patients with Parkinson's disease to be much lower than the values encountered in normal volunteers, and continued therapy with L-dopa suppressed PRA to undetectable levels. In another group of Parkinsonian patients, the renin response to orthostasis and salt restriction was normal, but L-dopa did not alter the rise in PRA caused by either stimulus (1062). Other investigators have noted that the normal orthostatic rise in PRA was not altered by prolonged treatment of Parkinsonian patients with L-dopa (564, 747). A single oral dose of L-dopa elicited an increase in RPF and GFR as well as natriuresis and a kaluresis (337), but only a mild natriuretic effect was noted during multiple dose therapy (564). Despite the continued loss of sodium, PRA did not increase in these patients (564).

Blair et al. (102) found that a single dose of L-dopa elevated PRA and MAP when given to anesthetized dogs, but the coadministration of carbidopa, to inhibit peripheral L-aromatic amino acid decarboxylase, reversed these effects such that PRA and MAP decreased. Renal perfusion pressure, which was lowered by 30 to 50 mm Hg during the control period by a suprarenal aortic clamp, was maintained at a constant level throughout these studies. In animals with acutely denervated kidneys, L-dopa with carbidopa lowered MAP but had no consistent effect on PRA. Thus, in the absence of carbidopa, catecholamines formed from L-dopa in the peripheral circulation increased PRA and MAP, but in the presence of carbidopa, catecholamines formed from L-dopa in the brain caused a decrease in the activity of the renal sympathetic nerves leading to a decrease in PRA and MAP. The latter conclusion is consistent with the observations that: 1) L-dopa given directly into the brain lowers MAP (62); 2) this central depressor effect of L-dopa (62) is not blocked by vagotomy and therefore is due to a decrease in sympathetic tone (22); and 3) this central depressor effect is accompanied by a decrease in splanchnic nerve activity (1176). In later studies, Blair et al. (102a) reported that the suppression of renin release

by L-dopa plus carbidopa was not due to an increase in the release of AVP. In addition, the rise in PRA was partially impaired by pretreatment with either propranolol or phenoxybenzamine but was completely inhibited when both adrenergic receptor antagonists were given prior to L-dopa plus carbidopa.

Considering these findings of Blair et al. (102), it would be of interest to evaluate the effects of L-dopa on PRA in Parkinsonian patients receiving L-dopa in the presence and absence of carbidopa.

D. PHENYLEPHRINE. Phenylephrine was found to block the rise in PRA caused when isoproterenol was given to anesthetized rats with filtering (732) or nonfiltering (735) kidneys. Isoproterenol was thought to elevate PRA in these anesthetized animals by activation of the carotid baroreceptor, and phenylephrine was thought to inhibit renin release either by preventing the vasodilation or by antagonizing the direct effect of isoproterenol on the granular JG cells (732, 735). After bilateral adrenalectomy, PRC increased 5.7-fold and basal MAP decreased (112). A small dose of phenylephrine that did not affect RPF or GFR suppressed PRC by 42% and 50% in normal and adrenalectomized rats, respectively. Phenylephrine increased MAP in both groups but had less of a pressor effect in adrenalectomized animals. Adrenalectomy also elevated PRC in animals with a single nonfiltering kidney, an effect also inhibited by phenylephrine. Boll et al. (112) suggested that phenylephrine lowered PRC 1) by antagonizing the vasodepression caused by adrenalectomy, 2) by constricting the afferent glomerular arterioles, or 3) by a direct effect on the granular JG cells.

As mentioned in the section concerning the control of renin release by the renal baroreceptor, Fray (350) found that phenylephrine increased renin release from the isolated perfused rat kidney if renal perfusion pressure was held at the control value (110 mm Hg). However, if renal perfusate flow was held constant and renal perfusion pressure was allowed to rise (200 mm Hg) as a result of the vasoconstrictor properties of phenylephrine, then renin release was suppressed. These observations are consistent with the belief that a decrease in afferent arteriolar radius at a constant renal perfusion pressure leads to a decrease in circumferential stress and thereby activation of the renal baroreceptor controlling renin release. Strang et al. (1055) found that phenylephrine, in nonvasoconstrictor or vasoconstrictor doses, did not affect renin release from the isolated perfused rat kidney. Phenylephrine had no effect on renin secretion from rat renal cortical slices in vitro (771a).

In normal subjects, an infusion of phenylephrine decreased RPF, GFR, and sodium excretion and caused a nonsignificant rise in PRA (730). The addition of phentolamine to the infusate resulted in a further, though nonsignificant, elevation of PRA and partially reversed the renal hemodynamic effects of phenylephrine. On the other hand, Hsu et al. (504) found a 33% decrease in PRA in normal subjects given phenylephrine. Blood pressure increased and heart rate decreased. Levy et al. (653) reported that a dose of phenylephrine, which elevated MAP by 40% and lowered heart rate by 45%, suppressed PRA by 35% in normotensive humans on a normal or low salt diet. Conversely, the same dose of phenylephrine raised MAP by 25% and lowered the pulse rate by 40% in hypertensive patients, but failed to alter PRA on either diet.

Thus, the general trend is that phenylephrine suppresses renin release in vivo, but it is not known whether this inhibition results from systemic or renal hemodynamic changes.

E. METHOXAMINE AND METARAMINOL. In 1968, Maebashi et al. (687) discovered that methoxamine rapidly increased PRA by 3-fold and slowly increased blood pressure in anesthetized dogs. Metaraminol, a directly and indirectly acting alpha-adrenergic agonist, rapidly raised arterial pressure but had no effect on renin release. Methoxamine was thought to stimulate PRA by constricting the afferent glomerular arterioles. Later, Leenen et al. (1125) found that both methoxamine and isoproterenol elevated PRA in supine normotensive humans despite the fact that the two drugs had exactly opposite hemodynamic effects. A small dose of methoxamine, which had no effect on blood pressure or heart rate, elevated PRA by 70%, and a larger dose, which raised blood pressure by 14% and decreased heart rate by 22%, caused PRA to rise 2.3-fold. The stimulatory effects of both methoxamine and isoproterenol on renin release were blocked by pretreatment with propranolol. Despite the latter observation, methoxamine was believed to elicit renin release by constricting the afferent arterioles.

Subsequently, methoxamine has been demonstrated to inhibit renin release by 43% in conscious sodium-depleted rats (894). In the same experiment, clonidine lowered SRA by 84%. After pretreatment of conscious, sodium-depleted animals with chlorisondamine, which lowered MAP by 37%, the vasoconstrictor effects of methoxamine and clonidine were potentiated, and equipressor doses of methoxamine and clonidine decreased SRA by 54% and 75%, respectively. Pettinger et al. (894) believed that methoxamine inhibited renin release by its systemic pressor effects and/or a direct effect on inhibitory alpha-adrenergic receptors located on the granular JG cells. As mentioned previously, the ability of clonidine to inhibit renin release was independent of the hemodynamic effects of the drug. The observation that methoxamine inhibited renin release to a lesser extent than clonidine was thought to result from the fact that clonidine possessed a greater "specificity" for the alpha-adrenergic receptors on the granular JG cells that are inhibitory to renin release.

In studies performed with the isolated perfused rat kidney, methoxamine did not affect renin release, but the renin release seen with methoxamine plus saline was less

than that seen with saline alone (1125, 1133). Methoxamine also blunted by 77% the stimulation of renin release caused by isoproterenol, but this inhibitory effect was accompanied by a rise in renal perfusion pressure. Like phenylephrine, methoxamine has been reported to elevate renin release from the isolated perfused rat kidney if renal perfusion was not allowed to increase from the control level (350). Thus, intrarenal alpha-adrenergic stimulation with methoxamine appeared to inhibit renin release, but the actual site of action, i.e. the vasculature or the granular JG cells, was not ascertained.

It is possible that methoxamine could mildly stimulate renin release at very low doses and inhibit at higher doses, a pattern previously reported for epinephrine in the rat (890). Findings with methoxamine in an in vitro system are consistent with this speculation. Methoxamine (10^{-6} M) has been shown to induce renin release from rat renal cortical slices, and this effect was blocked by propranolol but not by phentolamine (1197). Moreover, methoxamine blocked the stimulation caused by isoproterenol in this system. When methoxamine and phenoxybenzamine were infused together into isolated perfused rat kidneys, renin release was not altered significantly (1133). Thus, methoxamine appears to be able to act as a partial agonist at the beta-adrenergic receptor controlling renin release (1125, 1133, 1197). Therefore, like any partial agonist, methoxamine will stimulate renin release in the absence of a full agonist and inhibit renin release in the presence of a full agonist. However, even though methoxamine inhibited renin release in vitro in the presence of the full agonist isoproterenol, methoxamine does not appear to inhibit renin release by beta-adrenergic receptor blockade. For example, larger doses of methoxamine (10^{-5} to 10^{-3} M) have been shown to inhibit renin release from rat renal cortical slices in vitro (771a). This suppression was reversed by phentolamine. In cases in which methoxamine inhibits renin release in vivo (894), this inhibition may be the result of hemodynamic alterations or direct stimulation of alpha-adrenergic receptors located on the granular JG cells. Further studies are required to determine how methoxamine suppresses renin release in vivo.

F. TYRAMINE. Although tyramine has little direct sympathomimetic activity, it does elicit the release of endogenous norepinephrine from noradrenergic neurons. In an early report, Bunag et al. (164) discovered that the administration of tyramine to anesthetized dogs increased renin release. In rat renal cortical slices in vitro, tyramine alone or in combination with pheniprazine, an inhibitor of monoamine oxidase, did not affect renin secretion (24). However, the addition of the phosphodiesterase inhibitor theophylline to tyramine and pheniprazine resulted in a stimulation of renin secretion that was blocked by propranolol but not phentolamine. Theophylline alone failed to alter renin secretion. A high concentration of tyramine did not change the stimulation of renin secretion caused by norepinephrine and therefore had no direct toxic effect on the granular JG cells. In addition, the blockade of neuronal amine uptake with cocaine prevented the stimulation of renin secretion by the tyramine-pheniprazine-theophylline combination. Because cocaine alone did not alter renin secretion, the latter observation indicated that tyramine elicited renin secretion by releasing norepinephrine in the region of the granular JG cells.

In conscious rats, in which renin release was previously stimulated with an infusion of isoproterenol, a small dose of tyramine brought about a further increment in PRC, and larger doses, which did not alter the hypotension caused by isoproterenol, inhibited isoproterenol-induced renin release in a dose-dependent fashion (733). Increasing the dose of isoproterenol overcame the inhibitory effect of tyramine. Phenoxybenzamine potentiated the renin release caused by isoproterenol and prevented the fall in PRC caused by tyramine. Because renal denervation or treatment with reserpine also abolished the inhibory effect of tyramine on isoproterenol-elicited renin release, Meyer and Hermann (733) suggested that tyramine released intrarenal norepinephrine, which suppressed renin release by the activation of inhibitory alpha-adrenergic receptors in the kidney. Furthermore, the smallest dose of tyramine was believed to have released an amount of norepinephrine that, although too small to activate alpha-adrenergic receptors, was sufficient to activate stimulatory beta-adrenergic receptors. This suggestion is consonant with the greater potency of norepinephrine at postjunctional beta-adrenergic receptors as compared to postjunctional alpha-adrenergic receptors (9). Thus, the effect of tyramine on renin release appears to be a function of the amount of norepinephrine released by a particular dose of this agent.

In summary, alpha-adrenergic agonists tend to suppress renin release, but the exact mechanism(s) involved in this inhibition has not been identified clearly. The suppression of renin release by clonidine appears to be independent of the hemodynamic effects of this drug. Some researchers believe that clonidine lowers renin release by the centrally mediated withdrawal of renal sympathetic nerve activity whereas others maintain that clonidine has a direct inhibitory effect on the secretory function of the granular JG cells. The renal nerves also appear to play an important role in the inhibition of renin release by methyldopa, but in this case a peripheral site of action is indicated. L-Dopa has been shown to decrease PRA in Parkinsonian patients, and studies with animals have suggested that this effect results from the central conversion of L-dopa to norepinephrine, which causes a decrease in the level of activity of the renal sympathetic nerves. The alpha-adrenergic agonists phenylephrine and methoxamine also inhibit the release of renin under most circumstances, but it is not known whether this inhibition results from systemic or renal hemodynamic changes or a direct effect on the granular

JG cells. The effect of the indirectly acting agonist tyramine on renin release is highly dose-dependent. The small amount of norepinephrine released by a small dose of tyramine stimulates renin release, but larger doses of tyramine cause the release of quantities of norepinephrine sufficient to stimulate alpha-adrenergic receptors in the kidney that inhibit renin release.

2. Alpha-adrenergic antagonists. Although alpha-adrenergic antagonists are not used widely in the treatment of disease, they are important tools in pharmacologic and physiologic research. Because these drugs are especially useful in cardiovascular studies, it is important to understand how these agents affect renin release.

A. PHENOXYBENZAMINE. The noncompetitive alpha-adrenergic receptor blocking agent phenoxybenzamine, when administered systemically, has been reported to increase PRA in anesthetized (12, 866) and conscious (736, 894) rats, anesthetized dogs (372, 373, 667, 929), and hypertensive patients with low initial PRA values (1150). Other investigators found no change in PRA after giving phenoxybenzamine to anesthetized dogs (4, 31, 875) or hypertensive humans (745), and an actual decrease in PRA was noted in hypertensive patients with high initial PRA levels (1150) or pheochromocytoma (1151).

In 1970, Alexandre et al. (12) discovered that phenoxybenzamine elevated PRA by 2.4-fold in anesthetized rats, and they suggested that this drug stimulated renin release by: 1) decreasing renal perfusion pressure; 2) decreasing the sodium load at the macula densa; and/or 3) directly activating beta-adrenergic receptors on the granular JG cells. In the ensuing years, the administration of phenoxybenzamine to experimental animals was found to potentiate the increase in renin release caused by physostigmine (12), insulin-induced hypoglycemia (29), stimulation of the renal nerves (372), and the infusion of epinephrine (29, 1078), norepinephrine (1078), and isoproterenol (736, 1078). The fact that the renin release brought about by each of these stimuli was blocked by propranolol strengthened the idea that phenoxybenzamine-induced renin release involved the activation of intrarenal beta-adrenergic receptors. Loeffler et al. (667) noted that phenoxybenzamine caused PRA to triple as it lowered arterial pressure by 30% in anesthetized dogs. Pretreatment with propranolol did not alter the fall in blood pressure but did block the rise in PRA. As a result, it was concluded that the decrement in blood pressure caused by peripheral alpha-adrenergic receptor blockade triggered a reflexly mediated increase in the activity of the renal sympathetic nerves. This conclusion is consistent with the fact that the administration of phenoxybenzamine has been demonstrated to 1) increase the plasma concentration of epinephrine in anesthetized dogs, 2) increase the plasma concentration of norepinephrine in anesthetized rats (930), 3) increase the urinary excretion of norepinephrine, epinephrine, and their metabolites from conscious rats (83), 4) increase the urinary excretion of norepinephrine and epinephrine from conscious dogs (73), and 5) increase splenic nerve activity in anesthetized cats (288). The effects of phenoxybenzamine in the latter two studies (73, 288) were prevented by ganglionic-blocking drugs.

Other evidence supports the notion that phenoxybenzamine-induced renin release occurs via reflex activation of the renal sympathetic nerves. For example, the intrarenal injection of phenoxybenzamine does not elicit renin release (534, 933). In addition, phenoxybenzamine had no effect on renin release from the isolated perfused rat kidney (1133, 1135) or rat renal cortical slices in vitro (805). However, in the latter experiments, phenoxybenzamine did potentiate the stimulation of renin release by norepinephrine, presumably by inhibiting the neuronal uptake of the catecholamine. Thus, phenoxybenzamine does not stimulate renin release by a direct renal action or a direct effect on the granular JG cells.

In studies with hypertensive patients on a salt-restricted diet, Michelakis and McAllister (745) found that phenoxybenzamine caused little or no change in supine or upright PRA. Since Pettinger et al. (894) noted that the increase in PRA after phenoxybenzamine was larger in sodium-depleted rats as compared to normal animals, the failure of Michelakis and McAllister (745) to demonstrate a rise in PRA after phenoxybenzamine was probably related to the absence of a fall in blood pressure rather than the prior alteration in sodium intake. However, Johnston et al. (538) found that 2 weeks of treatment of hypertensive patients with phenoxybenzamine did not decrease blood pressure but did increase PRA and plasma norepinephrine concentration. In contrast, Vetter et al. (1150) reported that prolonged treatment of hypertensive patients with phenoxybenzamine blunted the circadian rhythm of renin release and decreased PRA in both the supine and upright position, especially in subjects with high initial PRA levels. In like fashion, phenoxybenzamine lowered arterial pressure and renin release in patients with pheochromocytoma (1151). Based on these clinical data, Vetter et al. (1150, 1151) suggested that phenoxybenzamine inhibited renin release at a point distal to the blockade of specific adrenergic receptors.

B. PHENTOLAMINE. Phentolamine is a short-acting, competitive alpha-adrenergic antagonist that possesses some direct vasodilating effects. Phentolamine has been shown to stimulate renin release in anesthetized (734, 737, 738, 866, 887) and conscious (571, 572, 890, 894) rats, anesthetized cats (231), and normotensive (653, 728) and hypertensive (293, 486, 504, 653, 974) humans. In conscious rats, phentolamine caused a dose-related elevation of PRA (890) that developed rapidly (894) and was associated with a marked rise in heart rate (571, 572).

As in the case with phenoxybenzamine, a wealth of evidence indicates that phentolamine elicits renin release by reflex activation of the renal sympathetic nerves.

Meyer et al. (737) were the first to demonstrate that propranolol blocked the increase in PRA caused by phentolamine in anesthetized rats, and this observation was subsequently confirmed in conscious rats (571, 572, 890). In conscious rats, small doses of propranolol blocked by 75% to 90% the 7- to 15-fold elevation of PRA brought about by phentolamine (571, 572, 890). In later studies, Meyer and co-workers (734, 738) found that phentolamine-induced renin release was potentiated by desipramine and amitriptyline, two compounds that inhibit the neuronal uptake of norepinephrine but have no effect on renin release by themselves. Furthermore, neither of these drugs enhanced the stimulation of renin release caused by isoproterenol. In addition, the 4- to 9-fold rise in PRA seen after the administration of phentolamine was completely prevented or greatly attenuated by pretreatment with reserpine, the noradrenergic neurotoxin 6-hydroxydopamine, or the ganglionic blockers pempidine or camphidonium. The *l*- and *d*-isomers of propranolol blocked phentolamine-induced renin release by 80% and 25%, respectively.

In later studies with conscious rats, Keeton et al. (572) found that the 10- to 15-fold increase in PRC caused by phentolamine was associated with a 35% decrease in MAP and a 33% elevation of heart rate. Phentolamine-induced renin release, hypotension, and tachycardia were potentiated by the AII antagonist saralasin, and the renin release elicited by phentolamine alone or phentolamine plus saralasin was inhibited by 73% and 90%, respectively, when the animals were pretreated with propranolol. Propranolol attenuated the synergistic hypotensive effect of the phentolamine-saralasin drug combination (K. Keeton, unpublished observations); however, this observation alone could not account for the blockade of the synergistic renin release seen after phentolamine and saralasin.

Because the hypotension caused by a single dose of phentolamine led to a decrease in GFR, RPF, urinary volume, and sodium excretion in conscious rats (136), Keeton and Pettinger (571) examined the possibility that a portion of the renin release caused by phentolamine resulted from a decrease in the sodium load at the macula densa and/or the decrease in blood pressure per se. The treatment of conscious rats with DOCA and saline drinking fluid suppressed basal PRA by 90% and slightly elevated MAP. The administration of phentolamine to these animals raised PRA from 0.2 to 19.6 ng of AI/ml/hr whereas a rise from 2 to 32 ng of AI/ml/hr was noted in normal rats given the same dose. Thus, although the elevation of PRA seen after phentolamine did not reach the same absolute values in the two groups of animals, the relative increase in the DOCA-salt rats (98-fold) was much greater than that seen in normal animals (16-fold). The hypotensive effect of phentolamine was blunted somewhat in the DOCA-salt group, but the degree of tachycardia attained was not affected by salt-loading. Based on these data, it was concluded that the alteration in renal sodium metabolism that follows phentolamine-induced hypotension had little to do with the renin release caused by this agent. Despite the fact that propranolol completely prevented the stimulation of renin release elicited by phentolamine in conscious rats, beta-adrenergic receptor blockade did not affect the vasodepression caused by phentolamine. Therefore, only a minor portion of the renin release produced by phentolamine could be attributed to activation of the renal baroreceptor (571).

Like phenoxybenzamine, phentolamine did not affect renin release when injected directly into the kidneys of anesthetized dogs (534) or added to rat renal cortical slices in vitro (272, 669, 805, 1197). Phentolamine did potentiate the renin release caused by small doses of norepinephrine in vitro (805) and did reverse the inhibition of renin release seen after large doses of norepinephrine in vitro (669, 805). These observations, combined with the data obtained with phentolamine and propranolol in vivo (571, 572, 734, 737, 738, 890), make it unlikely that the renin release elicited by phentolamine resulted from blockade of the intrarenal alpha-adrenergic receptors that have been shown to suppress renin release (894).

One group of researchers (1226–1228) have suggested that phentolamine is able to inhibit renin release at a site distal to specific adrenergic receptors. The elevation of renin release caused by: 1) hemorrhage or adrenalectomy in anesthetized rats; 2) a decrease in renal perfusion pressure in anesthetized dogs; 3) the infusion of isoproterenol, norepinephrine, or cyclic AMP into anesthetized dogs; and 4) the assumption of upright posture in humans was reported to be prevented by prior treatment with phentolamine. However, it is important to note that none of the findings with phentolamine have been corroborated by other researchers. A similar mechanism of action has been proposed for phenoxybenzamine (1150, 1151).

Phentolamine-induced renin release in humans occurs in associated with a fall in blood pressure and a rise in heart rate (293, 504, 653), but neither the increment in PRA nor the rise in heart rate were correlated with the decrement in arterial pressure (293). Drayer et al. (293) found that PRA increased the same percentage in patients with low-, normal-, or high-renin hypertension, and prior sodium depletion did not affect the percentage increase in PRA caused by phentolamine. In like fashion, Levy et al. (653) did not see any significant difference in the stimulation of renin release by phentolamine when normotensive and hypertensive humans were on an unrestricted or restricted salt intake. However, although the PRA values of the two groups were not different on an ad libitum salt diet, salt restriction elevated renin release to a greater extent in the hypertensive subjects. As a result, the percentage increase in PRA after sodium depletion and phentolamine were the same in both groups, but the absolute PRA values were three times

higher in the hypertensive patients. Other researchers (538) have found that a single dose of phentolamine given i.v. to hypertensive patients did not affect PRA, but this observation is not surprising since blood pressure and heart rate were not changed by the drug.

Hodler et al. (486) reported that oxprenolol prevented the increase in PRA and heart rate seen after the i.v. injection of phentolamine into hypertensive patients on a low-sodium diet. Beta-adrenergic blockade did not alter the decrease in blood pressure, GFR, sodium excretion, and urinary volume caused by a single dose of phentolamine.

C. PRAZOSIN. Although prazosin was originally believed to lower blood pressure by active vasodilatation, it has now been shown to elicit vasodepression by alpha-adrenergic blockade (409, 814). Accordingly, prazosin is classified as an alpha-adrenergic antagonist rather than as a peripheral vasodilator. When given to hypertensive humans, prazosin has been found to lower blood pressure and total peripheral resistance; to cause little or no change in heart rate; and to increase cardiac index, GFR, and RPF (678, 700). Thus, unlike phentolamine and phenoxybenzamine, prazosin-induced hypotension does not result in a reflexly-mediated tachycardia.

Massingham and Hayden (701) gave either a single (i.v.) dose or multiple (oral) doses of prazosin to conscious dogs with renovascular hypertension and noted no change in PRA or heart rate even though blood pressure decreased by 15%. When Graham et al. (408) injected prazosin into anesthetized dogs, both PRA and blood pressure decreased. The subsequent administration of the vasodilator diazoxide then elevated PRA without causing further vasodepression.

Prazosin does elicit a tachycardia in conscious rats, and consistent with the mechanism by which alpha-adrenergic antagonists increase PRA, prazosin stimulates renin release in this species (411). Graham and Pettinger (411) observed that both phentolamine and prazosin brought about a dose-related decrease in MAP and increase in SRA and heart rate, but for a given reduction in MAP, phentolamine caused a greater increase in SRA and heart rate than did prazosin. The authors felt that the difference in the magnitude of the rise in SRA caused by equihypotensive doses of phentolamine and prazosin resulted from the fact that prazosin had little or no activity in blocking the prejunctional alpha-adrenergic receptors that have been shown to attenuate the release of nerve-stimulated norepinephrine release (290, 1035).

As a general rule, either short- or long-term treatment of hypertensive patients with prazosin leads to no change or a decrease in PRA (113, 459, 958, 1048). After 50 days of therapy with a dose of prazosin sufficient to lower blood pressure by 16%, PRA decreased by 75% (459). When patients with hypertension were divided into high-, normal-, and low-renin subgroups and treated with prazosin, PRA decreased in all of the high-renin patients and four of the 12 normal-renin patients (958). The remainder of the normal-renin patients and the two low-renin patients exhibited no change in PRA. Prazosin did not elevate heart rate in any of these studies (113, 459, 958). It could be argued that no change in PRA in the face of a decrease in arterial pressure represents an actual suppression of renin release since hypotension per se should cause an increase in PRA. The reason for a lack of increase in renin release and heart rate during the administration of prazosin to hypertensive humans is unknown.

D. OTHER DRUGS WITH ALPHA-ADRENERGIC RECEPTOR BLOCKING ACTIVITY. The injection of dibenamine directly into the renal artery of anesthetized dogs resulted in no change in renal venous PRA (1109). The ergot derivatives obtained from *Claviceps pupurea* possess alpha-adrenergic receptor blocking activity. Dihydroergotamine had little effect on basal or upright PRA in patients with labile hypertension (1266), and a mixture of dihydroergocornine, dihydroergocristine, and dihydroergocryptine lowered blood pressure by 12% in rats but had little effect on PRA (866).

The neuroleptic agents chlorpromazine (699) and clozapine (60) have been shown to be antagonists at alpha-adrenergic receptors. Robertson and Michelakis (940) found that a single dose of chlorpromazine caused a 3-fold increase in PRA in normotensive patients with schizophrenia. Blood pressure decreased slightly. Pettinger et al. (894) noted that clozapine stimulated renin release in conscious rats on a normal or low salt diet. As with phentolamine, clozapine caused a greater percentage increase in SRA in normal rats than in sodium-depleted animals.

The renin-releasing properties of other alpha-adrenergic antagonists such as tolazoline, azapetine, and piperoxane are unknown. Similarly, the ability of other neuroleptic agents with marked activity at alpha-adrenergic receptors to alter renin release has not been tested.

E. IMPORTANCE OF PRE- AND POSTJUNCTIONAL ALPHA-ADRENERGIC BLOCKADE IN THE RENIN RESPONSE TO ALPHA-ADRENERGIC ANTAGONISTS. During the past decade, a wealth of evidence has accumulated to support the existence of prejunctional alpha-adrenergic receptors that modulate the neuronal release of norepinephrine (290, 1035). Stimulation of these receptors by alpha-adrenergic agonists inhibits the exocytotic liberation of norepinephrine, and the blockade of these prejunctional alpha-adrenergic receptors results in a greater release of norepinephrine at low frequencies of nerve stimulation. Alpha-adrenergic antagonists differ in their ability to cause receptor blockade at pre- and postjunctional alpha-adrenergic receptors. For example, yohimbine preferentially antagonizes norepinephrine at prejunctional sites, with postjunctional blockade occurring only at higher concentrations of the drug. In contrast, prazosin appears to be a preferential postjunctional alpha-adrenergic an-

tagonist, and phentolamine appears to possess equal activity at both sites. These conclusions are based mostly on data obtained from experiments conducted in vitro, but recently the results of studies conducted in vivo have given strong support to the functional significance of prejunctional alpha-adrenergic modulation of sympathetic function (412).

Graham et al. (412) measured the reflexly-mediated increase in plasma norepinephrine concentration that resulted from giving *equihypotensive* doses of hydralazine, prazosin, phenoxybenzamine, and phentolamine to conscious rats. Hydralazine, a peripheral vasodilator that does not block alpha-adrenergic receptors, elicited a 4.2-fold increase in the amount of norepinephrine found in the plasma. Prazosin, phenoxybenzamine, and phentolamine elevated plasma norepinephrine concentration by 5.5-, 7.5-, and 8.9-fold, respectively. Thus, the relative ability of these three alpha-adrenergic antagonists to increase the plasma level of norepinephrine was in the same rank-order as their ability to block prejunctional alpha-adrenergic receptors in vitro. These data also help to explain the observation that for a given reduction in MAP, phentolamine caused a greater increase in SRA than did prazosin (411). The exceptional prejunctional selectivity of yohimbine was evidenced by the fact that a small dose of this drug did not lower blood pressure but did elicit a tachycardia and a 3.6-fold elevation in the circulating levels of norepinephrine (412). More recently, yohimbine has been found to cause a dose-related increase in SRA and heart rate in conscious rats even though blood pressure was not decreased (905a). The increases in SRA and heart rate were blocked by propranolol. These results serve to explain earlier suggestions that drugs such as phentolamine (293, 1259) and chlorpromazine (940) possessed agonistic activity at beta-adrenergic receptors. In other words, alpha-adrenergic antagonists, by acting at prejunctional sites, increase the release of norepinephrine onto postjunctional renal and cardiac beta-adrenergic receptors rather than stimulating them directly.

In summary, alpha-adrenergic antagonists stimulate the release of renin by reflex activation of the renal sympathetic nerves secondary to a decrease in MAP. This increase in renin release is blocked by beta-adrenergic antagonists. Prazosin is the exception to this generalization since it may lower blood pressure in some cases without eliciting an increase in renin release or heart rate. These unique properties of prazosin deserve further study.

3. Beta-adrenergic antagonists and agonists. As seen previously, the renal sympathetic nerves play an important role in the stimulation of renin release, and this response is mediated via beta-adrenergic receptors located on the granular JG cells. In fact, much of the evidence for the latter conclusion is based on the fact that beta-adrenergic receptor-blocking drugs prevent sympathetically mediated renin release, irrespective of whether the renal nerves are activated directly or indirectly (vide supra). In addition, the renin response to beta-adrenergic antagonists has been a subject of great interest ever since Buhler et al. (158) suggested that the magnitude of the hypotensive effect of these drugs was dependent on the initial PRA value and the magnitude of suppression of renin release. Thus, the renin response to the various beta-adrenergic antagonists is of interest in basic and clinical research as well as in clinical therapeutics. Here, we will describe the effects of these agents on basal renin release in animals and humans with special emphasis on those situations in which different drugs are compared in the same experimental system.

In 1969, some five years after propranolol was first synthesized, Winer et al. (1228) discovered that propranolol blocked orthostasis-induced renin release in normal humans without lowering supine PRA values. A year later, Stokes et al. (1046) reported that propranolol lowered peripheral and renal venous activity in hypertensive patients and, soon thereafter, Salvetti et al. (972) noted that oxprenolol suppressed both supine and upright renin release in normotensive humans on either a normal salt or low salt diet.

In 1972, Michelakis and McAllister (745) found that therapy with multiple small doses of propranolol suppressed both supine and upright PRA in hypertensive and normotensive humans without affecting blood pressure. The suppression of renin release by propranolol was dose-related, and propranolol lowered both supine and upright PRA by 50% in the salt-depleted state. At the same time, Zehr and Feigl (1267) observed that propranolol lowered PRA by 60 to 70% in salt-deprived and normal anesthetized dogs, and Buhler et al. (158) hypothesized a relationship between the ability of propranolol to lower renin release and its ability to lower blood pressure. In the same year, Salvetti et al. (971) reported that oxprenolol decreased renin release in the supine and upright positions in patients with normal-renin hypertension but was without effect in low-renin hypertension. Since 1972, hundreds of papers have been published concerning the effects of beta-adrenergic antagonists on renin release, and the results of many of these studies are summarized in table 2.

As shown in table 2, all beta-adrenergic antagonists tested to date inhibit renin release in animals and humans, but these drugs differ in their efficacy and potency. Propranolol, the first drug listed in table 2, usually is used as the standard of comparison for all other beta-adrenergic antagonists. Some general points can be made concerning the effects of beta-adrenergic antagonists on renin release. First, renal beta-adrenergic receptor blockade does not suppress basal (supine) renin release to zero in humans; therefore, factors other than renal nerve activity maintain renin release in the supine position. Secondly, many of these drugs block the increase in PRA

TABLE 2

*The alteration of renin release by beta-adrenergic receptor blocking drugs**

Experimental Subjects	Dose/Time	Inhibition of Renin Release (%)	Comments	Reference
	PROPRANOLOL: A nonselective agent with membrane stabilizing effects but no intrinsic activity			
NT humans	0.08 mg/min, i.v., 1 hr	89	Upright PRA	1228
HT humans	8–15 mg, i.v.	57	Renal venous PRA	1046
NT/HT humans	80 mg/day, p.o., 3 days	50	Supine PRA, normal salt diet	745
		50	Supine PRA, low salt diet	
		30–50	Upright PRA, normal salt diet	
		60–65	Upright PRA, low salt diet	
HT humans, upright	2 mg/kg/day, p.o., 7 days	65	Low-renin HT	158
		60	Normal-renin HT	
		80	High-renin HT	
NT/HT humans	10 mg, i.v., 2 hr	71	Supine PRA	133
HT humans	2 mg/kg/day, p.o., 4–7 days	51	Supine PRA	763
NT/HT humans, supine	5 mg, i.v., 15 min	5	NT humans	1024
		5	HT humans	
		0	Renal HT without renal failure	
		0	Renal HT with renal failure	
NT humans, upright	160 mg/day, p.o., 2 wk	31	Normal salt diet	839
		6	Low salt diet	
HT humans, supine	2.5 μg/min/kg, i.v., 1 hr	80	Borderline HT	1058
		50	Sustained HT	
HT humans, upright	640 mg/day, p.o., 2 wk	48	Normal-renin HT	500
		69	High-renin HT	
NT humans, upright	160 mg/day, p.o., 2 wk	58	Exercise-induced release	114
HT humans, supine, renin secretion rate	9–18 μg/kg, i.v., 10 min	63	Low salt diet	1061
		0	High salt diet	
NT humans	40 mg, p.o., 1 hr	16	Supine PRA	34
HT humans, upright	80 mg/day, p.o., 4–6 days	88–90	Chronic renal failure	766
HT humans, upright	240 mg/day, p.o., 3 wk	51	Plasma propranolol levels, 40–200 ng/ml	799
HT humans	160 mg, p.o., 2 hr	45	Supine PRA	767
HT humans	320 mg/day, p.o., 8 wk	68	Upright PRA	559
HT humans	40 mg/day, p.o., 5–7 days	79	Supine PRA	650
		50		
HT humans	0.15 mg/kg, i.v., 45 min	25	Low-renin HT	172
		28	Normal-renin HT	
		26	High-renin HT	
HT humans	0.15 mg/kg, i.v., 45 min	33	Low-renin HT } exercise induced release	172
		37	Normal-renin HT	
		51	High-renin HT	
HT humans, upright, sodium-depleted	120–320 mg/day, p.o., 3 days	57	Essential HT	384
		68	Renovascular HT	
		81	HT with renal failure	
HT humans, upright	120–320 mg/day, p.o., 3 days	73	Renal insufficiency present	384
NT humans, upright	0.13 mg/kg, i.v., 40 min	0	*d*-Propranolol	1095
		50	*d,l*-Propranolol	
NT humans	0.8 mg/kg, i.v., 1 hr	20	Supine PRA	1156
		32	Upright PRA	
NT humans, supine	1.5 mg/kg/day, p.o., 4 days	67	Low salt diet	1152
HT humans	240 mg/kg/day, p.o., 3–14 mo	66	Supine PRA	1050
		70	Upright PRA	
HT Humans	480 mg/day, p.o., 1 wk	29	Supine PRC	660
		36	Upright PRC	
NT humans	160 mg, p.o., 2 hr	33	Seated PRA	627
		47	Exercise-induced release	
HT humans, seated	2.5 mg/kg/day, p.o., 4 mo	56	Normal-renin HT	157
NT humans	100 mg, p.o., 2 hr	24	Supine PRA	157
		50	Exercise-induced release	
Conscious NT dogs	1 mg/kg, i.v., 1 hr	67	Normal salt diet	1267
		65	Low salt diet	

* Abbreviations used are: NT, normotensive; HT, hypertensive, hypertension; PRA, plasma renin activity; PRC, plasma renin concentration; AII, angiotensin II.

TABLE 2—*continued*

Experimental Subjects	Dose/Time	Inhibition of Renin Release (%)	Comments	Reference
Pentobarbital-anesthetized, NT dogs	0.6 mg/kg, i.v., plus 0.3 mg/kg/hr, i.v., 90 min	50 0	Low salt diet Normal salt diet	373
Conscious, NT dogs	1 mg/kg, i.v., plus 0.6–0.67 mg/kg/hr, i.v., 1 hr 1 mg/kg, i.v., plus 1.5–1.8 mg/kg/hr, i.v., 1 hr	66 77	Low salt diet Low salt diet	1255
NT dogs	1 mg/kg, i.v., plus 0.5 mg/kg/hr i.v., 90 min	84 84	Conscious Pentobarbital anesthesia	1254
Pentobarbital-anesthetized, NT dogs	0.6 mg/kg, i.v., plus 0.3 mg/kg/hr, i.v., 30 min	43	Renal venous PRA	828
Conscious, NT rabbits	1 mg/kg, i.v., 60 min	49		1186
Conscious, NT rats	6 mg, i.m., 20 days	50		345
Anesthetized, NT rats	5 mg/day, p.o., 20 days	0	Pentobarbital anesthesia	561
Anesthetized rats, pinealectomy-induced HT	5 mg/day, p.o., 20 days	25	Pentobarbital anesthesia	561
Conscious, HT rats	40–80 mg/kg/day, p.o., 3–4 wk	35 0	PRC in two-kidney Goldblatt HT PRC in one-kidney Goldblatt HT	862
Ether-anesthetized, NT rats	30 mg/kg/day, p.o., 3 wk	44 3	Normal salt diet Low salt diet	1033
Ether-anesthetized, rats	1 mg/kg, i.m., 30 min	50	PRC	737
Conscious, NT rats	1 mg/kg, i.v., plus 0.5 mg/kg/hr, 6 hr	64 0	*d,l*-Propranolol *d*-Propranolol	1185
NT rats	0.25 mg/kg, i.v., 1 hr 1.0 mg/kg, i.v., 1 hr	0 50	Thiobarbitone anesthesia	816
Conscious, NT rats	15 mg/kg, i.p., 30 min	53		890
Conscious, HT rats	2 mg/kg/day, i.m./p.o., 2 wk	0	Okamoto strain rats	346
Conscious, HT rats	20 mg/kg/day, s.c., 15 days	0	Two-kidney Goldblatt HT	642
Conscious HT rats	60 mg/day, p.o., 6 wk	16	Stenosis of aorta between renal arteries	328
Conscious, NT rats	60 mg/kg/day, 2 wk	47		328
Conscious, HT rats	2.6 mg/kg/day, i.p., 20 days	40 27 47 3 0	0 3 5 12 20 Days after stenosis of aorta between the renal arteries	327
Ether-anesthetized, HT rats	75 mg/kg/day, p.o., 3 wk	9	Wellcome strain rats	641
Ether-anesthetized, NT rats	75 mg/kg, day, 3 wk	53		641
Conscious, NT rats	1.5 mg/kg, s.c., 30 min	32	Sodium-depleted rats	894
Conscious, NT rats	1.5 mg/kg, s.c., 30 min	50		185
Conscious rats	1.5 mg/kg, s.c., 30 min	64 54	HT rats, Okamoto strain NT rats, Wistar-Kyoto	893
ALPRENOLOL: A nonselective agent with membrane-stabilizing effects and marked intrinsic activity				
HT humans	600 mg/day, p.o., 6 wk	52	Upright PRA	225
HT humans	600–1200 mg/day, p.o., 1 mo	47	Supine PRC	884
BUFURALOL: A cardioselective agent with membrane-stabilizing effects and some intrinsic activity				
HT humans	320 mg/day, p.o., 4–6 wk	69	Upright PRA	1192
NT humans	20 mg, p.o., 2 hr	23 50	Supine PRA Exercise-induced release	157
BUNOLOL: A nonselective agent with no membrane-stabilizing effects or intrinsic activity				
HT humans	15–30 mg/day, p.o., 5 days	71	Seated PRA	379
BUPRANOLOL: A nonselective agent with no membrane-stabilizing effects or intrinsic activity				
NT rats	30 μg/kg, i.m., 30 min 1000 μg/kg, i.m., 30 min	30 80	Ether anesthesia	909
OXPRENOLOL: A nonselective agent with no membrane-stabilizing effects but marked intrinsic activity				
NT humans, supine	40 mg, p.o., 1 hr	51	Plasma oxprenolol levels, 100–700 ng/ml	623

TABLE 2—*continued*

Experimental Subjects	Dose/Time	Inhibition of Renin Release (%)	Comments	Reference
HT humans	3.4 mg/kg/day, p.o., 2 mo	62	Seated PRA	159
	160 mg, p.o., 8 hr	60		
NT humans	100 mg, p.o., 1 day	61	Supine PRA	975
		58	Upright PRA	
HT humans, upright PRA	100 mg, p.o., 1 day	70	High-renin HT	975
		65	Normal-renin HT	
		66	Low renin HT, no change in 9/19 patients	
		61	Renovascular HT, no change in 14/36 patients	
NT humans	80 mg, p.o., 1 day	40	Supine PRA	973
		66	Upright PRA	
HT humans	240 mg/day, p.o., 2–3 wk	38	Supine PRA	250
		26	Upright PRA	
HT humans, seated	3.4 mg/kg/day, p.o., 2 mo	53	Normal-renin HT	157
NT humans	80 mg, p.o., 1 day	73	Supine PRA, low salt diet	972
		91	Upright PRA	
		40	Supine PRA, normal salt diet	
		76	Upright PRA	
NT humans	100 mg, p.o., 1 day	71	Upright PRA	971
HT humans, upright	100 mg, p.o., 1 day	68	Normal-renin HT	971
		0	Low-renin HT	
NT humans	100 mg, p.o., 2 hr	15	Supine PRA	157
		46	Exercise-induced release	
Conscious, NT rabbits	1 mg/kg, i.v., 2 hr	50		1186
Conscious, NT rabbits	1 mg/kg, i.v., plus 0.063 mg/kg/hr, i.v., 6 hr	57		1185
PENBUTOLOL: A nonselective agent with no membrane-stabilizing effects or intrinsic activity				
HT humans	40–60 mg/day, p.o., 3–8 mo	59	Supine PRA	493
		72	Upright PRA	
		82	Exercise-induced release	
HT humans	4–8 mg/day, p.o., 4 hr	60	Supine and upright PRA	442
PINDOLOL: A nonselective agent with no membrane-stabilizing effects but marked intrinsic activity				
HT humans, supine	1.2 μg/min/kg, i.v., 1 hr	54	Borderline HT	1058
		0	Sustained HT	
HT humans, supine	40 mg/day, p.o., 1 mo	33	Borderline HT	1058
		20	Sustained HT	
HT humans, supine	15–45 mg/day, p.o., 6 wk	60	High-renin HT	628
		44	Normal-renin HT	
		47	Low-renin HT	
HT humans	15–35 mg/day, p.o., 16 wk	19	Supine PRA	135
		30	Upright PRA	
HT humans	20 mg, p.o., 2 hr	15	Supine PRA	767
NT humans, supine	0.5 mg/kg/day, p.o., 5 days	67	Low-sodium diet	1152
HT humans	45 mg/day, p.o., 3 mo	9	Supine PRA	812
HT humans	20 mg, p.o., 4 hr	6	Upright PRA	17
HT humans	60 mg/day, p.o.	54	Upright PRA	17
HT humans	Not stated	42	Supine PRA	1030
HT humans	10 mg/day, p.o., 1 mo	31	Upright PRA	367
	14 mg/day, p.o., 1 mo	35		
	19 mg/day, p.o., 1 mo	12		
HT humans	10 mg/day, p.o., 3 mo	49	Supine PRA	1079
		51	Upright PRA	
NT humans	5 mg, p.o., 2 hr	11	Supine PRA	157
		38	Exercise-induced release	
Conscious, NT rabbits	0.1 μg/kg/min, i.a., into kidney, 1 hr		2.5-fold increase in renin secretion	1183
	0.1 μg/kg/min, i.v., 1 hr		No change in renin secretion	
Conscious, NT rabbits	0.125 mg/kg, i.v.		1.4-fold increase, 1 hr postinjection 1.8-fold increase, 2 hr postinjection 2.8-fold increase, 3 hr postinjection	1186
Conscious, NT rabbits	0.125 mg/kg, i.v., plus 0.063 mg/kg/hr, i.v., 6 hr		3.4-fold increase in PRA	1185

TABLE 2—*continued*

Experimental Subjects	Dose/Time	Inhibition of Renin Release (%)	Comments	Reference
	SOTALOL: A nonselective agent with no membrane-stabilizing effects or intrinsic activity			
HT humans, upright	230–1200 mg/day, p.o., 13 wk	74	High-renin HT	1149
PRC		3	Low-renin HT	
	TIMOLOL: A nonselective agent with no membrane-stabilizing effects or intrinsic activity			
HT humans	30 mg/day, p.o., 2 mo	64	Upright PRA	204, 205
Supine humans	46 mg/day, p.o., 6 days	21	NT	679
		50	HT	
NT humans	10 mg, p.o., 2 hr	28	Supine PRA	157
		31	Exercise-induced release	
Conscious, HT dogs	1.5 mg/day, p.o., 4 days	17	Cellophane-wrap, renal HT	1067
Conscious dogs	8 mg/day, p.o., 1 wk	0	NT dogs	779
		10	Renal HT dogs	
Conscious, NT rabbits	0.125 mg/kg, i.v., plus 0.0625 mg/kg/hr, i.v., 1 hr	49	PRC	410
NT rats	0.2 mg/kg, i.p., 1 hr	54	Conscious	410
		84	Ether anesthesia	
Conscious rats	2 mg/kg, p.o., 1 hr	30	HT rats, Okamoto strain	936
		0	NT rats, Wistar-Kyoto	
		0	NT rats, Sprague-Dawley	
Conscious rats	2 mg/kg/day, p.o., 4 days	75	HT rats, Okamoto strain	936
		60	NT Rats, Wistar-Kyoto	
		8	NT Rats, Sprague-Dawley	
Pentobarbital-anesthetized rats	20 mg/kg/day, p.o., 8 days	13	HT rats, Okamoto strain	779
		6	NT rats, Wistar	
	LL21-945: A nonselective agent with no intrinsic activity			
HT humans, seated	0.1 mg/kg/day, p.o., 68 days	63	Normal-renin HT	157
NT humans	2.5 mg, p.o., 2 hr	23	Supine PRA	157
		47	Exercise-induced release	
	ACEBUTOLOL: A cardioselective agent with membrane-stabilizing effects and some intrinsic activity			
HT humans	2 g/day, p.o., 2 days	61	Upright PRA	724
HT humans	800 mg/day, p.o., 6 wk	31	Upright PRA	347
	ATENOLOL: A cardioselective agent with no membrane-stabilizing effects or intrinsic activity			
HT humans	200 mg/day, p.o., 2 mo	56	Supine PRA	1263
		65	Upright PRA	
HT humans	50 mg/day, p.o., 1 mo	50	Supine PRA	1213
HT humans	200 mg/day, p.o., 2 mo	70	Supine PRA	985
		65	Upright PRA	
HT humans	200 mg/day, p.o., 1 mo	75	Supine PRA	6
HT humans	600 mg/day, p.o., 3 wk	8	Seated PRC [PRC, total plasma renin by method of Skinner et al. (268)]	319
HT humans	75 mg/day, p.o., 1 wk	7	Supine PRC	15
		40	Upright PRC	
HT humans	75 mg/day, p.o., 1 wk	7	Supine PRC	660
		40	Upright PRC	
	600 mg/day, p.o., 1 wk	14	Supine PRC	
		10	Upright PRC	
NT humans	100 mg, p.o., 2 hr	34	Supine PRA	157
		47	Exercise-induced release	
NT rats	2.5 mg/kg, i.v., 1 hr	64	Thiobarbitone anesthesia	816
	20 mg/kg, i.v., 1 hr	68		
	METOPROLOL: A cardioselective agent with slight membrane-stabilizing effects but no intrinsic activity			
HT humans	300 mg/day, p.o., 3 wk	67	Supine PRA	1164
		73	Upright PRA	
NT humans	40 mg, p.o., 1 hr	29	Supine PRA	34
HT humans	150–450 mg/day, p.o., 3 mo	49	Supine PRA	443
		46	Upright PRA	
HT humans	150 mg/day, p.o., 1 mo	67	Supine PRA	905
		69	Upright PRA	
HT humans	150 mg/day, p.o., 3 mo	36	Upright PRA	1168

TABLE 2—*continued*

Experimental Subjects	Dose/Time	Inhibition of Renin Release (%)	Comments	Reference
HT humans	300 mg/day, p.o., 1–3 wk	80	PRA, posture not stated	16
		19	PRC, posture not stated [PRC, "total plasma renin" by method of Skinner et al. (268)]	
HT humans	150–450 mg/day, p.o., 3 mo	39	Supine PRA	441
		43	Upright PRA	
NT humans	0.8 mg/kg, p.o., 1 hr	19	Supine PRA	1156
		29	Upright PRA	
HT humans	200 mg, p.o., 2 hr	0	Seated PRA	627
		48	Exercise-induced release	
HT humans, seated	3.2 mg/kg/day, p.o., 7 wk	67	Normal-renin HT	157
NT humans	125 mg, p.o., 2 hr	29	Supine PRA	157
		38	Exercise-induced release	
Conscious, NT rabbits	2.5 mg/kg, i.v., plus 1.25 mg/kg/hr, i.v., 6 hr	31		1185
NT rats	2.5 mg/kg, i.v., 1 hr	57	Thiobarbitone anesthesia	816
	20 mg/kg, i.v., 1 hr	59		
PRACTOLOL: A cardioselective agent with no membrane-stabilizing effects and marked intrinsic activity				
HT humans	800 mg/day, p.o., 6 mo	34	Supine PRA	317
		65	Upright PRA	
NT humans	400 mg, p.o., 2 hr	22	Supine PRA	157
		55	Exercise-induced release	
NT humans	300 mg, p.o., over 18 hr	12	Supine PRA	971
		41	Upright PRA	
Conscious, NT rabbits	2.5 mg/kg, i.v., plus 1.25 mg/kg, i.v., 6 hr	22		1185
NT rats	2 mg/kg, i.v., 1 hr	19	Thiobarbitone-anesthesia	816
	16 mg/kg, i.v., 1 hr	19		
TOLAMOLOL: A cardioselective agent with no membrane-stabilizing effects or intrinsic activity				
NT humans	100 mg, p.o., 2 hr	30	Supine PRA	157
		47	Exercise-induced release	
HT humans	300–900 mg/day; p.o., 2–4 mo	68	Upright PRA	1159
Pentobarbital-anesthetized rats	10 mg/kg/day, p.o., 20 days	14	NT rats, Wistar	562
		51	Pinealectomy-induced HT rats	
LABETALOL: A competitive antagonist at both alpha- and beta-adrenergic receptors that is a nonselective beta-adrenergic antagonist. Labetalol is more potent at beta- than at alpha-adrenergic receptors				
HT humans, upright	300–1200 mg/day, p.o., 8 days	28	High initial PRA	723
		2.2-fold increase	Low initial PRA	
HT humans, supine	1.5–2 mg/kg, i.v., 3 hr	33	Decrease in plasma AII concentration	952
HT humans	1200 mg/day, p.o., 8–16 mo	77	Exercise-induced release	597
HT humans	1500 mg/day, p.o., 2 wk	32	Supine PRA	1193
		40	Upright PRA	
NT humans	400 mg, p.o., 2 hr	12	Supine PRA	157
		44	Exercise-induced release	
HT humans	1.65 g/day, p.o., 2 wk	73	Supine PRA	320
		100	Exercise-induced release	
NT rats	1 mg/kg, s.c., 30 min	2.3-fold increase		573
	3 mg/kg, s.c., 30 min	2.8-fold increase		
	10 mg/kg, s.c., 30 min	3.1-fold increase		
	30 mg/kg, s.c., 30 min	4.4-fold increase		

that results from the attainment of upright posture in humans. This blockade of orthostasis-induced renin release has been demonstrated with propranolol (650, 660, 728, 745, 971, 972, 1050, 1156, 1228), acebutolol (347), atenolol (15, 660, 985, 1263), metoprolol (441, 443, 905, 1156, 1164), oxprenolol (250, 973, 975), penbutolol (442, 493), pindolol (135, 628, 1079), practolol (317, 971), and labetalol (1193). In a similar fashion, exercise-induced

renin release in humans has been prevented by pretreatment with propranolol (114, 157, 172, 627), atenolol (157), bufuralol (157), metoprolol (157, 627), oxprenolol (157), penbutolol (493), pindolol (157), practolol (157), timolol (157), tolamolol (157), and labetalol (157, 597). Next, and in accord with the original suggestion of Buhler et al. (158), other clinicians have observed that beta-adrenergic receptor blockade with propranolol (172, 500), bunolol (379), oxprenolol (971, 975), pindolol (628), and sotalol (1149) lowered PRA by a greater percentage in high-renin hypertensive patients than in low-renin hypertensive patients. It is important to note, however, that this differing response of renin release to beta-adrenergic blockade was detected when the patients were in the upright position (172, 379, 500, 628, 975, 1149). Usually, no difference in renin suppression was observed in recumbent high- and low-renin hypertensive patients after beta-adrenergic blockade (172). In only one case was beta-adrenergic blockade with pindolol (628) found to suppress PRA in the supine position to a greater extent in high-renin hypertensive humans.

There is some controversy (839, 1033) as to whether beta-adrenergic antagonists have the ability to lower the elevated PRA values found in sodium-depleted animals and humans, but the majority of the evidence indicates that they do suppress this stimulated renin release to a certain extent. For example, propranolol has been noted to lower PRA by 50% to 70% in salt-depleted humans (133, 384, 745, 763, 1061, 1152), dogs (373, 1255, 1267), and rats (894). In like fashion, pindolol (1152) and oxprenolol (972) lowered PRA in sodium-depleted humans. However, even with this degree of inhibition of renin release in the salt-depleted state, the absolute PRA values encountered are usually greater than, or at least equal to, the PRA values found in the states of normal sodium balance. On the other hand, some researchers have noted that propranolol had no effect on PRC in orthostatic, hypertensive patients (839) and ether-anesthetized rats (1033) in a sodium-depleted state. In each of the experiments (133, 384, 745, 763, 839, 1033, 1061, 1152) referenced above, sodium-depletion was achieved primarily by the ingestion of a low salt diet with only a minimal use of diuretic drugs (133, 384, 1255). In each case, diuretic therapy had been withdrawn several days before the administration of the beta-adrenergic antagonist. This inhibition of renin release by beta-adrenergic blockers during sodium-depletion is comparable to the effect of these drugs on thiazide-induced renin release, and this suppression has been taken as evidence that the stimulatory effect of the renal sympathetic nerves on renin release is increased during sodium-depletion and the subsequent contraction of plasma volume.

Even though the degree of inhibition of renin release by the beta-adrenergic receptor antagonists propranolol (345), oxprenolol (623), and metoprolol (441) has been found to be closely correlated with the plasma concentration of these drugs, it is not safe to assume that their ability to suppress renin release is always dependent on the blockade of the beta-adrenergic receptors located on the granular JG cells. For example, Johns and Singer (527) found that propranolol lowered renin release from the denervated kidneys of anesthetized cats by 60%, and Osborn et al. (847) observed that both *d*- and *d,l*-propranolol inhibited renin secretion in anesthetized dogs with denervated, nonfiltering kidneys. Moreover, both *d*- and *d,l*-propranolol blocked furosemide-induced renin release and renal vasodilatation in dogs with nonfiltering and denervated, nonfiltering kidneys (235, 847). Although it was originally reported that propranolol blocked renal baroreceptor-stimulated renin release in anesthetized dogs (1226), other investigators (231, 440, 1145) have been unable to confirm this finding. In a well-designed study in conscious dogs, Hanson et al. (440) elicited a 2-fold increase in PRA by decreasing renal perfusion pressure with an inflatable cuff implanted around the renal artery. Pretreatment with propranolol had no effect on this renal baroreceptor-mediated renin release.

Analogous studies have been conducted in humans in that the effect of oxprenolol on orthostasis-induced renin release was examined in patients with functioning renal allografts, i.e. denervated kidneys (973). In these patients, the increase in PRA after attainment of the upright position (69, 654, 798, 973, 1095) is not as rapid as it is in humans with intact renal innervation (846), but the magnitude of the increase is the same. This increase in PRA might result from the release of catecholamines by the adrenal gland (69) or activation of the renal baroreceptor. Salvetti et al. (973) observed that five of six patients with functioning renal transplants exhibited an increase in PRA with orthostasis some three to five months after surgery. After the administration of oxprenolol, the postural rise in renin release was reduced in only two of six patients. Therefore, it is not known whether beta-adrenergic antagonists can block renal baroreceptor-mediated renin release in humans.

Nevertheless, propranolol does have direct effects on the renal vasculature. Carriere (198) reported as early as 1969 that the infusion of small doses of propranolol directly into the renal artery of anesthetized dogs reduced RBF without causing systemic hemodynamic changes. More recently, Sullivan et al. (1061) discovered that the i.v. administration of small doses of propranolol caused a 15% to 20% drop in RBF and a 15% to 20% rise in renal vascular resistance in both salt-depleted and salt-loaded hypertensive patients. No change in blood pressure or heart rate was observed after propranolol, and renin secretion was reduced only in the sodium-depleted state. Thus, a renal vascular site of action for beta-adrenergic receptor antagonists, propranolol in particular, always must be considered in interpreting changes in PRA after beta-adrenergic receptor blockade.

The effects of beta-adrenergic receptor blockers on

renal salt and water metabolism also cannot be ignored in experiments in which renin release is estimated. While these drugs as a class appear to have marked effects on salt and water excretion, the results to date are contradictory. Propranolol has been reported to cause an antinatriuresis in dogs (173, 800) but, on the other hand, propranolol has been judged to elicit a natriuresis and diuresis in rats (195, 414, 648). Carrara and Baines (195) noted that *d,l*-, but not *d*-, propranolol produced a transient 2- to 3-fold increase in sodium excretion in rats infused with ADH and aldosterone and in water-loaded rats. The natriuresis produced by propranolol was dependent on postganglionic nerve activity but was independent of renal alpha-adrenergic receptors. In normotensive and SH rats, timolol had a natriuretic and diuretic effect equivalent to bendroflumethazide (779). Of greater interest is the observation that the natriuretic effects of timolol and bendroflumethazide were synergistic in the normotensive rats and additive in hypertensive animals. Along these same lines, Lee and Simpson (640) found that continued treatment of genetically hypertensive rats with propranolol for six weeks decreased total body exchangeable sodium as it lowered blood pressure. In a similar fashion, Brecht et al. (135) discovered that four months of therapy with pindolol resulted in a significant decrement in total body exchangeable sodium and an increment in total body potassium content in hypertensive humans. The latter observation is consistent with the findings of Sweet and Gaul (1066), who noted that the administration of timolol to dogs for 4 days resulted a 0.3 mEq/l rise in plasma potassium concentration. Timolol also attenuated the hypokalemia usually attendant to therapy with hydrochlorothiazide (1066). Elevations of plasma potassium levels of 0.3 mEq/l have been reported after the continued treatment of hypertensive humans with propranolol (158). It has been suggested (158, 1066) that the reduction in PRA by beta-adrenergic antagonists leads to a fall in plasma levels of AII, a subsequent reduction in aldosterone production, and the retention of potassium by the kidney. Since small changes in plasma potassium content can suppress renin release (vide supra), Buhler et al. (158) felt that propranolol-induced hyperkalemia might contribute to the inhibition of renin release by this drug. In conclusion, the effects of beta-adrenergic antagonists on renal salt and water metabolism cannot be ignored when critical experiments involving renin release are planned or analyzed.

The advent of the cardioselective beta-adrenergic antagonists generated a great deal of interest in the pharmacologic characterization of the renal beta-adrenergic receptor controlling renin release. In 1967, Lands et al. (629) presented evidence that beta-adrenergic receptors can be subdivided into $beta_1$- and $beta_2$-subtypes, with the $beta_1$-receptors mediating positive chronotropic and inotropic responses in the heart and $beta_2$-receptors subserving broncho- and vasodilatation. During the last few years, researchers have used $beta_1$- and $beta_2$-adrenergic antagonists and agonists, either singly or in combination, in an attempt to determine whether renin release is mediated via $beta_1$- or $beta_2$-adrenergic receptors.

With this aim in mind, Weber et al. (1185) studied the effects of *d,l*-propranolol, *d*-propranolol, pindolol, oxprenolol, metoprolol, practolol, and H35/25 on both basal and isoproterenol-stimulated renin release in conscious rabbits. With the exception of *d*-propranolol and pindolol, all of these antagonists lowered basal PRA during the course of a 6-hr i.v. infusion. The decrement in PRM seen after the cardioselective blockers metoprolol (−31%) and practolol (−22%) was significantly less than that observed after the nonselective drugs *d,l*-propranolol (−64%) and oxprenolol (−57%). In addition, practolol and metoprolol inhibited the chronotropic effects of isoproterenol but not the increase in PRA caused by isoproterenol. In an opposite fashion, the $beta_2$-adrenergic receptor blocker H35/25 prevented the rise in PRA, but not the increase in heart rate, elicited by isoproterenol. Oxprenolol, pindolol, and *d,l*-propranolol blocked the renin release and tachycardia caused by isoproterenol. The *d*-isomer of propranolol did not alter basal or stimulated renin release, and pindolol caused a 3.4-fold increase in PRA in association with a marked tachycardia. If PRA, MAP, and heart rate had previously been lowered by an i.v. infusion of *d,l*-propranolol, the addition of pindolol to the infusate raised PRA and heart rate back to the prepropranolol control values without affecting blood pressure. Because pindolol stimulated renin release and reversed the ability of propranolol to suppress PRA, but prevented isoproterenol-induced renin release, it was concluded that the stimulatory effect of pindolol on PRA and heart rate resulted from the marked intrinsic sympathomimetic activity of pindolol. Therefore, those drugs that possess prominent $beta_2$-adrenergic blocking activity (*d,l*-propranolol, oxprenolol, pindolol, and H35/25) had a greater inhibitory effect on basal and isoproterenol-stimulated renin release than those agents with $beta_1$-adrenergic receptor activity (practolol and metoprolol). Weber et al. (1185) concluded that the effects of beta-adrenergic blockers on renin release in rabbits depended on the sum of their direct effects, either agonistic or antagonistic, on $beta_2$-adrenergic receptors in the kidney.

The variable effects of pindolol on renin release stress the importance of considering the direct sympathomimetic activity of beta-adrenergic receptor antagonists. As seen in table 2, a single dose of pindolol had little effect on PRA in humans (17, 157, 767) even though continued therapy usually resulted in a fall in PRA equal to that seen with other beta-adrenergic receptor blockers (17, 367, 628, 1030, 1058, 1079). When hypertensive patients previously treated with propranolol were changed to pindolol, blood pressure was still reduced but PRA increased 2- to 3-fold in the recumbent and upright position (1050). More recently, Weber et al. (1183) found that

pindolol infused directly into the renal artery of conscious rabbits brought about a 2.5-fold increase in renin secretion without altering RBF and MAP. The same dose given i.v. did not affect renin secretion. Furthermore, after intrarenal arterial administration, a good correlation was noted between renin secretion and the concentration of pindolol in the renal venous blood. The ability of small doses of pindolol to elevate renin secretion was thought to be due to the marked sympathomimetic effect of pindolol. A single bolus injection of pindolol or oxprenolol also has been shown to elevate renin release and heart rate in conscious rabbits (1186). The intrinsic activities of pindolol and oxprenolol are 56% and 29% respectively, at cardiac chronotropic receptors when compared with isoproterenol (59), and the agonistic properties of these drugs are fully expressed in the rabbit kidney (1185, 1186) and partially expressed in the human kidney (1050).

Johns and co-workers (526, 529) have presented evidence that renin release is a $beta_2$-adrenergic receptor phenomenon in the cat. In anesthetized cats, both propranolol and the cardioselective antagonist atenolol lowered basal PRA; however, only propranolol lowered PRA in a dose-related manner. Propranolol and atenolol inhibited renal nerve-stimulated renin release in a dose-dependent fashion, but atenolol was 5.5-times less potent than propranolol in effecting this inhibition (529). In feline renal cortical cell suspensions, both isoproterenol and the $beta_2$-adrenergic receptor agonist salbutamol stimulated the release of renin, with salbutamol about one-third as potent as isoproterenol. Because the relative potency of salbutamol and isoproterenol at JG cell beta-adrenergic receptors, Johns et al. (526) concluded that $beta_2$-adrenergic receptors controlled renin release in the cat. However, other investigators (273) have pointed out that the collagenase treatment used by Johns et al. (526) to prepare their cell suspensions may have altered the beta-adrenergic receptors of the granular JG cells.

In conscious dogs, Himori et al. (482a) found that orally administered atenolol, a $beta_1$-adrenergic antagonist, blocked the renin release and tachycardia caused by an i.v. infusion of isoproterenol. The vasodepression caused by isoproterenol was not affected. Conversely, the $beta_2$-adrenergic antagonist IPS-339 prevented the decrease in blood pressure caused by isoproterenol but did not impair isoproterenol-induced renin release or tachycardia. In these studies, *d,l*-propranolol blocked the renin release, tachycardia, and vasodepression seen with isoproterenol but *d*-propranolol did not. Based on these data, it was concluded that $beta_1$-adrenergic receptors mediated renin release in the dog.

Oates et al. (816) studied the effects of propranolol, atenolol, metoprolol, practolol, and butoxamine on renin release in rats anesthetized with thiobarbitone. Prior to the experiments involving the measurement of PRA, the doses of the beta-adrenergic antagonists necessary to achieve equal $beta_1$- and $beta_2$-adrenergic receptor blocking effects against isoproterenol were determined in anesthetized rats treated with the ganglionic blocker pentolinium. Atenolol, metoprolol, and propranolol, at doses that produced equal $beta_1$-adrenergic receptor blockade, suppressed PRA by 35%, 41%, and 40%, respectively, despite the fact that these doses of atenolol and metoprolol exhibited no $beta_2$-adrenergic receptor blocking activity. If the doses of atenolol and metoprolol were increased by 8-fold in order to achieve $beta_2$-adrenergic receptor blockade, little additional suppression of renin release was noted. Conversely, when equipotent $beta_2$-adrenergic receptor blocking doses of atenolol, metoprolol, propranolol, and butoxamine were tested, PRA was lowered by atenolol and metoprolol but not by propranolol and butoxamine. Neither $beta_1$- or $beta_2$-adenergic receptor-blocking doses of practolol affected PRA, and this lack of effect was attributed to the high intrinsic activity of practolol. It was concluded that sympathetically mediated renin release in the rat occurred via $beta_1$-adrenergic receptors (816). The work of Desaulles et al. (273) and Campbell et al. (180) support this contention. In the former case, a positive correlation was found between the degree of inhibition of isoproterenol-induced renin release in rat renal cortical slices in vitro and the pA_2 values of propranolol, atenolol, practolol, and IPS 339 (a selective $beta_2$-receptor blocker) at cardiac $beta_1$-receptors (273). More recently Campbell et al. (180) found that the cardioselective $beta_1$-adrenergic receptor agonist H 133/22 at doses that increased heart rate but did not affect blood pressure, increased PRA 8-fold in conscious rats (192).

Taken collectively, these results (180, 273, 816) indicate that $beta_1$-adrenergic receptors are involved in the control of renin release in rats, but a comprehensive study conducted in vitro by Capponi et al. (188) has clouded the issue. These investigators examined the ability of 15 beta-adrenergic receptor antagonists, over a dose range of 10^{-8} to 10^{-5} M, to alter isoproterenol (10^{-6} M) stimulated renin release from rat renal cortical slices. Metoprolol, acebutolol, labetalol, and *d*-propranolol had no effect on adrenergically stimulated renin release at any concentration whereas pindolol and bufuralol demonstrated some inhibitory activity at the highest drug concentration. Isoproterenol-induced renin release was completely blocked by *d,l*-propranolol, *l*-propranolol, alprenolol, and sotalol at concentrations between 5×10^{-6} M and 10^{-6} M, but the renin response to isoproterenol reappeared as the concentration of antagonist was increased. Finally, practolol, oxprenolol, timolol, nadolol, and atenolol caused a dose-related inhibition of beta-adrenergic receptor-mediated renin release. Interestingly, the inhibitory effects of these drugs could not be explained on the basis of $beta_1$- or $beta_2$-adrenergic receptor selectivity, intrinsic activity, or local anesthetic effects. Despite these findings of Capponi et al. (188), data obtained from experiments conducted in vivo are consistent with $beta_1$-receptor-mediated renin release in the rat (180, 660, 816).

Similar attempts have been made to assess the type of

beta-adrenergic receptor controlling renin release in humans (157, 253, 530, 971, 1210). Based on the observation that practolol blocked orthostasis-induced renin release in normal subjects, Salvetti et al. (971) first suggested that renin release was a $beta_1$-adrenergic receptor event in humans. Later, Buhler et al. (157) determined the activity of a group of beta-adrenergic receptor blockers on supine and exercise-induced renin release in normotensive humans. The cardioselective agents atenolol, bufuralol, practolol, and metoprolol; the nonselective antagonists LL/21945, oxprenolol, pindolol, propranolol, and timolol; and the combined alpha- and beta-adrenergic receptor blocker labetalol were administered in doses that caused an equal blockade of exercise-induced tachycardia. All of these drugs lowered stimulated PRA by 30% to 55%. With the exception of oxprenolol, pindolol, and labetalol, all of these beta-adrenergic receptor blockers also caused a significant suppression of supine PRA. After comparing the data, Buhler et al. (157) concluded that cardioselective beta-receptor antagonists with no intrinsic activity, such as atenolol, suppressed basal PRA best. The least inhibition of PRA under basal conditions occurred with nonselective beta-blockers that possessed a significant amount of intrinsic activity, such as pindolol.

The $beta_2$-adrenergic receptor agonist salbutamol also has been used to identify the type of beta-adrenergic receptors controlling renin release in humans (253, 530). Johnson et al. (530) chose doses of isoproterenol and salbutamol that elicited equal increments in systolic blood pressure, heart rate, and PRA and equal decrements in diastolic blood pressure in supine, normal subjects. The infusions of these beta-adrenergic receptor agonists were repeated after three days of treatment with practolol. The elevation of heart rate and PRA elicited by either agonist was blocked by practolol in a competitive fashion, as was the fall in diastolic blood pressure caused by isoproterenol. However, practolol did not prevent the decrement in diastolic blood pressure elicited by salbutamol. Davies et al. (253) also compared the effects of isoproterenol and salbutamol on PRA in normal, recumbent humans. The doses of isoproterenol and salbutamol used in these studies lowered MAP by 14% and elevated heart rate by 47 and 27 beats/min, respectively. Plasma renin activity was increased 80% by isoproterenol but salbutamol failed to alter PRA despite its equal hypotensive effect. Salbutamol is a partial agonist at renal beta-adrenergic receptors since this drug markedly attenuated isoproterenol-induced renin release in humans (1210). Metaproterenol, another beta-adrenergic receptor agonist with moderate selectivity for $beta_2$-adrenergic receptors, has been found to stimulate renin release in normal humans, and this stimulatory effect was prevented by pretreatment with propranolol (116, 728). However, the doses of metaproterenol used in these studies (116) were sufficient to increase heart rate indicating a considerable amount of $beta_1$-adrenergic receptor activation. Thus, studies (116, 253, 530, 728) with $beta_2$-adrenergic receptor agonists have given support to the belief that $beta_1$-adrenergic receptors mediate renin release in humans.

The only major objection to renin release being a $beta_1$-adrenergic receptor event in humans arose from the observation that atenolol (319) and metoprolol (16) did not lower PRC in hypertensive humans. However, in both cases (16, 319), PRC was determined by the method of Skinner et al. (1021), which measures "total plasma renin" after the activation of an inactive form of plasma renin (prorenin) by the dialysis of plasma at pH 3.3. Although plasma does contain an inactive form of renin, propranolol has been shown to suppress PRA without altering PRC (measured as "total plasma renin") (268). Likewise, metoprolol was observed to lower PRA by 80% in hypertensive patients even though PRC was unchanged (16). Therefore, the fact that atenolol (319) and metoprolol (16) did not lower PRC as measured by the method of Skinner et al. (1021) is not inconsistent with $beta_1$-adrenergic receptor mediation of renin release in humans.

In conclusion, beta-adrenergic receptor antagonists suppress basal renin release in animals and humans, and this inhibition appears to be due to the blockade of beta-adrenergic receptors located on the granular JG cells of the kidney. These drugs appear to have some effects on renal salt and water metabolism and RBF, but it is not known if these other pharmacologic actions contribute to their ability to suppress renin release. $Beta_2$-adrenergic receptors appear to mediate renin release in rabbits and cats whereas renin release in rats, dogs, and humans is subserved by $beta_1$-adrenergic receptors.

4. Phosphodiesterase inhibitors. Several investigators have attempted to determine the role of endogenous cyclic AMP in the control of renin release by using inhibitors of phosphodiesterase such as papaverine and theophylline. The idea was that by inhibiting the degradation of cyclic AMP to 5′-adenosine monophosphate, these drugs should elevate the concentration of cyclic AMP in the granular JG cells. Papaverine, which, as a phosphodiesterase inhibitor, has been reported to be 20 times more potent than theophylline (694), has been used to impair the actions of the renal baroreceptor in renin release experiments (350, 357, 405, 535, 1231, 1232). In 1971, the tentative location of the renal baroreceptor was determined to be at the level of the afferent arteriole since papaverine, which has been found to prevent renal autoregulation by dilatation of the renal afferent arterioles (1091), blocked hemorrhage-induced renin secretion from denervated, nonfiltering kidneys in anesthetized dogs (1231). Papaverine also decreased renin release in dogs with constriction of the thoracic segment of the vena cava (1232). Later, Johnson et al. (535) reported that the stimulation of renin secretion caused by an intrarenal arterial infusion of epinephrine into the nonfiltering kidneys of anesthetized dogs was prevented by papaverine. The renin secretion elicited by a similar infusion of norepinephrine or renal nerve stimulation was not affected by papaverine. Even though the increased

renin secretion that results from ureteral occlusion appears to result from the activation of the renal baroreceptor (304), papaverine did not alter the rise in renin secretion caused by ureteral obstruction in anesthetized dogs (357). Gotshall et al. (405) saw no change in renin secretion when papaverine was given directly into the kidneys of normal, anesthetized dogs.

On the other hand, several investigators (233, 368, 1231) have reported that an intrarenal arterial infusion of papaverine stimulated renin release. For example, both Witty et al. (1231) and Corsini and Bailie (233) noted that renin secretion doubled and RBF increased when papaverine was infused intrarenally into anesthetized dogs with a single nonfiltering denervated kidney. More recently, Gaal et al. (368) found that the intrarenal infusion of papaverine into anesthetized dogs resulted in a rapid 2.5-fold increase in renin secretion and a 22% rise in RBF. Blood pressure did not change. Sodium excretion increased by 55% despite the fact that GFR and the amount of filtered sodium were depressed by about 25%; therefore, the increase in sodium excretion probably resulted from the direct inhibition of sodium transported by papaverine (739). The stimulation of renin secretion by papaverine (368) no doubt represented the arithmetic summation of the positive and negative stimuli to renin release. The natriuresis caused by papaverine constitutes a negative stimulus to renin release as does the renal vasodilatation at a constant renal perfusion pressure. However, Gaal et al. (368) found that papaverine caused a concentration-related stimulation of renin release from canine renal cortical slices in vitro. In these experiments, papaverine (10^{-5} M) produced a 33% rise in renin release associated with an 80% increase in the cyclic AMP content of the tissue. Therefore, the increase in cyclic AMP within the granular JG cells appears to be responsible for the stimulation of renin release by papaverine in vivo, and this stimulus to renin release must override the inhibitory effect of increased salt transport at the macula densa. The possibility that papaverine inhibits ion transport at the macula also must be considered.

In passing, it should be mentioned that Fray (350) reported that "cumulative perfusate renin activity" was decreased in the isolated rat kidney perfused with 4×10^{-4} M papaverine. It was suggested that vasodilatation inhibited renin release by depolarizing the granular JG cells, but for various technical reasons (see the section on the renal baroreceptor mechanism), the exact significance of this finding is not easily discerned. In addition, Lyons and Churchill (682a) found that papaverine inhibited renin secretion from rat renal cortical cell suspensions in vitro.

The effects of theophylline on renin release have been characterized more thoroughly. Theophylline has been found to elevate renin release in normotensive humans (670, 1228, 1265) and normal-renin hypertensive patients (671, 1265); anesthetized dogs (13, 929, 1112), cats (527), and rabbits (671); and the isolated perfused kidneys of rats (882) and rabbits (1157).

Winer et al. (1228) observed a 3-fold increase in PRA and sodium excretion when theophylline was administered to normotensive humans. Mean arterial pressure did not change. Pretreatment with propranolol or phentolamine inhibited theophylline-induced renin release. In contrast, Zehner et al. (1265) noted that neither propranolol nor practolol, both of which suppressed basal PRA by 30%, altered the 3-fold increase in renal venous PRA elicited by the i.v. injection of theophylline into patients with essential hypertension.

In like fashion, Reid et al. (929) found that pretreatment with phenoxybenzamine or propranolol did not affect the 2-fold elevation of PRA caused by theophylline in anesthetized dogs. Treatment with theophylline did not alter MAP or the plasma levels of norepinephrine and epinephrine. These authors (929) suggested that although theophylline might stimulate renin release via its diuretic effect, a more likely explanation was the ability of the drug to increase the intracellular levels of cyclic AMP in the granular JG cells and thus mimic beta-adrenergic stimulation. In subsequent studies, the same group of investigators (805) discovered that theophylline alone did not stimulate the release of renin from rat renal cortical slices in vitro, but this agent did potentiate the release of renin caused by norepinephrine in this system. These findings were confirmed when other researchers (24) found that theophylline brought about a 3-fold enhancement of norepinephrine-induced renin release from rat renal cortical slices in vitro. The latter observations (24, 805) are consistent with the original hypothesis, formulated by Reid et al. (929), that theophylline, by inhibiting phosphodiesterases, increased the concentration of cyclic AMP in the granular JG cells and thereby potentiated beta-adrenergically mediated renin release. However, in the absence of measurements of renal cortical cyclic AMP levels after treatment with theophylline in vivo, the evidence for such a mechanism is only circumstantial.

Johns and Singer (527) measured the effect of theophylline on renin release in anesthetized cats with denervated kidneys. In the absence of adrenergic innervation to the kidney, theophylline did not alter PRA or RBF. Furthermore, pretreatment with theophylline did not affect furosemide-induced renin release in these animals. These observations (527), combined with those made with renal cortical slices in vitro (24, 805), support the idea that intact sympathetic renal innervation is required for theophylline to stimulate renin release.

On the other hand, theophylline has been demonstrated to elevate renin release from the isolated perfused kidneys of rats (882) and rabbits (1157). In the isolated perfused rat kidney, theophylline elicited a concentration-related increase in renin release that was not blocked by propranolol (882). The doubling of renin release in the

presence of theophylline was not accompanied by a change in perfusion pressure or flow. Peart et al. (882) pointed out that theophylline had been demonstrated to cause the release of norepinephrine from sympathetic nerve endings, but the negative results obtained with propranolol weighed against a role for the renal nerves in theophylline-induced renin release. A similar conclusion was reached by Viskoper et al. (1157). They noted that theophylline decreased renal vascular resistance by 40%, and increased renin release and urinary sodium excretion by 50% and 40%, respectively, in the isolated blood-perfused rabbit kidney. Propranolol did not alter the elevation of renin release brought about by theophylline. Furthermore, studies involving the administration of theophylline before and after ureteral occlusion supported the idea that theophylline stimulated renin release via the renal baroreceptor, whereas the concomitant natriuresis caused by theophylline exerted the opposite effect by increasing sodium transport to the macula densa. These studies (882, 1157) do not support the contention that the renal sympathetic nerves are necessary for theophylline to induce renin release.

In other pharmacologic studies, Oliw et al. (829) observed that an i.v. infusion of theophylline increased PRA by 3-fold in anesthetized rabbits. Sodium and potassium excretion, creatinine clearance, and the urinary clearance of cyclic AMP were elevated, but the concentration of cyclic AMP in the plasma did not change. Pretreatment with indomethacin did not attenuate the rise in PRA after theophylline but did lessen theophylline-induced saluresis. Although indomethacin depressed the renal clearance of cyclic AMP, theophylline enhanced the clearance of cyclic AMP to the same extent in the presence and absence of indomethacin. The data indicated that prostaglandins did not appear to mediate the increased release of renin caused by theophylline even though they might be concerned with the natriuretic action of the drug. Furthermore, the renal clearance of cyclic AMP was determined by changes in GFR rather than by the inhibition of phosphodiesterases. Lastly, Oliw et al. (829) pointed out that the rise in RBF seen after the administration of theophylline might result from the antagonism of the renal vasoconstrictor effects of endogenously generated adenosine (849).

Several questions concerning theophylline-induced renin release remain unanswered. Are the renin-releasing effects of theophylline demonstrable in the denervated nonfiltering kidney in situ? Does theophylline potentiate the renin release caused by direct stimulation of the renal nerves? Is there any relationship between the potency of different inhibitors of phosphodiesterase and their ability to stimulate renin release?

Caffeine, in a dose that increased plasma caffeine levels from 0 to 12 μg/ml, was observed to cause PRA to rise from 1.0 to 1.6 ng of AI/ml/hr in nine healthy supine individuals who were not taking any medication and who had abstained from coffee, tea, or chocolate for 21 days (938). In two subjects on a low sodium diet, the ingestion of caffeine raised PRA from 6 to 16 ng of AI/ml/hr. Robertson et al. (938) observed a 14 mm Hg rise in MAP, an increase in sodium excretion, a 2.5-fold increase in plasma epinephrine concentration, and a 1.8-fold increase in plasma norepinephrine levels in the volunteers ingesting a normal sodium diet. Thus, caffeine, like theophylline, stimulated renin release in humans, but caffeine-induced renin release may be secondary to the increase in plasma catecholamines.

The effects of inhibitors of phosphodiesterase, such as papaverine and theophylline, on renin release have been studied, but the results obtained with papaverine are not consistent. Papaverine has been reported to cause an increase, a decrease, and no change in PRA. However, papaverine did elicit renin release from canine renal cortical slices in vitro, and this stimulation was associated with a rise in the cellular content of cyclic AMP. Theophylline has been found to elevate PRA in humans and animals and in the isolated perfused kidneys of animals, but had no effect on renin release from renal cortical slices in vitro. Although some investigators believe that intact renal innervation is necessary for theophylline to increase renin release, propranolol does not inhibit theophylline-induced renin release. In addition, indomethacin did not affect the rise in PRA caused by theophylline. Theophylline appears to be a specific antagonist of the effects of adenosine in the kidney, but it is not known whether the ability of theophylline to stimulate renin release is related to the antagonism of the inhibitory action of adenosine, a direct effect on cyclic AMP levels in the granular JG cells, or the renal hemodynamic effects of the compound. Caffeine has been shown to elicit a modest increase in PRA in supine humans.

5. Other drugs that affect the sympathetic nervous system and endogenous catecholamines. A. RESERPINE. Reserpine is an alkaloid of natural origin that depletes both central and peripheral catecholamines and indoleamines by "poisoning" their storage granules in the neurons. The effects of reserpine on renin release have not been well characterized, but a few reports are available.

In 1961, Dunihue et al. (296) discovered that a single dose of reserpine prevented the usual increase in the granular JG cell index seen in rats after four days of salt restriction. In the ensuing years, reserpine was reported to cause an increase (37, 89, 865), no change (569, 733, 738), or a decrease (736, 1014) in PRA in experimental animals. The treatment of renal hypertensive dogs with reserpine for three days led to a 2.5-fold elevation of PRA in association with a 20% decrease in MAP (37). Palazzoadriano et al. (865) noted that either single or multiple doses of reserpine caused a modest (40% to 50%) increase in PRA in conscious, water-loaded rats. Propranolol did not prevent the increase in PRA caused by reserpine,

and the rise in PRA after reserpine was believed to result from the hypotension caused by the drug. However, the increase in PRA measured after single or multiple doses of reserpine was the same despite the fact that the change in systolic blood pressure after multiple doses (−28%) was much greater than that seen after a single dose (−3%).

When blood for the determination of PRA was drawn from rats after anesthesia with ether, single (569) and multiple (569, 733, 738) doses of reserpine did not alter PRA. In these studies, three to four days of therapy with reserpine lowered the norepinephrine content of the heart (738) and kidney (569) by 90% and 64%, respectively, but the concentration of epinephrine in the adrenal gland (738) was depressed by only 26%. In conscious rats, two doses of reserpine given over a 16-hr period reduced MAP and heart rate by 20% and 30%, respectively, but in one series of experiments (736) PRC decreased by 50% and in the other case (733) it was unchanged. Pretreatment of conscious rats with reserpine did potentiate the ability of isoproterenol to stimulate renin release and lower blood pressure (736) and blocked the ability of tyramine to inhibit renin release (865).

Silverman and Barajas (1014) found that PRA fell from 5.0 to 2.4 ng of AI/ml/hr in ether-anesthetized rats given reserpine 4 hr before sacrifice. Concomitantly, tissue renin content and the granular JG cell index increased 3-fold. At this time, all monoamine-specific fluorescence in the kidney had disappeared, and this disappearance coincided with the depletion (−81%) of the norepinephrine content of the kidney.

Thus, reserpine appears to be capable of decreasing the concentration of norepinephrine in the kidney (569, 1014) and lowering blood pressure (37, 733, 736, 865) in experimental animals, but no consistent pattern of change in renin release has been observed. The effects of reserpine on renin release are in need of further study.

B. GUANETHIDINE AND BRETYLIUM. Guanethidine and bretylium prevent the release of norepinephrine from peripheral sympathetic neurons but do not inhibit the release of catecholamines from the adrenal medulla (118). In addition, guanethidine also depletes catecholamine stores in peripheral sympathetic neurons. Both drugs block the neuronal uptake of catecholamines and thus produce supersensitivity toward circulating catecholamines (476). Multiple dose therapy with these sympathetic neuronal blocking agents leads to a decrease in blood pressure.

Guanethidine has been reported both to increase (542, 672, 736, 894) and decrease (569, 737) PRA in experimental animals and hypertensive humans. Meyer et al. (736) found that guanethidine increased PRC by 3.7- and 2-fold in conscious normal and adrenalectomized rats, respectively. Blood pressure was not altered by guanethidine in either group of animals, but a significant decrease in heart rate occurred. Guanethidine also potentiated the elevation of PRC caused by isoproterenol. The administration of guanethidine 24 hr before sacrifice, to deplete the neuronal levels of norepinephrine, and 2 hr prior to sacrifice, to "paralyze" the sympathetic neurons, resulted in a 25% increase in SRA in conscious, sodium-depleted rats (894).

When blood for the determination of PRA was obtained from rats after anesthesia with ether, guanethidine (569, 737) and bretylium (737) decreased PRA by 25% to 45%. A single dose of guanethidine depleted the renal stores of norepinephrine by 35% but did not cause a change in renal renin concentration (569). Guanethidine potentiated the renin release elicited by phentolamine, and bretylium accentuated the renin release caused by hydralazine. As a result, Meyer et al. (737) suggested that guanethidine and bretylium decreased PRA by preventing the release of norepinephrine from peripheral sympathetic neurons and potentiated the renin-releasing effects of phentolamine and hydralazine by enhancing the action of catecholamines released from the adrenal medulla. Guanethidine did not block the stimulation of renin release seen during renal ischemia in anesthetized rats (568).

In hypertensive patients treated chronically with guanethidine, renin release was stimulated (542, 672) in association with a decrease in the urinary excretion of norepinephrine (542). In one of these clinical studies (672), guanethidine was found to elevate PRA into the normal range in patients with low-renin hypertension, and this stimulation appeared to be related to the hypotensive action of the drug. The treatment of hypertensive patients with guanethidine has been noted to result in a large decrease in RPF and GFR in the standing position (934), and Lowder and Liddle (672) felt this may be the mechanism by which guanethidine stimulated renin release.

C. INHIBITORS OF NEURONAL CATECHOLAMINE UPTAKE. The effects of these agents on renin release have been studied very little. Meyer and Hertting (734) measured PRC in ether-anesthetized rats pretreated with cocaine, desipramine, and amitriptyline. These inhibitors of uptake$_1$ had no effect on basal PRC or the renin release caused by isoproterenol. However, as might be expected, these drugs did enhance the renin release elicited by phentolamine. The latter observation is consistent with the fact that phentolamine stimulates renin release by reflexly increasing the release of norepinephrine from the renal sympathetic nerves. Cocaine caused a 45% elevation of renin release from rat renal cortical slices in vitro (24), presumably by preventing the neuronal uptake of norepinephrine being released spontaneously by the tissue.

The effect of chronic therapy with the various tricyclic antidepressants on renin release in humans and experimental animals has not been studied.

D. 6-HYDROXYDOPAMINE. The neurotoxin 6-hydroxydopamine is taken up by the peripheral sympathetic neurons, which are then destroyed by an intracellular action of the compound. Because 6-hydroxydopamine is

frequently used to produce functional adrenergic denervation in cardiovascular studies, it is important to know how this agent affects renin release.

Meyer et al. (738) gave multiple i.v. doses of 6-hydroxydopamine to rats and found that cardiac norepinephrine stores were decreased by 84% whereas the concentration of epinephrine in the adrenal gland rose by 33%. Basal PRC, after ether anesthesia, was unchanged. The renin release elicited by isoproterenol was enhanced, but the rise in PRC caused by phentolamine was greatly reduced. Other investigators (569) found that the treatment of rats with 6-hydroxydopamine reduced the norepinephrine content of the heart by 88% but reduced the stores in the kidney by only 38%. Plasma renin activity and the renin content of the kidney were not changed after ether anesthesia and the renin release caused by renal ischemia was not prevented. When blood for the measurement of SRA was obtained from 6-hydroxydopamine-treated animals after decapitation, SRA was unchanged even though the norepinephrine concentration of the kidneys was decreased by 35% (T.K. Keeton, unpublished observations). The intracerebroventricular injection of 6-hydroxydopamine into young spontaneously hypertensive rats attenuated the development of high blood pressure and led to a 3-fold elevation of PRA (845).

Porlier et al. (913) administered 6-hydroxydopamine to conscious, normotensive dogs and noted that blood pressure decreased rapidly. This hypotension was accompanied by a 6-fold elevation of PRA and a 3-fold increase in plasma catecholamine levels. Plasma renin activity remained elevated for one week but had returned to the control levels, as had MAP, by the end of 2 weeks. The stimulation of renin release after 6-hydroxydopamine was thought to be the result of 1) a decrease in blood pressure, 2) an increase in the circulating levels of catecholamines, and/or 3) a decrease in the sodium load at the macula densa.

E. GANGLIONIC STIMULANTS. Dimethylphenylpiperazinium, given either i.v. or intrarenally, has been reported to increase renin release in anesthetized dogs (164). In urethane-anesthetized rats, Alexandre et al. (12) found that the pressor effects of physostigmine were accompanied by a rise in PRA. The beta-adrenergic antagonists propranolol, oxprenolol, and pindolol inhibited the increase in PRA but enhanced the hypertension caused by physostigmine. Conversely, phenoxybenzamine blocked the pressor effects of physostigmine but did not alter the ability of this drug to elevate PRA. Thus, the generalized increase in peripheral sympathetic nerve activity caused by physostigmine appeared to result in an increase in the stimulation of beta-adrenergic receptors located on the granular JG cells. In this particular case, it must be assumed that the stimulatory effect of nerve activity on renin release overrode the inhibitory effect on renin release of an increase in renal perfusion pressure.

6. Cholinergic antagonists. A. NICOTINIC ANTAGONISTS. Ganglionic-blocking drugs inhibit neurotransmission in the paravertebral ganglia by occupying nicotinic receptors. The changes in heart rate and blood pressure seen after these drugs have been administered are dependent on the preexisting state of sympathetic and cholinergic tone. In man, where vagal tone usually predominates, a mild tachycardia often accompanies ganglionic blockade (1163), but in the rat, where sympathetic tone predominates, a bradycardia is observed after ganglionic blockade (571). Similarly, the high incidence of orthostatic hypotension in humans treated with ganglionic blockers emphasizes the importance of existing sympathetic tone in determining the magnitude of the vasodepressor response (1163). Ganglionic blockade had been demonstrated to decrease the concentration of norepinephrine in the plasma of humans (538) and rats (930). Concerning the renal effects of ganglionic blockade, Murphy et al. (779) have shown that urine flow and RBF are maintained after the administration of hexamethonium to anesthetized dogs despite the fact that blood pressure decreased. In addition, pentolinium restored RBF to above control levels after renal vasoconstriction was induced reflexly by reducing carotid sinus pressure to 45 mm Hg in anesthetized dogs (885).

In 1967, Bozovic and Castenfors (123, 124) reported that pentolinium attenuated the rise in PRA induced by swimming exercise and pain in rats. This agent also significantly lessened the renin release elicited by hemorrhage, hydralazine, and hemorrhage plus hydralazine in anesthetized rats but had only a modest inhibitory effect on the elevation in PRA caused by bilateral carotid occlusion. When given to anesthetized rats, pentolinium itself caused PRA to double. In contrast, one group of investigators (593) reported that pentolinium decreased PRC as blood pressure was lowered in anesthetized rats. Pettinger et al. (890) found that chlorisondamine brought about a dose-related elevation of SRA in conscious rats that was not affected by pretreatment with propranolol. Chlorisondamine also increased SRA by 2-fold in sodium-depleted rats (894). Although pempidine did not alter PRC in anesthetized rats, Meyer et al. (736, 738) observed that trimethidinium elevated PRC by 3-fold in conscious rats, and phenylephrine prevented this effect of trimethidinium. The same investigators found that camphidonium elevated PRC by 2-fold in one group of anesthetized rats (731) but had no effect in another series of experiments (738). Chlorisondamine, given either i.p. or s.c., has been found to lower MAP in conscious rats, but PRA was increased only after the drug was given s.c. (W.B. Campbell, unpublished observations). However, differences in the route of injection cannot explain the disparate results obtained with camphidonium (731, 738).

In more recent studies designed to determine the mechanism by which ganglionic blockade stimulates renin release, Keeton and Pettinger (571) found, in conscious rats, that chlorisondamine increased SRA by 2-fold and decreased MAP and heart rate by 40% and 14%,

respectively. Since propranolol did not alter the renin-releasing effects of chlorisondamine, it was reasoned that the reduction in MAP caused by this drug activated renin release via the renal baroreceptor and/or the macula densa. To test the latter possibility, animals were treated with deoxycorticosterone acetate and saline drinking water for two days. Even though salt-loading lowered basal SRA by 90%, the ability of chlorisondamine to stimulate renin release was not blunted. In fact, the elevation of SRA by chlorisondamine after salt-loading was actually much greater than the percentage increase seen after chlorisondamine in states of normal sodium balance. In salt-loaded rats, chlorisondamine decreased MAP and heart rate by 30% and 11%, respectively. Based on these data, the authors concluded that chlorisondamine elevated renin release by the hypotensive activation of the renal baroreceptor. Chlorisondamine also was found to inhibit by 72% the rise in SRA induced by phentolamine.

Prostaglandins appear to play an important role in chlorisondamine-induced renin release. Campbell et al. (180) discovered that the 2.7-fold increase in SRA seen after s.c. administration of chlorisondamine to conscious rats was completely blocked by a dose of indomethacin that prevented arachidonate-induced hypotension and markedly suppressed the urinary excretion of PGE_2 and $PGF_{2\alpha}$. The hypotension and bradycardia caused by chlorisondamine was not affected by indomethacin.

When MAP was lowered from 140 to 65 mm Hg with trimethaphan in conscious renal hypertensive dogs, PRA increased 3-fold (37). Lifschitz and Horwitz (658) noted that PRA increased by 60% when the blood pressure of conscious dogs was lowered by 17 to 37 mm Hg with pentolinium. Conversely, an earlier report (1238) indicated that pentolinium decreased blood pressure in normal dogs and dogs with coarctation of the aorta, but PRA did not change. Nolan and Reid (803) observed that PRA fell by 55% when renal perfusion pressure was held constant during pentolinium-induced hypotension in anesthetized dogs. They believed that this fall in PRA was due to the decrease in renal sympathetic tone that ensued after ganglionic blockade and that this decrease in PRA was usually masked by the stimulation of renin release by hypotensive activation of the renal baroreceptor. Ganglionic blockade also prevented the renin release precipitated by hemorrhage in anesthetized dogs (164).

In hypertensive patients, pentolinium (509, 538) and trimethaphan (259, 768) decreased blood pressure by 20 to 25 mm Hg but did not change PRA. In one of these studies (538), plasma norepinephrine content decreased by 32% after pentolinium. It is conceivable that in humans the decrement in renin release that occurred after decreasing sympathetic nerve activity was counterbalanced by the stimulation of renin release by the renal baroreceptor. Kaneko et al. (554) found that the increase in PRA and decrease in RBF caused by the administration of a hypotensive dose of sodium nitroprusside to normotensive and hypertensive humans was prevented by either pentolinium or trimethaphan.

B. MUSCARINIC ANTAGONISTS. Very little information is available about the effects of muscarinic antagonists on renin release. Atropine has been reported to cause a 2-fold increase in PRA in conscious rats, but the mechanism of this release is unknown (894). Clonidine reversed the ability of atropine to elevate PRA.

C. *Cardiac Glycosides*

Despite the widespread use of cardiac glycosides in the treatment of congestive heart failure in humans, little is known of the effects of this class of drugs on renin release. In a brief report published in 1976, Antonello et al. (23) reported that PRA decreased by 50% within 30 min after the i.v. injection of digoxin into supine hypertensive patients. Plasma renin activity remained suppressed by 40% for up to 3 hr and then slowly increased during the next 2-hr period. The inhibition of renin release was related to the plasma concentration of digoxin. In a more recent brief report (330) from the same laboratory, the rise in PRA brought about by the administration of a single oral dose of furosemide to hypertensive patients was greatly attenuated by the subsequent administration of digoxin. The inhibitory effect of digoxin developed rapidly, when the concentration of digoxin in the plasma was still quite low, and was thought to be related to the concentration of digoxin in the tubular urine. An intrarenal infusion of ouabain has also been demonstrated to prevent furosemide-stimulated renin secretion in conscious sheep (99). Pretreatment of the patients with the beta-adrenergic antagonist oxprenolol partially blocked furosemide-induced renin release, but digoxin was not able to prevent the residual response to furosemide (330). As pointed out by Ferrari (330), the digitalis glycoside could affect renin release by inhibiting ion transport (presumably at the granular JG cells or the macula densa), causing hemodynamic changes or exerting an antiadrenergic effect. The last mechanism was favored because of the data obtained with oxprenolol and furosemide.

The idea that cardiac glycosides inhibit renin release by altering sympathetic neurotransmission is supported by data obtained in experimental animals (727, 1082). For example, both digitoxin and acetyldigitoxin reduced the cardiac chronotrophic response to sympathetic nerve stimulation and epinephrine in anesthetized dogs with denervated hearts (7). Thames (1082) demonstrated that the intracoronary injection or epicardial application of acetylstrophanthidin caused a reflex reduction in renal sympathetic nerve activity via cardiac receptors with vagal afferent fibers. Decrements in renal nerve activity were evoked by small doses of acetylstrophanthidin that did not reflexly lower MAP or heart rate. It was also mentioned that an intracoronary injection of ouabain caused a bradycardia, hypotension, and a decrease in renin release, but this effect of ouabain on renin release was not studied systematically. In addition, the reflex, hemodynamic responses to acetylstrophanthidin were

similar to those observed after the intracoronary injection of the veratrum alkaloid cryptenamine (1081). Cryptenamine also lowered heart rate, blood pressure, and renin secretion in anesthetized dogs by the activation of ventricular receptors with vagal afferents. These similar effects of digitalis and veratrum alkaloids, as pointed out by Thames (1082), may result from the marked structural similarities between the two classes of compounds. There is evidence to support the belief that the renal nerves are responsible for the renal vasoconstriction (57) and augmented renin release (1179) seen in congestive heart failure, and cardiac receptors with vagal afferent fibers may have a reduced sensitivity in heart failure. This being the case, Thames (1082) suggested that the effect of digitalis on renin release would be greatest in congestive heart failure since basal renal nerve activity would be high and basal cardiac receptor stimulation would be low. In this respect, the relative ability of cardiac glycosides to inhibit renin release in normal humans and patients with congestive heart failure needs to be determined.

Ouabain did not affect basal renin release in anesthetized dogs (218) or conscious sheep (99), but the intrarenal infusion of ouabain did block the rise in renin secretion caused by ureteral occlusion or a decrease in renal perfusion pressure (218). Because ouabain was known to increase the intracellular concentration of sodium ion (703), it was concluded that ouabain inhibited the stimulation of renin release caused by these two interventions by increasing the intracellular concentration of sodium in the cells of the macula densa. This conclusion gained support from the observation that renin release from rat renal cortical slices in vitro did appear to be inversely related to the intracellular concentration of sodium (680). Renin release from the slices was directly related to the sodium concentration of the medium; however, when the normal extrusion of sodium from the cells was impaired by inhibiting sodium-potassium ATPase with ouabain, renin release was inversely related to the sodium content of the medium (680).

A slightly different ionic mechanism of action was suggested to account for the blockade by ouabain of furosemide-induced renin release in conscious sheep (99). Furosemide had been determined to stimulate renin release by an action at the macula densa in conscious, papaverine-treated sheep (96). Presumably, furosemide decreased the transport of chloride into the macula densa, thus enhancing renin release, and ouabain blocked this action by depolarizing the macula densa cells and allowing the passive redistribution of chloride into these cells. However, it should be pointed out that ouabain did not change the magnitude or the duration of the renin release that followed the addition of ethacrynic acid to isolated, superfused rat glomeruli (64). Ouabain did not affect the basal release of renin from isolated, superfused rat glomeruli (64) or renal cortical cell suspensions in vitro (681), but did suppress renin release from renal cortical slices in vitro (213a, 873). The suppression of renin release in the latter case was shown to be dependent on the presence of extracellular calcium.

D. Diuretics

The scientific literature concerning the effects of diuretic agents on renin release, like that concerning renin release in general, is almost overwhelming. We have already noted that changes in sodium (and possibly chloride) transport within the renal tubule have a profound effect on renin release, and, as would be expected from this observation, diuretic drugs have the ability to alter renin release. In general, diuretic drugs increase renin release because they decrease plasma volume and thus activation of the renal baroreceptor and sympathetic nervous system mechanisms controlling renin release. After prolonged treatment with diuretics, the depletion of total body sodium leads to activation of the macula densa. It is also possible for diuretic agents to cause an immediate increase in renin release by inhibiting sodium and/or chloride transport at the macula densa, by direct activation of the renal baroreceptor, by altering renal sympathetic nerve traffic, or by a direct effect on the granular JG cells. Therefore, we must try to distinguish between the direct effects of the drugs on renin release and their indirect effects on renin release that are mediated via changes in salt and water balance.

1. Furosemide, ethacrynic acid, and bumetanide. Furosemide and ethacrynic acid, which were introduced for clinical use in the mid-1960s, and the more recently developed drug bumetanide, are powerful natriuretic and diuretic drugs that are commonly referred to as "loop" or "high-ceiling" diuretics. Furosemide has been demonstrated to increase renin release in anesthetized rabbits (740, 510, 830), anesthetized cats (527, 1040), anesthetized dogs (44–46, 72, 235, 294, 373, 516, 518, 787, 847, 1082a, 1120), conscious dogs (75), anesthetized rats (171, 451, 955, 1063, 1240, 1241), conscious rats (539, 637, 864), and conscious sheep (96, 99). Ethacrynic acid has been shown to increase renin release in anesthetized (230, 303, 357, 516) and conscious (1042) dogs while bumetanide increased renin release in both anesthetized (516) and conscious dogs (835) and in rats (796). Both ethacrynic acid (391) and bumetanide have (834) low diuretic potency in the rat, and, as a result, the ability of these two drugs to alter renin release in this species has not been studied extensively. All three agents significantly increase PRA in humans (vide infra).

The elevation of PRA elicited by these "loop" diuretics, furosemide in particular, is of great interest for three reasons. First, furosemide enjoys widespread use in clinical medicine, and this drug can cause iatrogenic changes in renin and aldosterone secretion. Secondly, furosemide is used diagnostically to determine renin responsiveness for the classification of patients with low-renin hypertension (556). Lastly, furosemide alters renin release by several different mechanisms that appear to be preferentially activated as a function of the dose and time after administration of furosemide.

The renal effects of furosemide (1219), ethacrynic acid (1219), and bumetanide (834) have been reviewed recently, but their actions on ion transport and RBF are of more immediate importance in our discussion since these actions can affect renin release. In 1973, Burg and Green (168) and Rocha and Kokko (943) presented firm evidence for the active transport of chloride, rather than sodium, in the medullary and cortical segments of the thick ascending limb of the loop of Henle. Sodium reabsorption in this segment of the renal tubule appears to occur passively. Subsequently, it was demonstrated that both furosemide (169) and ethacrynic acid (167) inhibit active chloride transport, and thus sodium reabsorption, in the ascending limb of Henle's loop. Because the cellular effects of bumetanide in this region of the renal tubule are very similar to those of furosemide (512), it is probable that bumetanide also inhibits active chloride transport in the ascending limb of Henle's loop. In addition, tubuloglomerular feedback of urine flow rate in the early proximal tubule in the rat is critically dependent on chloride transport across the macula densa cells, and this feedback is blocked by furosemide (989). Wright and Schnermann (1235) have found that ethacrynic acid failed to alter tubuloglomerular feedback in rat nephrons, but this drug is also relatively ineffective in inhibiting chloride transport in the loop of Henle in this species. Therefore, it is tempting to speculate that all "loop" diuretics will inhibit chloride transport at the macule densa if they have the ability to inhibit chloride transport in the loop of Henle. In this respect, it is of interest to note that the cells of the macula densa are morphologically similar to the epithelial cells of the thick ascending limb of Henle's loop (1236).

It is also important to realize that furosemide, ethacrynic acid, and bumetanide have direct effects on RBF that are not related to their diuretic activity. Soon after furosemide and ethacrynic acid were introduced, it was learned that these drugs increased renal cortical blood flow and decreased flow in the juxtamedullary cortex and outer renal medulla (93). Many investigators have noted that furosemide (44, 46, 75, 93, 235, 294, 491, 501, 675, 740, 787, 1120), ethacrynic acid (284, 303, 357, 501, 1222), and bumetanide (832, 834, 835) increased total RBF in several species of animals by lowering renal vascular resistance. In fact, Dluhy et al. (284) have suggested that renal vasodilatation might be a characteristic effect of diuretic agents that act at the loop of Henle. It should also be pointed out that furosemide (294) and ethacrynic acid (284, 303) have been shown to block the autoregulation of RBF in the canine kidney; however, the effect is short-lived. Bailie et al. (46) originally suggested that the increment in RBF caused by furosemide in anesthetized dogs was due either to a direct effect on the renal vasculature or was a consequence of the increase in intratubular pressure that accompanies high rates of urine flow. However, Corsini et al. (235) noted that furosemide elevated RBF in anesthetized dogs with a single nonfiltering kidney. Since urine was not being produced in these kidneys, furosemide-induced vasodilatation would appear to result from a direct effect of the drug rather than the increase in intratubular pressure accompanying diuresis. At about this same time, Williamson et al. (1220, 1221) discovered that indomethacin prevented the 25% increase in RBF caused by a small dose (0.2 mg/kg) of furosemide but did not significantly affect the natriuretic and diuretic activity of this drug in the anesthetized dog. Since the renal venous concentration of PGE, but not PGA or PGF, was elevated by this dose of furosemide, and since indomethacin also prevented the increase in PGE production, they hypothesized that furosemide-induced vasodilatation was mediated by PGE. Bailie et al. (44) found that indomethacin blocked the renal vasodilatation caused by a large dose (5 mg/kg) of furosemide in anesthetized dogs, and similar results have been reported by other investigators (247, 294). Subsequently, indomethacin was observed to prevent the renal vasodilatation elicited by ethacrynic acid (1222) and bumetanide (832) in anesthetized dogs.

Researchers have noted that the increase in RBF precipitated by treatment with furosemide depends on the initial status of renal vascular resistance (303, 675, 1040). For example, furosemide has been shown to elevate RBF to a greater extent in anesthetized, laparotomized dogs than in conscious dogs (676, 1273). Likewise, the effect of indomethacin on RBF varies with the animal preparation employed. For example, Terragno et al. (1080) found that a significant portion of RBF in surgically stressed dogs, unlike RBF in conscious or anesthetized dogs, was maintained by the production of a vasodilatory prostaglandin. Along these same lines, Olsen and Ahnfelt-Ronne (835) found that bumetanide elevated the renal production of PGE in conscious dogs but Neilson and Arrigoni-Martelli (796) failed to do so in anesthetized, laparotomized dogs. In both cases (796, 835) indomethacin prevented the increase in RBF elicited by bumetanide. Therefore, the effects of "loop" diuretics and indomethacin on RBF and renal prostaglandin production are partially dependent on the absence or presence of anesthesia and/or surgical stress.

Even though PGE has been implicated as the mediator of the renal vasodilatation caused by furosemide (1221), ethacrynic acid (1222), and bumetanide (796), the possibility that another vasodilatory prostaglandin might mediate the response cannot be discounted. For example, furosemide reduced renal vascular resistance in the isolated perfused rat kidney, a model in which PGE_2 increased renal vascular resistance; however, as in other systems, furosemide-induced vasodilatation was blocked by indomethacin (765). It is tempting to speculate that the renal vasodilatation elicited by "loop" diuretics is due to the increased production of PGI_2 within the renal vasculature. On the other hand, Olsen and Ahnfelt-

Ronne (835) have suggested that the elevation of RBF observed in conscious dogs after the injection of bumetanide may result from an increase in activity of the kallikrein-kinin system. In this case, bumetanide also increased the urinary concentration of PGE, but PGE production had returned to normal at a time when RBF was still augmented; therefore, the time course of the increase in RBF correlated more closely with the time course of increased kallikrein excretion. Indomethacin attenuated the increase in urinary kallikrein excretion as it blocked the elevation of RBF brought about by bumetanide (835). Olsen (832) also reiterated the suggestion (46) that the increase in urine flow induced by "loop" diuretics may be the cause of the afferent arteriolar vasodilatation. In addition, the 2- to 4-fold elevation of renal capsular pressure caused by these diuretic agents (832) will result in a mechanical rise in interstitial pressure that can itself activate the synthesis of prostaglandins (834).

In conclusion, the exact mechanism by which furosemide, ethacrynic acid, and bumetanide elevate RBF cannot be stated with certainty, but it appears that this hemodynamic effect is mediated via prostaglandins, the kallikrein-kinin system, an increase in proximal tubular pressure, or some combination of these factors. It is generally agreed that inhibitors of prostaglandin synthetase will prevent the increment in RBF elicited by these drugs.

In the years since Fraser et al. (349) and Laragh et al. (631) first noted that furosemide increased PRA in humans, several different mechanisms have been proposed to account for this effect of furosemide. Despite the concerted efforts of many groups of investigators, the exact mechanism(s) by which furosemide elevates renin release is still a subject of controversy and confusion. Meyer et al. (740) found that furosemide caused a 3- to 5-fold increment in PRA in anesthetized rabbits with a single kidney. Expansion of the extracellular fluid volume with isotonic saline or albumin partially prevented the rise in PRA caused by furosemide, and these investigators concluded that furosemide stimulated renin release by an intrarenal mechanism, either by increasing the sodium concentration of the tubular urine in the area of the macula densa or by inhibiting sodium transport at the macula densa. It should be remembered that these studies were performed at a time when there was a controversy as to whether an increase or decrease in sodium transport at the macula densa stimulated renin release. Meyer et al. (740), like earlier researchers (93), noted that furosemide caused a 25% to 30% increase in RBF that was thought to be due to a direct action of furosemide on the renal vasculature.

Vander and Carlson (1120) determined that small doses of furosemide (0.1 mg/kg), in anesthetized dogs, caused a significant natriuresis without altering renin release whereas larger doses (0.5 to 2.5 mg/kg) caused an immediate increase in renal venous PRA. However, if sodium depletion was allowed to occur after a small dose of furosemide, renin release was eventually increased but could be returned to control values if the salt and water losses were restored. Renin release elicited by the larger doses of furosemide was not affected by the replacement of salt and water losses and was thought to be due to furosemide-mediated inhibition of sodium transport at the macula densa cells. Cooke et al. (230) came to a similar conclusion when they observed that the elevation of renal venous PRA caused by ethacrynic acid in anesthetized dogs was not due to a decrement in plasma volume. Other researchers have presented data to indicate that ethacrynic acid blocks the chemoreceptor function of the macula densa cells (357). Thus, ethacrynic acid, like furosemide, appeared to have a direct effect on renin release that might involve the macula densa. Imbs et al. (516) found that furosemide (20 mg/kg) caused a biphasic elevation of renin secretion from the denervated kidneys of anesthesized dogs. Renin secretion increased 12-fold at 15 min, returned to near control values at 1 hr, and then rose to 13 times the control levels during the 3- to 5-hr period after the i.v. injection of furosemide. In agreement with Vander and Carlson (1120), Imbs et al. (516) found that the prevention of salt and water losses, effected by an anastomosis of the ureter with the iliac vein, did not block the immediate stimulatory effect of furosemide on renin secretion. However, this intervention did prevent the secondary rise in renin secretion normally observed 3 to 5 hr after furosemide. Lastly, volume expansion with an i.v. infusion of saline did not prevent furosemide-induced renin release in anesthetized rats (115).

At this time, many researchers began to combine both physiologic and pharmacologic interventions in an attempt to discern the mechanism(s) by which furosemide stimulated the release of renin. Ganong (373) found that furosemide (5 mg/kg) elicited a 2-fold elevation of PRA in anesthetized dogs with the peak increase occurring at 15 to 30 min. This increased renin release did not appear to involve volume depletion since the excreted urine was infused into the venous circulation, and the elevation of PRA had completely subsided by 120 min after injection. Pretreatment with propranolol failed to change the magnitude or the time course of furosemide-induced renin release. Although phenoxybenzamine elevated basal renin release, furosemide still produced an additional increment in PRA. Johns and Singer (527) found that furosemide (2.5 mg/kg) elicited a 3-fold increase in PRA in anesthetized cats with denervated kidneys. Although propranolol suppressed basal renin release by 60%, it did not affect the increase in PRA caused by furosemide. In addition, the phophodiesterase inhibitor theophylline did not alter furosemide-induced renin release; therefore, they concluded that furosemide did not elevate renin release by a cyclic AMP-dependent mechanism. The

latter observation is consistent with the finding that the adenylate cyclase system does not seem to be involved in the diuretic action of furosemide in the rat (850). Consistent with earlier reports, Iacobelli et al. (510) noted that oxprenolol did not affect the magnitude or the chronology of the renin release elicited by furosemide (10 mg/kg) in conscious rabbits.

On the other hand, Corsini et al. (235) and Osborn et al. (847) noted that *d*- and *d,l*-propranolol were able to prevent the increase in renin secretion caused by furosemide (5 mg/kg) in the nonfiltering kidney, but not in the filtering kidney, of the anesthetized dog. The lack of an effect of propranolol on furosemide-induced renin release in the filtering kidney is consistent with earlier observations (373, 527). Of great interest was the fact that furosemide did not vasodilate either the filtering or nonfiltering kidney in the presence of *d*- or *d,l*-propranolol (235, 847). Thus, the ability of furosemide to elicit renin release in the filtering kidney in the presence of propranolol appeared to be due to the presence of the macula densa control mechanism, and propranolol seemed to prevent the stimulation of renin release from the nonfiltering kidney by blocking the vascular effects of furosemide. Whereas *d*-propranolol lowered the basal rate of renin secretion in both the filtering and nonfiltering kidney, lidocaine had no consistent effect on basal renin secretion but did impair furosemide-induced renin secretion in the nonfiltering kidney. In addition, either *d*- or *d,l*-propranolol prevented the elevation of renin secretion elicited by furosemide in the denervated, nonfiltering kidney. Thus, the ability of propranolol to mitigate the increase in renin secretion that follows treatment of the nonfiltering canine kidney with furosemide appeared to be due in part to the membrane-stabilizing effects of propranolol. Furthermore, this dose (5 mg/kg) of furosemide stimulated renin secretion by an action on both the renal baroreceptor and the macula densa (235, 847). Consistent with these conclusions, Imbs et al. (516) discovered that propranolol or ureterovenous anastomosis prevented the late, but not the early, rise in renin secretion that follows the injection of furosemide (5 mg/kg) into anesthetized dogs with denervated kidneys. The early stimulation by furosemide was probably due to an action at the macula densa whereas the stimulation at later times was due to activation of the renal baroreceptor, by volume depletion, and thus was blocked by propranolol or volume repletion (516). Propranolol also has been shown to prevent furosemide-induced renin release in saline-expanded, anesthetized rats (115).

Since propranolol appears to antagonize the vascular effects of furosemide, it cannot be used to determine whether a component of furosemide-induced renin release is mediated by the sympathetic nervous system. However, this problem can be circumvented by observing the effect of furosemide on renin release in the presence and absence of the renal sympathetic nerves. Naughton et al. (787) studied the effects of small doses (0.05 to 0.10 mg/kg/hr) and large doses (0.5 to 2 mg/kg/hr) of furosemide on renin secretion in anesthetized dogs with a single innervated or devervated kidney. In dogs with innervated kidneys, small doses of furosemide slowly elevated renin secretion if salt and water losses were not replaced; however, large doses of furosemide caused an immediate 3-fold increase in renin secretion even when salt and water losses were replaced. Large, but not small, doses of furosemide also lowered renal vascular resistance. Renal denervation decreased basal renin secretion by 90%, caused a 3-fold increase in sodium excretion, and decreased renal vascular resistance by 33%. More importantly, denervation greatly impaired the renin secretion caused by furosemide even when a large volume deficit was allowed to occur. Likewise, when renin secretion was stimulated from innervated kidneys for 1 hr by the infusion of a large dose of furosemide (in the absence of volume depletion), renal denervation led to a drop in the rate of renin secretion. It was concluded that renal neurogenic tone was a necessary factor for the increase in renin secretion seen during the early phase of volume depletion caused by a low dose of furosemide that did not have an effect on the renal vasculature or the macula densa. Similarly, neurogenic tone was thought to be a necessary factor for the release of renin by a large dose of furosemide in the absence of volume depletion (787).

Stella and Zanchetti (1040) also examined the effects of renal denervation on small (0.75 mg/kg) and large doses (6 mg/kg) of furosemide infused into anesthetized cats. In each animal, one kidney was denervated and the innervation of the other kidney was left intact, and the change in renin secretion was measured 30 min after drug treatment. Injection of the small dose of furosemide caused a 3.5-fold elevation of renin secretion from the innervated kidney with no significant change (1.6-fold increase) occurring in the denervated kidney. However, the large dose of furosemide increased renin secretion to the same extent in both the innervated and denervated kidney. None of these responses was affected by adrenalectomy. Therefore, the immediate stimulatory effect of furosemide appeared to have a neural component at small doses but was independent of the renal nerves at large doses. Since the larger dose of furosemide used by Naughton et al. (787) did not exceed the smaller dose used by Stella and Zanchetti (1040), the observations made in these two studies are in agreement. Stella and Zanchetti (1040) proposed that renal nerve activity may be stimulated indirectly by furosemide. Furosemide has been shown to increase venous capacitance (280), and the subsequent decrement in venous return to the heart would decrease nerve activity in the vagal afferent fibers arising from the low pressure volume receptors in the cardiopulmonary region. A lack of activation of these vagal afferents would then lead to an increase in renal nerve traffic. Of course, a similar neural activation would occur with larger doses of furosemide, but denervation would have no effect in this case because these larger

doses of furosemide increased renin secretion by other nonneural mechanisms. Imbs et al. (516) also have shown that furosemide (5 mg/kg), ethacrynic acid (5 mg/kg), and bumetanide (0.25 mg/kg) elicited a 6- to 11-fold increase in renin secretion from the denervated kidneys of anesthetized dogs.

More recently, Thames and DiBona (1082a) determined the effect of a low frequency of stimulation of the renal sympathetic nerves on renin secretion in the presence and absence of furosemide. When a small dose of furosemide (1 mg/kg by bolus followed by 0.017 mg/kg/min) was infused i.v. into anesthetized dogs, renin secretion increased 4.8-fold. Although the stimulation of the renal nerves at 0.25 Hz did not affect renin secretion or RBF, it did potentiate (16.4-fold increase) the elevation of renin secretion caused by the simultaneous administration of furosemide. Consistent with the previous report of Stella and Zanchetti (1040), these investigators (1082a) found that this dose of furosemide elicited a greater rise in renin secretion from innervated kidneys as compared to denervated kidneys. Based on these data, Thames and DiBona (1082a) concluded that a very low level of renal nerve activity, which by itself had no effect on renin secretion, augmented the renin release mediated by nonneural mechanisms.

Considerable evidence supports the idea that "loop" diuretics increase renin release by activating the renal baroreceptor mechanism. For example, these drugs elicit renal vasodilatation and renin secretion in the denervated, nonfiltering canine kidney, an action that suggests a vascular mechanism (847). If "loop" diuretics do indeed elevate renin release through vasodilatation, then prior dilatation of the renal vasculature should decrease the ability of these agents to elicit renin release. In this respect, prior dilatation of the nonfiltering kidneys of anesthetized dogs with an intrarenal arterial infusion of acetylcholine or papaverine prevented the increase in renin secretion and RBF usually observed after furosemide (5 mg/kg) (235). However, furosemide still stimulated renin secretion from the acetylcholine-dilated, filtering kidney via a macula densa mechanism (235). Eide et al. (303) studied the effects of ethacrynic acid (3 mg/kg) on renin secretion from anesthetized dogs with denervated kidneys. Fluid losses were constantly replaced with isotonic saline and the animals were given propranolol. Ethacrynic acid alone brought about a 54% increase in RBF and a 20-fold stimulation of renin secretion. If renal perfusion was lowered from 136 to 62 mm Hg, i.e. below the autoregulatory range, renin secretion increased 10-fold as renal vascular resistance decreased. The administration of ethacrynic acid at this point caused no further increment in renin secretion or decrement in renal vascular resistance. Therefore, ethacrynic acid was thought to stimulate renin secretion by a vascular action involving afferent arteriolar vasodilatation. This conclusion is in accord with the experiments of Freeman et al. (357), who noted that ethacrynic acid failed to elicit any further renin secretion during ureteral occlusion, a maneuver that also causes afferent arteriolar dilatation. It is interesting to note that propranolol did not block the renal vasodilatation caused by ethacrynic acid (303) whereas it did prevent the renal vasodilatation caused by furosemide (235, 847).

Blaine (96), with the same approach in conscious sheep during volume repletion, noted that furosemide (1 mg/kg) still elevated renin secretion 3-fold after vasodilatation of the kidney with an intrarenal arterial infusion of papaverine. Unfortunately, these experiments shed little light on the vascular action of furosemide since furosemide was able to stimulate renin secretion by either the macula densa or the sympathetic nervous system. Somewhat related to the vascular effects of furosemide on renin release, Lauterwein et al. (637) discovered that the vasoconstrictor agents AII, octapressin, and phenylephrine abolished the renin release caused by furosemide (10 mg/kg) in anesthetized rats.

Since "loop" diuretics, under certain experimental circumstances, can be shown to stimulate renin release by what appears to be a renal vascular mechanism, the question arises as to which inputs to the renal baroreceptor are altered. For instance, if the renal vasculature is dilated, i.e. r_i and r_o are increased, at a constant renal perfusion pressure, then circumferential stress would be increased and renin release would be inhibited. However, if renal interstitial pressure is elevated sufficiently by the "loop" diuretics (590, 617), both circumferential stress and the transmural pressure gradient would decrease in spite of the vasodilatation and renin release would be increased. Furthermore, bumetanide has been shown to elevate renal subcapsular pressure 3- to 4-fold in anesthetized dogs (832, 834), and, since the renal capsule is relatively inelastic, renal interstitial pressure also would rise (460, 834). With the formula for circumferential stress and the values of P_i, P_o, r_i, and r_o mentioned in the section on the renal baroreceptor, it can be calculated that an increase in interstitial pressure (P_o) from 5 to 25 mm Hg would result in a significant drop in circumferential stress even if the afferent arteriole was maximally dilated and renal perfusion pressure remained constant.

Prostaglandins also may be involved in the stimulation of renin release by "loop" diuretics. Bailie et al. (45) reported that indomethacin or meclofenamate prevented the rise in renin secretion caused by furosemide (0.1, 1.0, 4.0, or 7.0 mg/kg) in anesthetized dogs. Although pretreatment with indomethacin failed to alter the natriuretic or diuretic effects of furosemide (45), indomethacin suppressed basal renin secretion by 70% to 80% (44, 45 and blocked the vasodilatatory effects of furosemide (44). As would be expected, indomethacin suppressed renal PGE production to undetectable levels. Bailie et al. concluded that indomethacin antagonized furosemide-induced renin secretion at both the vascular and macula densa sites and that both control mechanisms might be modified by prostaglandins. Recently, Noordewier et al.

(806) found that the prostaglandin inhibitor tolmetin also prevented furosemide-induced renin release in anesthetized dogs.

Indomethacin also partially blocked the increase in renal venous PRA caused by furosemide (5 mg/kg) in anesthetized rabbits receiving fluid replacement (830). However, unlike previous studies in dogs (45, 1220), inhibition of prostaglandin synthesis with indomethacin severely reduced the natriuretic and diuretic effects of furosemide (830). Olsen and Ahnfelt-Ronne (835) have noted that indomethacin attenuated the absolute increase in urinary volume elicited by bumetanide in conscious dogs. In these studies, bumetanide (0.25 mg/kg) elevated PRA by 7-fold, RBF by 25%, urinary PGE concentration 3-fold, and urinary kallikrein excretion by 8-fold; all of these changes were prevented by pretreatment with indomethacin. As a result, it was suggested that activation of the intrarenal prostaglandin or kinin systems, rather than the macula densa, mediated the increase in renin release brought about by bumetanide. However, fluid losses were not replaced, and the partial inhibition of bumetanide-induced diuresis by indomethacin may have prevented activation of the low-pressure cardiopulmonary receptors that alter renal nerve traffic. Since careful examination of the data reveals that inhibition of prostaglandin synthesis depressed RBF, salt excretion, and urinary volume in anesthetized animals (45, 75, 324, 510, 1064, 1080), but not in conscious animals, (75, 835, 1064), the ability of nonsteroidal antiinflammatory drugs to alter the effects of "loop" diuretics on salt and water excretion appears to depend not only on a species difference but also on the experimental protocol. For these reasons, the experimental protocol must be considered when investigators invoke the hypothesis that indomethacin may prevent furosemide-induced renin release by altering the effects of furosemide on salt excretion or the chemoreceptor function of the macula densa.

If "loop" diuretics do indeed stimulate renin release by increasing the production of prostaglandins within the kidney, which prostaglandins are involved and how do they alter renin release? As mentioned in the section on prostaglandins, PGE_2, PGD_2, and PGI_2 elicit renin release and increase RBF in the absence of a change in salt or water excretion. These prostaglandins appear to elevate renin release by activation of the renal baroreceptor and/or by a direct effect on the granular JG cells. These prostaglandins, like the "loop" diuretics, may activate the renal baroreceptor by decreasing the transmural pressure gradient or circumferential stress at the afferent arteriole and may mediate part of the increase in renal interstitial pressure caused by "loop" diuretics. For this reason, it would be of great interest to determine whether furosemide can elicit an increase in renal subcapsular pressure in the nonfiltering kidney, and if such an increase can be prevented by indomethacin.

As for other drugs, the effects of "loop" diuretics on renin release from the isolated perfused kidney (491, 765, 1128, 1132) and renal cortical slices in vitro (64, 234, 681, 682) have been studied. When Hofbauer et al. (491) infused furosemide into an isolated rat kidney perfused with an electrolyte solution containing protein and bovine red blood cells, renin release increased about 4-fold while RPF and sodium excretion also rose. Other researchers (1128, 1132) have noted that furosemide stimulated renin release from the isolated perfused rat kidney in the absence of any change in perfusion pressure or flow. In these experiments, furosemide was believed to have a direct effect on the granular JG cells (1128). Moore and Hook (765) found that furosemide lowered renal perfusion pressure and elevated renin release 2-fold when injected into the isolated perfused rat kidney. Pretreatment with indomethacin prevented the vasodilatation, but not the stimulation of renin release, caused by furosemide. However, this perfusion system did not contain protein or dextran, and since both flow and sodium reabsorption in the isolated perfused kidney are highly dependent on the oncotic pressure of the perfusate (664), furosemide may have stimulated renin release by a nonprostaglandin dependent mechanism involving ion movement at the granular JG cells (64).

When Corsini et al. (234) tested furosemide in vitro at a concentration of 10^{-4} M, no statistically significant increase in renin release was observed. However, in these experiments the rat renal cortical slices did not respond to catecholamines either, so the results with furosemide were not conclusive. Lyon and Churchill (682) also found that 10^{-4} M furosemide failed to elevate renin release from rat renal slices in vitro, but later (681) they reported that furosemide in concentrations ranging from 10^{-5} to 10^{-3} M increased renin release (by 40%) from rat renal cortical cell suspensions. Similarly, ethacrynic acid (10^{-3} M) caused a 100% increase in renin release from isolated superfused rat glomeruli (64). DeSaulles and Schwartz (273a) found that the stimulation by furosemide (10^{-3} M) of renin secretion from rat renal cortical slices in vitro was not affected by indomethacin. Therefore, as predicted by the in vivo studies, these drugs can have a direct effect on the granular JG cells. It is not known whether this direct effect on renin release involves alterations in ion transport or cell volume.

To recapitulate briefly before considering the characterization of the renin-releasing effects of "loop" diuretics in humans, these agents appear to increase renin release by both a direct and indirect effect on the macula densa. The direct effect appears to involve the blockade of sodium or chloride transport into these chemoreceptor cells whereas the indirect effect develops slowly as a result of salt and water losses. These conclusions are supported by the fact that those researchers (787, 1120) who found that furosemide-induced renin release was prevented by volume repletion used small doses whereas those investigators (230, 740, 787, 1120) who reported that furosemide-induced renin release was not affected

by fluid replacement used larger doses. Larger doses of "loop" diuretics also increase renin release via the renal baroreceptor, possibly by elevating renal interstitial pressure. In addition, ongoing renal nerve activity appears to amplify the ability of these drugs to increase renin release. It is possible that the renin release caused by "loop" diuretics is mediated by renal prostaglandins since blockade of prostaglandin synthesis prevents the stimulation of renin release. Finally, "loop" diuretics can directly stimulate the release of renin from the granular JG cells by an unknown mechanism. Activation of each of these control mechanisms may depend on the dose of these drugs, the time after injection, and the species involved. It is easy to see why investigators in this field have presented so many different, and often conflicting, theories to explain the effects of "loop" diuretics on renin release.

In 1965, Fraser et al. (349) reported that i.v. furosemide caused an immediate 2-fold elevation of PRA in normotensive humans. In the ensuing years, many groups of investigators have reported similar results in normotensive and hypertensive humans. Unfortunately, most of these studies are purely descriptive and fail to give any insight into the mechanism by which "loop" diuretics increase renin release in man. Furosemide, in single and multiple doses of 0.29 to 1.14 mg/kg (assuming an average patient weight of 70 kg), caused a 1.3- to 5-fold increase in PRA in both normotensive and hypertensive humans (2, 3, 34, 190, 208, 228, 289, 291, 292, 299, 308, 349, 364, 477, 506, 543, 556, 622, 650, 741, 774, 822, 860, 877, 906, 955, 959, 966, 970, 1074, 1100, 1171, 1191, 1264, 1271). In a similar fashion, bumetanide (0.03 mg/kg) (1146) and ethacrynic acid (1.4 to 4.3 mg/kg) (369, 1228) elevated PRA by 2- to 5-fold in normotensive man. Unfortunately, in many of these studies (2, 3, 190, 208, 291, 292, 364, 543, 556, 1074, 1100, 1171) the administration of furosemide was followed by variable periods of ambulation before collecting blood for PRA measurements. Since attainment of upright posture in man increases renin release through activation of the renal sympathetic nerves (1261) and the renal afferent arteriolar baroreceptor (1065), mainly those studies (34, 369, 477, 506, 622, 650, 774, 822, 860, 906, 955, 959, 1171, 1191, 1264, 1271) conducted with the patients in a supine position will be considered in the analysis of furosemide-induced renin release in humans. The route and duration of treatment with furosemide are other factors that may determine the mechanism by which furosemide alters renin release (190, 208, 292, 308, 506, 877, 970, 1074, 1100, 1171). With regard to the direct renin-releasing effects of furosemide in humans, we consider those studies (34, 299, 506, 622, 650, 774, 822, 906, 955, 959, 1191, 1264, 1271) involving the measurement of PRA soon after the i.v. furosemide to recumbent subjects to be the most meaningful for purposes of pharmacologic analysis. It should be pointed out that the doses of furosemide (0.29 to 1.14 mg/kg) used in these studies (34, 228, 299, 364, 477, 622, 650, 774, 822, 860, 955, 959, 1191, 1264, 1271) correspond to the small doses of the drug used in the animal studies discussed above.

A single i.v. dose of furosemide (0.29 to 1.14 mg/kg) has been observed to cause a 2- to 5-fold peak elevation of PRA within 10 to 20 min in supine normotensive and hypertensive humans (364, 477, 955, 959, 1191, 1264), and renin release remained elevated during the next 1 to 2 hr (34, 228, 299, 308, 364, 477, 622, 774, 822, 860, 955, 959, 1191, 1264, 1271). Several investigators have noted a biphasic increase in PRA after either the i.v. (959, 1271) or oral (308) administration of furosemide. After an average 3-fold elevation of PRA at 10 to 20 min after the injection, PRA declined to about twice the control values. About 90 to 120 min after furosemide, PRA began to rise again (959, 1271). Ten min after injecting furosemide into normotensive humans, Rosenthal et al. (955) observed a 3.3-fold increase in PRA and a marked natriuresis, and Padfield et al. (860) found a close correlation between the change in PRC and urinary sodium output after the injection of furosemide. In contrast to the latter observation, other researchers (741, 822) found no relationship between the increment in PRC and sodium excretion after either furosemide (822) or ethacrynic acid (741). In a similar fashion, there is disagreement about the rate of decline of PRA after the initial stimulatory effect of furosemide in relation to sodium excretion. Like previous investigators (955), Weber et al. (1191) observed a 5-fold increase in PRA, associated with a vigorous natriuresis, within 10 min after the injection of furosemide into normal humans. Plasma renin activity declined over the next 50 min as the natriuretic effect of the drug peaked. On the other hand, Muiesan et al. (774) reported that PRA did not decline during the 30- to 60-min period after the injection of furosemide into normal subjects despite the fact that sodium excretion was greatly elevated at this time. The dose of furosemide was the same in both studies (774, 1191).

Because PRA began to increase in concert with an increase in hematocrit, Rosenthal et al. (955) concluded that furosemide-induced renin release was the result of a decrease in plasma volume. However, Hesse and Nielsen (477) determined that 0.5 liter of saline i.v. to normotensive subjects during the first 30 min after furosemide reduced or abolished the hemoconcentration without altering the rise in PRA. They also pointed out that the rise in PRA preceded the increase in packed cell volume. In a similar fashion, the oral administration of bumetanide to normal subjects led to an increase in PRA before natriuresis had begun (1146). Since the 2-fold elevation of PRA was accompanied by an increase in GFR, the initial increase in PRA was thought to be a result of renal vasodilatation rather than of a decrease in plasma volume. However, during the later period of bumetanide diuresis, when much more sodium had been excreted, a further elevation (4-fold) of renin release occurred. The observation that GFR was decreased at this point suggests that the later increment in PRA was

due to a decrease in plasma volume (1146). In this respect, the infusion of isotonic saline 2 hr after i.v. furosemide did suppress PRA values back to control levels (822, 1271). In addition, Meyer et al. (741) found that the 2-fold increase in PRA observed 60 min after i.v. ethacrynic acid (0.67 to 0.86 mg/kg) into normal humans was suppressed by the simultaneous infusion of polyvinylpyrrolidone or salt-free dextran. A close inverse correlation was noted between changes in PRA and variations in blood volume. These studies (477, 741, 822, 955, 1146, 1271) are in complete accord with the results obtained with furosemide (1120) and ethacrynic acid (230) in animals, i.e. the late, but not the early, renin-releasing effects of "loop" diuretics are due to a decrement in plasma volume.

In an attempt to elucidate the mechanism by which "loop" diuretics bring about an increase in renin release in humans, researchers (34, 228, 299, 308, 364, 369, 650, 679, 774, 877, 906, 959, 966, 995, 1074, 1228, 1264) have tested the ability of a variety of pharmacologic agents to alter this release. In 1969, Winer et al. (1228) reported that the increase in PRA brought about by i.v. ethacrynic acid in normal humans was blocked by propranolol. However, this observation is not surprising since the treatment with ethacrynic acid was followed by 3 hr of ambulation, a maneuver known to elevate renin release by activating the renal sympathetic nerves (1261). Some years later, Phillippi et al. (906) observed that a small i.v. dose of propranolol, which lessened the rise in PRA that attended the attainment of upright posture, failed to alter the increase in PRA elicited by furosemide in supine, normotensive humans. When a larger dose of propranolol was given by mouth before furosemide treatment, furosemide-induced renin release was blocked. They suggested that furosemide either caused a strong stimulation of the sympathetic nerves or propranolol was acting through a mechanism that did not involve beta-adrenergic antagonism. Timolol, a nonselective beta-blocker, lowered basal PRA and prevented the increase in PRA seen between 1 and 3 hr after i.v. furosemide in supine, normotensive, and hypertensive human (679, 995). In studies with normal, recumbent humans, Attman et al. (34) found that propranolol and the cardioselective beta-adrenergic antagonist metoprolol lowered basal PRA values and blocked 70% to 80% of the increment in PRA caused by i.v. furosemide. On the other hand, practolol, another $beta_1$-adrenergic antagonist, failed to alter the 2-fold elevation of renal venous PRA elicited by furosemide in hypertensive patients (1264). In these studies (1264), a small i.v. dose of propranolol prevented 65% of the rise in renal venous PRA seen after furosemide.

In a more comprehensive study, Leonetti et al. (650) studied the effect of increasing doses of propranolol on furosemide-induced renin release. While on a controlled sodium intake, hypertensive patients received increasing oral doses of propranolol for 5 to 7 days, and the renin response to furosemide was determined at the end of each propranolol treatment period. The smallest dose of propranolol suppressed basal PRA values by 80% and prevented 65% of furosemide-stimulated renin release. Larger doses of propranolol caused further, but less dramatic, decrements in basal PRA values and a greater inhibition of the renin release seen after furosemide. Leonetti et al. (650) concluded that this dose of furosemide increased PRA via a neural mechanism. This contention was strengthened by the observation that furosemide caused a 50% increase in plasma norepinephrine levels within 15 min in supine normotensive and hypertensive humans (774). Plasma epinephrine content was unchanged. In the latter studies, Muiesan et al. (774) discovered that oxprenolol did not affect basal PRA values but did block about 50% of the 3-fold increase in PRA observed 30 min after the injection of furosemide. The magnitude of furosemide-induced diuresis and natriuresis was the same in the presence and absence of oxprenolol. Also of interest is the fact that oxprenolol completely prevented the rise in plasma norepinephrine concentration brought about by furosemide. Muiesan et al. (774) also detected a striking increase in the urinary excretion of norepinephrine during the first 15 min after furosemide, but this 13-fold increase in urinary norepinephrine concentration was not affected by pretreatment with oxprenolol. Earlier investigators (464) found that both furosemide and ethacrynic acid caused a large increase in total catecholamine excretion in normal humans. In the case of furosemide, a marked diuresis preceded the increase in catecholamine excretion by 30 min. After ethacrynic acid, the rise in catecholamine excretion and the diuresis occurred concomitantly. Replacement of furosemide-induced volume losses prevented the observed increase in catecholamine excretion; therefore, it was concluded that the stimulation of the sympathetic nervous system was dependent on the total reduction in plasma volume and the rapidity of fluid loss. Thus, pretreatment with beta-adrenergic antagonists has been shown to prevent or attenuate both the early (774, 906, 1264) and late (650, 679, 774, 995) rise in PRA caused by the i.v. administration of furosemide to humans.

Taken collectively, these reports (34, 464, 650, 679, 774, 906, 995, 1228, 1264) do indeed indicate that furosemide stimulates renin release in humans by activation of the peripheral sympathetic nervous system. This idea is consistent with the animal experiments involving renal denervation and small doses of furosemide (787, 1040). The observations with beta-adrenergic antagonists made in animals and humans appear to be contradictory, since propranolol (235, 373, 830, 847) and oxprenolol (510) did not alter the increase in renin release precipitated by giving furosemide to anesthetized dogs, cats, and rabbits, but this discrepancy is probably related to the doses of furosemide used in the respective studies. That is, large doses (2.5 to 10 mg/kg, i.v.) of furosemide were used in the animal studies (373, 510, 527, 847, 1040) whereas small doses (0.57 to 0.70 mg/kg, i.v.) were employed in

human experiments (34, 650, 679, 774, 906, 995, 1228, 1264). As described above, the renin release caused by small doses of furosemide (0.75 mg/kg) in cats was prevented by prior renal denervation whereas renal denervation did not lessen the stimulation of renin release elicited by large doses (6 mg/kg) of furosemide (1040). Thus, the large doses of furosemide used in the beta-adrenergic-antagonist-furosemide studies in animals may have had direct stimulatory effects on renin release that were independent of patent renal innervation.

We return to the question of how furosemide stimulates renin release by a neural mechanism. Stella and Zanchetti (1040) have proposed that a decrease in right atrial pressure after furosemide may increase renal nerve activity via the low pressure cardiopulmonary receptors. In this respect, furosemide has been demonstrated to increase venous capacitance in patients with congestive heart failure (280) and to decrease left atrial pressure in hypervolemic, anesthetized dogs (119). In addition, Hesse et al. (477, 480) found that furosemide lowered right and left atrial pressures by 78% and 48%, respectively, in normotensive humans while increasing PRA by 2-fold. However, the parallel development of hemoconcentration and a decrease in right atrial pressure, with no change in venous tone, indicated that the decrement in filling pressure for the heart after furosemide was due to the contraction of plasma volume. Furthermore, replacement of volume losses by i.v. saline prevented the drop in right atrial pressure, but not the early rise in PRA, caused by furosemide. Based on these studies, Hesse et al. (477, 480) decided that the low pressure cardiopulmonary receptors are not involved in the immediate elevation of renin release brought about by furosemide in humans. In the final analysis, we are faced with two possibilities concerning the early rise in PRA caused by furosemide. Either furosemide indirectly activates the sympathetic nervous system by some pathway yet to be defined or beta-adrenergic antagonists prevent furosemide-induced renin release in humans by a mechanism that does not involve the blockade of beta-adrenergic receptors.

Little evidence supports the idea that "loop" diuretics increase renin release in humans by activating the renal baroreceptor even though furosemide (1165), bumetanide (525, 558), and ethacrynic acid (923) have been demonstrated to elevate RPF by 15% to 30% in humans. Furthermore, to our knowledge, no one has determined if furosemide stimulates vasodilatation and renin release in the denervated kidneys of humans who have a functioning renal allograft. On the other hand, do the "loop" diuretics elicit renin release and vasodilatation in the kidneys of anuric patients with nonfiltering kidneys? If furosemide does cause renin release and vasodilatation in the nonfiltering, human kidney, are these effects of furosemide blocked by propranolol? The answer to these questions will help researchers to discern if "loop" diuretics elevate PRA by a vascular action in humans and whether the vascular effects of these drugs are lessened by beta-adrenergic antagonists.

Several studies (364, 877, 966, 1074, 1191) strongly indicate that prostaglandins are involved in furosemide-induced renin release in humans. In 1975, Patak et al. (877) found that PRA values rose from 0.73 to 2.35 ng of AI/ml/hr and blood pressure fell after treating normotensive and hypertensive humans with furosemide orally for four days. Furosemide therapy was then discontinued for 4 days after which time the patients received the prostaglandin synthesis inhibitor indomethacin for four days. Indomethacin lowered basal PRA values to 0.17 ng of AI/ml/hr. When challenged again with furosemide in the presence of indomethacin, PRA rose to 0.51 ng of AI/ml/hr but blood pressure did not fall. The natriuretic effect of furosemide also was attenuated by indomethacin. Although these data (877) suggest that prostaglandins are involved in furosemide-induced renin release, several important points should be considered before accepting this interpretation. For instance, after prolonged treatment with furosemide, a decrease in plasma volume has been shown to be the major stimulus to renin release (970). Indomethacin blunted the natriuretic effect of furosemide enough to prevent a drop in blood pressure; therefore, indomethacin may have lessened the decrease in plasma volume caused by furosemide. In addition, although indomethacin lowered basal PRA values by 75%, the percentage increase (about a 3-fold) in PRA after furosemide was the same in the absence and presence of indomethacin. Thus, furosemide still stimulated renin release in the presence of indomethacin, but the absolute PRA value achieved was lower than the value observed in the absence of indomethacin.

In a similar fashion, Rumpf et al. (966) found that the renin response to furosemide was maintained at a lower level after chronic therapy with indomethacin. Four hours after giving an oral dose of furosemide to normal humans, PRA rose from 3.1 to 11.7 ng of AI per ml per hr (a 3.8-fold increase) in the absence of indomethacin whereas PRA climbed from 1.6 to 5 ng of AI per ml per hr (a 3.1-fold increase) after 2 days of treatment with indomethacin. Thus, renin release still increased after furosemide in indomethacin-treated patients, but the absolute PRA value observed was lower because indomethacin had suppressed basal PRA values by 50%. Other investigators (1074) have confirmed that therapy with multiple doses of indomethacin lessened the late rise in renin release observed after giving furosemide to normal humans, but these studies (877, 966, 1074) shed little light on the role of prostaglandins in the immediate stimulation of renin release caused by furosemide. In addition, the suppression of prostaglandin products was not verified in any of the studies. Fortunately, Frolich et al. (364) addressed this problem. When normal subjects were given indomethacin orally for 2 days, PRA and the urinary excretion of PGE were decreased by 45% and 55%, respectively. In the absence of indomethacin, furo-

semide (20 mg, i.v.) elevated PRA from 5.5 to 13.5 ng of AI per ml per hr at 10 min after the injection. When prostaglandin synthesis was inhibited, PRA rose from 3 to 3.5 ng of AI per ml per hr within 10 min after furosemide; therefore, indomethacin completely prevented the immediate increase in renin release elicited by furosemide. Accordingly, these authors (364) felt that the early effect of furosemide on renin release was due to an increase in renal prostaglandin production. As in previous studies (877), indomethacin significantly lessened the sodium loss elicited by furosemide, and this action of indomethacin was not due to a pharmacokinetic drug interaction (364). Although indomethacin itself lowered the urinary excretion of sodium, indomethacin has been shown to suppress renin release by a mechanism that does not appear to involve sodium retention (286, 966). Frolich et al. (364) concluded that indomethacin prevented the immediate stimulatory effect of furosemide on renin release by the inhibition of prostaglandin synthesis rather than by causing sodium retention. Parenthetically, indomethacin was shown not to affect the renin-renin substrate reaction in vitro (364).

The belief that prostaglandins are involved in furosemide-induced renin release was strengthened when Weber et al. (1191) discovered that furosemide caused the release of arachidonic acid, a prostaglandin precursor, into the blood of normal humans. Ten minutes after furosemide, the plasma levels of arachidonic acid were elevated by 60%, and PRA was increased 5-fold. At this point, PRA began to decline even though the plasma concentration of arachidonic acid remained elevated for at least 1 hr. The urinary excretion of $PGF_{2\alpha}$ increased after furosemide, and $PGF_{2\alpha}$ production peaked (2.8-fold increase) between 30 and 60 min, a time corresponding to the maximal excretion of sodium. Indomethacin pretreatment completely blocked the change in arachidonic acid, PRA, and $PGF_{2\alpha}$ seen after furosemide, but did not alter the amount of sodium excreted. Thus, the release of arachidonic acid, which is the rate limiting step in prostaglandin synthesis, appeared to be the primary mechanism by which furosemide increased prostaglandin biosynthesis and renin release. The scenario presented to explain the biphasic effect of furosemide on renin release was that furosemide first activated a phospholipase, which, in turn, catalyzed the liberation of arachidonic acid, possibly from cells of the vascular wall. The increased availability of arachidonic acid led to a greater production of PGE_2 in the kidney, which, in turn, elicited vasodilatation and renin release. This effect on renin release may have been enhanced by the fact that furosemide inhibits PGE_2-9-ketoreductase, the enzyme that converts PGE_2 to $PGF_{2\alpha}$ (1053). As sodium excretion increased, PGE_2-9-ketoreductase was activated, and renal $PGF_{2\alpha}$ production rose. The latter compound has been demonstrated to inhibit renin release in vivo (555) and in vitro (221). This was thought to account for the later fall in PRA. However, the reader must realize that the stimulatory prostaglandin is probably PGI_2 (1207a). In addition, although the "loop" diuretics and indomethacin have been demonstrated to cause a variable amount of inhibition of the enzymes involved in the metabolism of prostaglandins (947, 1053), the exact importance of these actions in vivo are unknown. Furthermore, it is not known how indomethacin prevents the release of arachidonic acid.

Other compounds have been demonstrated to alter the renin release caused by "loop" diuretics (228, 299, 308, 369, 959). Rosenthal et al. (959) reported that somatostatin (growth hormone release-inhibitory hormone) had no direct effect on renin release, and yet this peptide blocked about 50% of furosemide-stimulated renin release. The natriuretic and diuretic effects of furosemide were not affected by somatostatin, and somatostatin inhibited the late rise in PRA more than the immediate increase in PRA. The authors (959) pointed out that somatostatin had been shown to lower cyclic AMP levels in cells exposed to prostaglandins and concluded that somatostatin inhibited the increase in PRA caused by furosemide by an action on a renal adenylate cyclase system. Growth hormone itself had no effect on furosemide-induced renin release (228). Treatment with bromocriptine, a long-acting dopamine agonist, elevated basal PRA values and increased the maximal increase in PRA seen after i.v. furosemide in recumbent, normal humans. Urinary volume and electrolyte excretion were not altered by bromocriptine (228). The mechanism by which bromocriptine potentiates the renin release elicited by furosemide is unknown. The serotonin antagonist cyproheptadine has been shown to block 25% to 60% of the increase in PRA caused by treating normal volunteers with oral furosemide (308). Over the 4-hr period after furosemide, a bimodal elevation of PRA was observed, and cyproheptadine blocked the later increase in renin release more than the early increase. Although the authors felt that cyproheptadine acted via central serotoninergic pathways, it is possible that cyproheptadine may have attenuated the sodium loss precipitated by furosemide. Unfortunately, urinary volume and electrolyte excretion were not measured (308). In addition, cyproheptadine has weak activity as an inhibitor of prostaglandin synthetase (551). Finally, a chronic, pressor infusion of AII lowered basal PRA and completely prevented the stimulation of renin release caused by ethacrynic acid in supine, normal humans (369).

In general, the "loop" diuretics appear to stimulate renin release in humans by the same mechanisms that have been identified in animal studies. It appears that the "loop" diuretics, furosemide in particular, elevate renin release in humans by activation of 1) the macula densa cells, 2) the renal sympathetic nerves, and 3) the renal prostaglandin system. The strongest evidence, although indirect, supports an action of these saluretic drugs on the renal sympathetic nerves and the renal prostaglandin system. However, a great amount of com-

mitted research is needed to clarify the means by which "loop" diuretics increase PRA in humans.

2. Other diuretic drugs. While the "loop" diuretics (furosemide, ethacrynic acid, and bumetanide) appear to stimulate renin release via mechanisms that are not dependent on the loss of sodium and water, the renin release elicited by other diuretics probably results from volume and salt depletion per se since the replacement of salt and water losses decreases the ability of the latter drugs to elevate PRA. However, it should be remembered that the loss of sodium and water and the decrement in extracellular fluid volume that result from treatment with these non-"loop" diuretic drugs may stimulate renin release by activation of the renal baroreceptor, the renal sympathetic nerves, and/or the macula densa. In addition, renin release may be decreased immediately after the parenteral injection of the non-"loop" diuretics as a result of the increased delivery of sodium to the macula densa. As the diuretic activity of the drug wanes and the loss of sodium and water becomes significant, renin release begins to rise and becomes elevated. Thus, a single dose of a non-"loop" diuretic may cause a bimodal change in PRA, a decrease followed by an increase, whereas chronic treatment with these drugs usually elevates PRA.

A. OSMOTIC DIURETICS. Vander and Miller (1124) found that the induction of natriuresis and diuresis with the osmotic diuretics urea, mannitol, and sodium sulfate prevented or reversed the increase in renal venous PRA that normally accompanied a decrease in renal perfusion pressure in anesthetized dogs. These agents did not alter renal hemodynamics. Birbari (90) reported that the administration of a 20% solution of mannitol suppressed renin release by 30% in anesthetized dogs. Sodium excretion increased 5-fold (90). Churchill et al. (215a) found that mannitol-induced diuresis decreased renin secretion as it increased sodium load in the early distal tubule of the anesthetized rat. Lastly, a 30- to 60-sec infusion of 4 M urea or 4 M dextrose directly into the renal arteries of anesthetized dogs elevated renin release, RBF, and GFR, and this stimulation of renin release was thought to result from changes in the volume of the granular JG cells in response to the hyperosmolarity of the arterial blood (1250). Therefore, osmotic diuretics probably have a triphasic effect on renin release: an immediate, short-lived stimulatory effect, which may involve changes in granular JG cell volume (1250); a prolonged period of renin suppression resulting from an increase in sodium load at the macula densa (90, 1124); and an eventual elevation of renin release as the plasma volume becomes contracted. The latter effect, however, would be apparent only after long-term infusions of osmotic diuretics and, therefore, has not been studied well.

B. MERCURIAL DIURETICS. In 1965, White (1207) reported that mercaptomerin-induced natriuresis and diuresis suppressed the elevated renin release that accompanied renal arterial hypotension in anesthetized dogs. Later, chlormerodrin was found to exert a similar effect in conscious dogs (1123). Dimercaprol, which was known to prevent the diuretic action of mercurial diuretics, reversed the effect of mercaptomerin on renal baroreceptor-induced renin release (1207). A year later, Brown et al. (148) discovered that 2 hr after the administration of meralluride to anesthetized dogs, PRA was elevated by 2.5-fold even though sodium excretion was increased to 20 times the control value. Plasma renin activity was increased over 3-fold up to 6 hr after injection. When salt and water losses were continually replaced after treatment with meralluride, the natriuresis induced by this drug was potentiated, and the increase in PRA was blunted but not abolished. These authors (148) concluded that factors other than volume depletion were responsible for the stimulation of renin release by meralluride. On the other hand, Vander and Luciano (1123) found that the renin release elicited 30 to 120 min after chlormerodrin was prevented by volume repletion. As with meralluride, volume replacement potentiated the natriuretic effect of chlormerodrin. These differing effects of salt and water replacement on the ability of meralluride and chlormerodrin to bring about an increase in PRA might be the result of an action of meralluride on sodium chloride transport at the macula densa or an action on the renal baroreceptor. The former prospect is suggested by the fact that mercurial diuretics, like the "loop" diuretics, inhibit sodium reabsorption in the ascending limb of Henle's loop (79), and the various mercurial diuretics, which differ considerably in their structures, might also differ in their ability to block ion movement at the macula densa. With regard to the latter possibility, meralluride, unlike chlormerodrin, is covalently linked to theophylline, which is released from the mercurial moiety in vivo. Theophylline has been shown to cause renal vasodilatation and increase renin release from the isolated perfused rabbit kidney in the presence of a marked natriuresis (1157). However, the effect of meralluride on RBF is not known although chlormerodrin has been found to increase renal vascular resistance in anesthetized dogs (501). Thus, the presence of the theophylline moiety in meralluride may account for the inability of volume replacement to block meralluride-induced renin release in the dog.

In summary, the mercurial diuretics appear to elevate renin release by promoting the loss of sodium and by depleting plasma volume. Meralluride may raise PRA by another mechanism, possibly the renal baroreceptor.

C. INHIBITORS OF CARBONIC ANHYDRASE. Acetazolamide, which has been shown to inhibit sodium and bicarbonate reabsorption in the proximal and distal tubules (79), inhibited renal baroreceptor-mediated renin release in anesthetized dogs (1124). No information is available concerning the effects of acetazolamide on basal PRA values in animals or humans.

D. THIAZIDES. In 1962, Tobian et al. (1097) observed that the granularity of the JG cells of rats was greatly

increased after 9 weeks of treatment with chlorothiazide, and it was suggested that this increase in granulation reflected an enhancement of the secretory function of these cells. Several years later, Vander and Miller (1124) reported that chlorothiazide attenuated the increase in renal venous PRA caused by a decrease in renal perfusion pressure in the anesthetized dog, presumably by increasing the amount of sodium at the macula densa. Brown et al. (148) then reported that chlorothiazide elevated PRA by 2-fold over a 2- to 6-hr period in anesthetized dogs. At 2 hr after injection of chlorothiazide, sodium excretion was increased to about 20 times the control value, and PRA rose with time as the natriuretic effect of the drug began to wane. Volume repletion with saline blocked the rise in PRA at 2 hr, reduced PRA to 60% of the pretreatment value at 4 hr, and potentiated the magnitude and duration of the natriuresis. It was concluded that the decrease in plasma volume caused by chlorothiazide activated the renal baroreceptor mechanism controlling renin release. In this respect, hydrochlorothiazide has been found to elevate renal vascular resistance slightly in the anesthetized dog (501). Cooke et al. (230) confirmed that volume repletion, by i.v. infusion of the urine, prevented the renin release elicited by chlorothiazide in the anesthetized dog.

Many investigators have reported that the prolonged administration of thiazide diuretics to normal and hypertensive humans results in an elevation of PRA (134, 171, 204; 206, 221, 250, 325, 403, 428, 555, 624, 799, 970, 1065, 1199, 1213). For instance, an elevated PRA has been observed in humans after chronic treatment with hydrochlorothiazide (134, 171, 204, 206, 325, 428, 555, 624, 1199), chlorothiazide (555, 970), methyclothiazide (403), bendrofluazide (1065, 1213), bendrofluomethazide (799), and cyclopenthiazide (250). At first, it was thought that hydrochlorothiazide elevated PRA only during the initial stages of therapy, with PRA later returning to control levels (171), but the advent of more accurate techniques for the measurement of PRA revealed that this drug raised PRA by 2- to 6-fold when given daily for 6 to 24 weeks (134, 204, 206, 325, 624, 1199). Similar changes in PRA were seen after continued treatment with the other thiazide diuretics (250, 403, 799, 1065, 1213, 1234). It is of interest to note that treatment of hypertensive patients with either chlorothiazide or furosemide elevated PRA to the same extent after long-term therapy (970). Surprisingly, the thiazide diuretics seem to increase PRA to a greater extent in normotensive humans than in patients with hypertension (403, 1065). For example, Swales and Thurston (1065) found that 7 days of treatment with bendrofluazide increase PRA from 1.7 to 3.9 ng of AI/ml/hr in hypertensive patients whereas PRA rose from 1.9 to 11 ng of AI/ml/hr in normal individuals. In like fashion, the plasma levels of AII were twice as high in the normal humans, as compared to the hypertensive patients, after bendrofluazide (1065). In addition, patients with low-renin essential hypertension exhibited a much greater elevation of PRA after continued treatment with hydrochlorothiazide than did patients with normal-renin essential hypertension (325).

The effect of beta-adrenergic antagonists on thiazide-induced renin release gives some support to the idea that these diuretics stimulate renin release by indirectly activating the sympathetic nervous system. For instance, propranolol has been shown to block the renin release brought about by the i.v. injection of chlorothiazide into anesthetized dogs (1267). Later, Sweet and Gaul (1066) found that timolol completely blocked the 4-fold rise in PRA that usually accompanied hydrochlorothiazide treatment in conscious dogs. Timolol also attenuated the hypokalemia that usually developed during long-term treatment with this thiazide, but it was not known if this increase in plasma potassium concentration was involved in the suppression of renin release (1066). Similarly, in renal hypertensive and normotensive dogs, and SH and normotensive rats, bendroflumethiazide increased PRA by 4- to 6-fold and timolol prevented 40% to 90% of this elevation of PRA (797). The ability of timolol to lessen the rise in PRA caused by bendroflumethiazide in rats was especially interesting in light of the fact that timolol potentiated the natriuresis elicited by bendroflumethiazide. Again, timolol attenuated the hypokalemia caused by this thiazide (797).

Timolol (204, 206), pindolol (628), oxprenolol (159, 250, 555), propranolol (134, 500, 799, 1050), and atenolol (1213) have been reported to lessen or prevent the increase in PRA that results from prolonged treatment of humans with thiazide diuretics. Chalmers et al. (204, 206) found that hydrochlorothiazide raised PRA from 1.7 to 3.2 ng of AI/ml/hr in seated hypertensive patients whereas timolol suppressed PRA by 65% relative to the control values. Combined treatment with timolol and hydrochlorothiazide resulted in no change in PRA as compared to the pretreatment values. Similar changes were found by Nielsen et al. (799) who reported PRA to be 3.5, 6.4, 1.7, and 3.5 ng of AI/ml/hr during the control, bendrofluomethiazide, propranolol and bendrofluomethiazide plus propranolol periods, respectively. Such clear-cut findings (159, 204, 206, 799, 1050), however, are not always obtained since in many cases (134, 250, 500, 555, 628, 1213) thiazide-induced renin release was only partially attenuated by beta-adrenergic blockade. It also should be pointed out that other investigators have indicated that timolol (624) and oxprenolol (428) are incapable of suppressing the renin release caused by hydrochlorothiazide.

Zanchetti et al. (1261) found that continued therapy with chlorthalidone potentiated orthostasis-induced renin release, and, moreover, propranolol was more efficacious in suppressing the renin release caused by chlorthalidone when the patients were in the upright position. Unfortunately, differences in posture cannot account for the differing effects of beta-adrenergic blockade on thiazide-induced renin release. For example, some investigators have reported that timolol (204, 206) and oxprenolol (159, 250, 255) lower PRA in thiazide-treated patients in the standing position but other researchers have found

timolol (624) and oxprenolol (428) to have little effect under apparently identical conditions. Thus, beta-adrenergic antagonists appear to be able to suppress thiazide-induced renin release in humans (134, 148, 204, 206, 250, 555, 1213), dogs (797, 1066, 1267), and rats (797); however, this is not a universal observation (428, 624).

Two other observations indicate that the sympathetic nervous system is partially responsible for the elevation of PRA by thiazide diuretics. First, paraplegic patients with cervical spinal transection of short duration exhibited a normal renin response to therapy with hydrochlorothiazide, but patients with long-standing lesions responded very slowly to the diuretic (221). That is, PRA rose to the same extent as in patients with early transections, but the renin response was much delayed in patients with late transections. Secondly, the sympatholytic drug methyldopa lessened the ability of chlorothiazide to elevate PRA in supine, hypertensive humans (555). The role of the sympathetic nervous system in renin release elicited by thiazides and other non-"loop" diuretics is in need of further clarification.

Methyclothiazide had no effect on renin release from rat renal cortical slices in vitro (273a).

E. CHLORTHALIDONE. Chlorthalidone is a sulfonamide diuretic with properties very similar to those of the thiazides. Chlorthalidone has been shown to increase PRA by 3- to 9-fold when given to hypertensive humans for 4 to 14 weeks (315, 508, 1182, 1234, 1261). Weber et al. (1182) found that PRA, measured in the upright position, was elevated to a greater extent by chlorthalidone in patients with low-renin and high-renin hypertension than in patients with normal-renin hypertension. When Zanchetti et al. (1261) measured PRA in both the lying and standing position during chronic treatment of hypertensive patients with chlorthalidone, they found that the renin-stimulating activity of this diuretic gradually dissipated during continued administration of the drug. Cotreatment with reserpine plus methyldopa plus clonidine did not alter the stimulation of renin release caused by chlorthalidone, but propranolol did block the rise in PRA, especially in the standing position. Other clinicians have found chlorothalidone-induced renin release in hypertensive patients to be lessened by propranolol (384) and sotalol (1149), but labetalol was without effect (1193).

F. METOLAZONE. Metolazone is a quinethazone derivative that inhibits sodium reabsorption in the proximal tubule and cortical diluting segment (1039), and thus is similar in its actions to chlorthalidone and the thiazide diuretics. Lanzoni et al. (630) observed that metolazone raised PRA in hypertensive patients. Sambhi et al. (976) also observed an elevation of PRA that was greater during the first few weeks of therapy than after longer periods of treatment. In the latter case (976), propranolol initially suppressed the elevated PRA values, but this antagonism waned even when the dose of propranolol was increased progressively.

G. CLOPAMIDE. Clopamide inhibits sodium reabsorption in the proximal tubule and does not alter RPF or GFR (342). Imbs et al. (513) found that clopamide suppressed renin secretion by 50% in anesthetized dogs and attributed this suppression to an increase in salt load at the macula densa. By comparison, ethacrynic acid was found to elicit a 3.4-fold increase in renin secretion.

H. AMILORIDE AND TRIAMTERENE. Amiloride and triamterene act mainly on the distal tubule (420, 574) and are termed "potassium-sparing" diuretics. Amiloride has not been used widely in humans, but this drug has been noted to cause a 3- to 4-fold elevation of PRA in hypertensive patients (161, 315, 618). For example, Kremer et al. (618) observed that PRA tripled and plasma AII levels doubled after 6 weeks of treatment with amiloride. Plasma potassium levels increased by 0.7 mEq/l, and the total body sodium space was decreased. On the other hand, Esch et al. (315) found that amiloride elicited only a temporary increase in renin release with PRA values being in the control range after 3 weeks of therapy. Again, plasma potassium concentration was increased. It is unlikely that this rise in plasma potassium content suppressed renin release since the aldosterone antagonist spironolactone caused an equal degree of hyperkalemia and yet continually stimulated renin release (315). In addition, Keim et al. (574) reported that continued therapy with triamterene raised PRA by 2- to 3-fold in low- and normal-renin hypertensive patients.

I. SPIRONOLACTONE. Spironolactone, a competitive receptor antagonist of the mineralocorticoid aldosterone, blocks the reabsorption of sodium in exchange for potassium and hydrogen in the distal tubule (420). Spironolactone has been reported to stimulate renin release in hypertensive patients after 3 to 8 weeks of therapy (74, 315, 325, 499, 559, 1199). Weinberger and Grim (1199) found that spironolactone elicited a dose-related increase in PRA with a 9-fold increment being measured after 4 weeks. Patients with normal-renin hypertension exhibited a doubling of PRA whereas the response to low-renin hypertensive subjects was much greater (a 7-fold increase) (325). Propranolol blocked 78% of the increase in PRA caused by spironolactone in orthostatic patients with essential hypertension (559). Although a single dose of aspirin has been shown to prevent the natriuretic effect of spironolactone in mineralocorticoid-treated humans (1105), aspirin did not alter the increase in PRA caused by spironolactone in hypertensive humans (499). Spironolactone also evoked renin release and sodium loss in normotensive rats (311).

Canrenone, a major metabolite of spironolactone, elevated PRA and caused sodium loss and potassium retention in hypertensive subjects after two days of treatment (311). Erbler et al. (312) found that canrenone brought about a dose-dependent increase in PRA without altering the urinary excretion of sodium or potassium in diabetic humans. However, the inhibition by canrenone of sodium reabsorption in the distal part of the large bowel and the resultant intestinal loss of sodium would account for the increase in renin release (315). It should be pointed out that canrenone has been shown to inhibit AII-stimulated

aldosterone synthesis (311, 312), and this action may further exacerbate the loss of sodium caused by canrenone. The rise in PRA caused by spironolactone may not be caused by canrenone since oral treatment of rats with potassium carenoate increased PRA only during the first 3 weeks of therapy whereas spironolactone caused an increase in renin release throughout a 6-week regimen (311).

J. MINOR DIURETICS. Ammonium chloride is seldom used by itself as a diuretic; however, its effect on the renal metabolism of chloride and hydrogen ion make its effect on renin release of interest. Since the ammonium ion is converted to urea by the liver, leaving an excess of chloride, the ingestion of ammonium salts produces a metabolic acidosis. This excess of filtered chloride results in a natriuresis and diuresis until the kidney produces enough ammonium ions to balance the excess chloride ions in the tubular urine. Kisch et al. (594) found that the i.v. infusion of 75 mEq of ammonium chloride over a 60-min period suppressed PRA from 4.4 to 2.1 ng of AI/ml/hr in normal, sodium-depleted humans. They suggested that ammonium chloride suppressed renin release either by an indirect effect of increased sodium excretion on the macula densa or by a direct effect of hydrogen ion on the granular JG cells. With respect to the latter case, an infusion of hydrochloric acid into the renal arteries of anesthetized dogs suppressed renin secretion and increased sodium excretion (657). However, when ammonium chloride was given orally to normal humans on a low sodium diet, a slight increase in PRA occurred several hours after ingestion of the salt (886). The differences in route of administration and sampling intervals may have been responsible for these differing results (594, 886).

The methylxanthine compounds, theophylline and caffeine, have diuretic properties, but the effects of these compounds on renin release are discussed in section III B 4.

E. Inhibitors of the Renin-Angiotensin System

The successful synthesis of specific competitive antagonists of AII (698, 872, 924, 1103) and specific inhibitors of AI-converting enzyme (80, 840) during the past decade has enabled researchers to define more accurately the physiologic role of the renin-angiotensin system as well as its role in experimental and clinical hypertension. In 1970, Marshall et al. (698) demonstrated that 4-Phe-8-Tyr-AII was a competitive receptor antagonist of AII. In the ensuing years, other analogues of AII, with aliphatic amino acids (alanine, isoleucine, and glycine) substituted for the phenylalanine residue in the 8-position of AII, were produced in other laboratories (872, 924, 1103). In addition, in most of these compounds the 1 position was occupied by the nonmammalian amino acid sarcosine since this substitution was found to prolong the half-life of the peptides and thereby increase their potency (1103). The most extensively characterized receptor antagonist of AII is 1-Sar-8-Ala-AII, also known as saralasin (872). A nonapeptide (Pyr-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro) that has been shown to inhibit AI-converting enzyme was isolated from the venom of the fer-de-lance snake (*Bothrops jararaca*) by Ondetti et al. (841) in 1971. The synthetic form of this compound (Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro) was designated SQ 20881 (teprotide). Because teprotide was liable to enzymic degradation, and thus had to be given i.v. in order to have an effect, a program to develop an orally active inhibitor of AI-converting enzyme was initiated by Ondetti et al. In 1977, these researchers (840) indicated that some mercaptoalkanoyl and carboxyalkanoyl derivatives of amino acids were effective and selective inhibitors of AI-coverting enzyme with SQ 14,225 (D-3-mercapto-2-methylpropranoyl-L-proline) (captopril) being the most potent compound. Other authors have reviewed in detail the pharmacology of the AII receptor antagonists (257, 870, 871, 924), teprotide (80, 413, 841), and captopril (936), and in the discussion that follows, we will consider the effects of these agents on renin release in animals and humans.

1. Antagonists of Angiotensin II. In 1973, Bing (84) and Johnson and Davis (531, 532) first discovered that saralasin produced an increase in PRA in laboratory animals. In anesthetized dogs with constriction of the thoracic inferior vena cava of sufficient duration to produce sodium retention and ascites, Johnson and Davis (532) found that an i.v. infusion of saralasin reduced MAP by 32%. Plasma renin activity, which was already elevated as a result of the caval constriction, was doubled during the infusion of the AII analogue. However, saralasin did not alter renin release in normal anesthetized dogs; it caused an initial, transient pressor response of 5 to 10 mm Hg, but blood pressure did not change as the infusion was continued. These same investigators (531) also observed that both PRA and sodium excretion were elevated by saralasin in anesthetized sodium-depleted dogs. Blood pressure fell by 18% in these animals. Although normal anesthetized dogs exhibited no change in PRA or MAP during treatment with saralasin, an increase in renin release was observed when AII and saralasin were given simultaneously. Based on these data, Johnson and Davis (531, 532) suggested that saralasin-induced hypotension elicited renin release in sodium-depleted and caval-constricted dogs by activation of the renal baroreceptor and/or renal sympathetic nerves. This would account for the absence of a renin response in normal dogs. In addition, it was conjectured that saralasin also might have blocked the inhibitory effect of AII on renin secretion (531). In the latter case, it would have to be assumed that AII was causing a tonic inhibition of renin release during sodium restriction and thoracic caval constriction but had no such tonic effect in normal dogs.

Along these lines, McDonald et al. (711) also found 1-Sar-8-Gly-AII to have no effect on PRA in anesthetized dogs, but other workers (65) have reported that both

PRA and renin secretion were elevated by the i.v. infusion of saralasin into anesthetized dogs. In studies conducted with conscious, normal dogs on a salt-restricted diet, McCaa (706) found that the constant i.v. infusion of saralasin or 1-Sar-8-Ile-AII for 7 days resulted in a continued 5-fold elevation of PRA. Mean arterial pressure was decreased by an average of 14% throughout the infusion period but both sodium and potassium excretion were not changed. Bravo et al. (132) found that 1-Sar-8-Ala-, 1-Sar-8-Ile-, and 1-Sar-8-Thr-AII caused a 5- to 10-fold elevation of PRA in conscious sodium-depleted dogs. Although blood pressure fell after each antagonist, no relationship was noted between the reduction in blood pressure and the rise in PRA.

Freeman et al. (360) examined the effects of intrarenal arterial infusions of saralasin in anesthetized normal and caval-constricted dogs. An intrarenal infusion of saralasin did not significantly affect MAP, RBF, GFR, PRA, or sodium excretion in anesthetized normal dogs, but such an infusion doubled PRA in anesthetized sodium-depleted and caval-constricted dogs. In both groups of animals, saralasin increased RBF and decreased MAP but did not change GFR or sodium excretion. Due to the fall in MAP, the renin-releasing effects of saralasin could not be attributed to an intrarenal action of this drug. On the other hand, saralasin given directly into the kidney has been demonstrated to increase PRA in conscious, uninephrectomized dogs (39, 591). In conscious, sodium-depleted dogs, Kimbrough et al. (591) noted that basal PRA was increased from 3.3 to 8.3 ng of AI/ml/hr during sodium restriction, and the intrarenal infusion of a small dose of saralasin further increased PRA to 19.4 ng of AI/ml/hr. This mild stimulation of renin release was not associated with any change in MAP, RBF, GFR, or sodium excretion. In contrast to the results obtained with anesthetized dogs (360), MAP was unaltered and sodium excretion and GFR were increased. Interestingly, the 4-fold rise in sodium excretion, which normally would tend to suppress renin release, did not prevent saralasin-induced renin release.

The effect of AII blockade on renin release in pathophysiologic states other than caval constriction has been examined in dogs. An animal model of high output congestive heart failure can be effected by the surgical construction of a chronic aortic-caval fistula in dogs, and these animals exhibit a decrease in RBF, an increase in PRA, and sodium retention. An i.v. infusion of saralasin lowered blood pressure and elicited a 3-fold increase in PRA in these dogs with high output heart failure (360). When a small dose of saralasin was given directly into the kidneys of dogs with high output heart failure, RBF increased but PRA, GFR, and sodium excretion did not change. However, as the intrarenal dose of saralasin was increased, renin release was stimulated. Saralasin did not alter renin release or RBF in dogs with chronic ureteral obstruction (762). Freeman et al. (358) observed that saralasin potentiated hemorrhage-induced renin release and hypotension in conscious dogs. The progressive hemorrhage of anesthetized dogs led to a progressive rise in PRA until a MAP of 50 mm Hg was reached (65). The concentration of plasma renin substrate remained constant during hemorrhage, but the concentration of renin substrate fell by 70% if dogs were hemorrhaged during the i.v. infusion of saralasin. The rise in peripheral PRA and renin secretion seen during hemorrhage was potentiated by saralasin until renin substrate levels began to fall off significantly, then the values of PRA and renin secretion were considerably less than those observed with hemorrhage alone. Beatty et al. (65) concluded that plasma renin substrate levels were maintained during hemorrhage as a result of a positive feedback mechanism in which AII stimulated the production of renin substrate by the liver. Since saralasin was shown to block this positive feedback mechanism, it raises the possibility that in some situations saralasin might affect PRA by altering the concentration of plasma renin substrate rather than renin release per se.

Ayers et al. (38, 39) studied the effects of saralasin on renin release at different times after the stenosis of the renal artery in conscious, uninephrectomized dogs. During the first five days after surgery, PRA was elevated and the infusion of saralasin into the kidney elicited a 3- to 4-fold increase in PRA and a large decrease in renal vascular resistance but little change in MAP. In contrast, 10 to 14 days after surgery, basal PRA had decreased considerably, and an intrarenal infusion of saralasin had little effect on RBF yet PRA still rose 2-fold. Dietary sodium restriction restored the ability of saralasin to lower renal vascular resistance and increased basal PRA to a level slightly above that seen during the first 5 days after renal artery stenosis. Saralasin further increased PRA by 4-fold. Ayers et al. felt that intrarenally generated AII inhibited renin release by causing afferent arteriolar vasoconstriction, but it is important to note that saralasin caused a 3-fold elevation of PRA at a time when the antagonist had little effect on renal vascular resistance. This dissociation between the effects of saralasin on renin release and renal vascular resistance suggests that intrarenally generated AII was inhibiting renin release by a direct action on the granular JG cells. In agreement with the findings of Ayers et al. (38, 39), Freeman et al. (362) found that an i.v. infusion of saralasin had no effect on PRA in conscious dogs with chronic two-kidney renal hypertension unless the dogs had been placed on a sodium-deficient diet. Acute constriction of one renal artery in conscious dogs resulted in renin release and hypertension. An i.v. infusion of saralasin blocked the rise in blood pressure and potentiated the renin release.

Steele and Lowenstein (1037) observed that saralasin elicited a dose-related increase in PRA in conscious rabbits even though MAP remained constant. Prior sodium

depletion potentiated the renin response to saralasin, especially at the smaller doses of antagonist, even though the decrement in blood pressure was very slight. Stokes et al. (1047) infused saralasin directly in the kidneys of conscious, uninephrectomized rabbits and noted a dose-related elevation of the renal arteriovenous PRA difference. At the higher rates of infusion, both RBF and MAP were reduced significantly. The authors concluded that the stimulation of renin release by saralasin was due to blockade of the AII-mediated, negative feedback loop controlling renin release.

The renin release elicited by AII antagonists has been characterized most extensively in rats. Initially, Bing (84) reported that an i.v. infusion of saralasin increased PRA and PRC by 4- to 14-fold in conscious adrenalectomized rats, maintained with 1% saline drinking water and periodic injections of DOCA, but not in conscious, normal rats (84). In a more comprehensive study published some years later, Bing and Poulsen (86) found that saralasin elevated PRC by 12-fold in normal anesthetized rats, and this endocrine response was associated with a fall in systolic blood pressure of 25 to 45 mm Hg. The stimulation of renin release was apparent within 10 min of starting the infusion, it peaked at 30 to 60 min and PRC values then fell back to the control value despite the continued administration of saralasin. At this point, dihydralazine caused a large increase in PRC. Saralasin had no effect on renin release in conscious SH rats; however, in anesthetized SH rats, PRC increased 7-fold and blood pressure decreased. As seen previously, saralasin elicited renin release in adrenalectomized rats (maintained with 1% saline drinking water and DOCA), but the magnitude and duration of this stimulation was increased by anesthesia. In conscious or anesthetized adrenalectomized rats given only saline drinking water, basal PRC values were elevated and increased dramatically when saralasin was given. Blood pressure fell precipitously. Lastly, the increase in renin release usually seen in conscious and anesthetized normal rats after treatment with the converting enzyme inhibitor teprotide was blocked by saralasin. Because saralasin-induced renin release was associated with hypotension in most cases, and because the vasodilator dihydralazine caused hypotension and renin release in situations in which saralasin had no effect on either parameter, Bing and Poulsen (86) concluded that saralasin-induced hypotension was the major stimulus to renin release rather than interruption of the negative feedback of AII on renin release. In addition, saralasin was shown to possess a partial agonist effect at the AII receptors of the granular JG cells.

Other researchers (818, 1003, 1010, 1029, 1047) have noted that saralasin elicited renin release in anesthetized rats. When MAP was decreased to 70 mm Hg in anesthetized, vagotomized rats treated with atropine and pentolinium, an infusion of saralasin elevated PRC by 7-fold even though no further decrease in MAP occurred (818, 1047). Sen et al. (1003) treated normal and two-kidney renal hypertensive rats chronically with 1-Sar-8-Ile-AII before drawing blood samples under ether anesthesia. Plasma renin activity was increased 3-fold in the hypertensive animals but was not changed in normal rats. Hemodynamic changes were not reported. In a similar study in conscious, two-kidney hypertensive rats, Carretero and Gulati (197) found that saralasin produced no consistent pattern of change in PRA, even though blood pressure was lowered, and yet a 3-fold elevation of PRA was seen in hypertensive rats that did not exhibit a vasodepressor response to saralasin. Saralasin also was observed to bring about an equivalent 4-fold rise in SRA in conscious SH and Wistar-Kyoto rats (893). In each of these cases (197, 818, 893, 1003, 1010, 1047), the authors believed that these antagonistic analogues of AII elevated PRA by preventing the inhibitory action of AII on the secretory mechanism of the granular JG cells.

In 1975, Campbell et al. (185) discovered that saralasin potentiated minoxidil-induced renin release in conscious rats. Either saralasin or minoxidil alone increased SRA by 6-fold, but the combination of the two drugs caused a 150-fold increase in SRA. Because Pettinger and Keeton (892) had shown that saralasin also potentiated minoxidil-induced hypotension in conscious rats, Campbell et al. (185) suggested that saralasin and minoxidil had synergistic effects on renin release because of the greater fall in blood pressure with the drug combination. After the development of a radioimmunoassay for saralasin (895), Keeton et al. (572) made a thorough study of the effect of salt balance and adrenergic blockade on the renin release elicited by this AII antagonist. After s.c. injection into normal, conscious rats, saralasin consistently caused a slight decrease in PRA at 10 min followed by a 5-fold increase at 20 min. Plasma renin activity had returned to the control value by 40 min despite the fact that plasma saralasin levels were still elevated. In sodium-depleted rats, this same dose of saralasin caused an initial 70% decrease in PRA at 10 min, and then elevated PRA by 8-fold at 20 min. Animals treated with DOCA and saline showed no renin response to saralasin. The alteration of the renin-releasing abilities of saralasin by changes in sodium balance was seen in a more dramatic fashion when dose-response curves were constructed. Saralasin did not elicit significant renin release in normal-sodium rats until a dose of 10 mg/kg was given, and 30 mg/kg induced a further increase in PRC. Sodium-loaded, volume-expanded rats were refractory to the renin-releasing effects of saralasin even at plasma saralasin levels as high as 1300 ng/ml. Sodium depletion dramatically increased the sensitivity of the rats to the renin-releasing action of saralasin, and a dose as low as 0.3 mg/kg caused a 19-fold increase in PRC. The 30 mg/kg dose brought about a 260-fold rise in PRC. Saralasin did not alter MAP or heart rate in normal-sodium rats and caused only a 15% decrease in blood pressure in sodium-depleted rats at the largest dose used. Tachycardia was not observed consistently during saralasin-induced hypotension in these animals. Hydralazine, in a dose that produced the same

degree of hypotension and tachycardia as did saralasin, caused only a 3.5-fold increase in PRC in sodium-depleted rats whereas a 42-fold increase in PRC was seen after saralasin. Thus, saralasin appeared to have a stimulatory effect on renin release over and above its hypotensive effect.

Pretreatment with propranolol inhibited saralasin-elicited renin release by 99% in normal rats and by 75% in sodium-depleted rats without altering the hypotensive effect of saralasin in the latter group. Saralasin also potentiated phentolamine-induced renin release, hypotension, and tachycardia in normal rats. Saralasin or phentolamine alone elevated PRC by 5-fold and 15-fold, respectively, but the combination of these two drugs resulted in a 1000-fold increase in PRC. This potentiated renin release was inhibited by 90% with propranolol. Although propranolol also lessened the potentiated hypotensive response to this drug combination (T. K. Keeton, unpublished observations) it is unlikely that this effect could account for the 90% blockade of the 1000-fold increase in PRC seen with saralasin and phentolamine. These data indicated that a portion of saralasin-elicited renin release in sodium-depleted and phentolamine-treated rats was mediated by hypotensive activation of the carotid baroreflex that increased sympathetic nerve activity in the kidney.

Based on these data, Keeton et al. (572) concluded that: 1) the major portion of saralasin-induced renin release in conscious normal and sodium-depleted rats was the result of disinhibition of AII suppression of renin release; 2) the importance of the "short-loop" suppression of renin release by intrarenally generated AII is amplified by sodium deprivation; 3) the "short-loop" negative feedback mechanism controlling renin release is closely associated with intrarenal beta-adrenergic-receptors, presumably located on the granular JG cells; and 4) saralasin, under certain circumstances, acts temporarily as an agonist at the intrarenal AII receptors inhibitory to renin release and thereby decreases renin release. It should be pointed out that the agonistic properties of saralasin are modulated by dietary sodium and that sodium depletion minimizes the ability of saralasin to act as a partial agonist (754a). Lastly, because AII had been shown to inhibit adenylate cyclase in rat tail artery (1161), and because beta-adrenergically renin release appeared to involve the production of cyclic AMP, it was suggested that saralasin increased renin release by releasing granular JG cell adenylate cyclase from the inhibitory effect of AII (572).

Since inhibitors of prostaglandin synthesis prevented other forms of sympathetically mediated renin release (180), Campbell et al. (181) probed the role of prostaglandins in saralasin-induced renin release in normal rats. This AII antagonist increased SRA from 2.7 to 16.2 and 22.5 ng of AI/ml/hr at 10 and 30 mg/kg, respectively, without markedly altering blood pressure and heart rate. Pretreatment with indomethacin, which resulted in a greater than 70% suppression of the urinary content of PGE_2 and $PGF_{2\alpha}$, blocked 90% of the rise in SRA seen after either dose of saralasin. In like fashion, meclofenamate inhibited saralasin-elicited renin release in normal rats. In agreement with previous studies (572), Campbell et al. (181) noted that sodium-depletion sensitized rats to the renin-releasing properties of saralasin. A small dose of saralasin increased SRA by 10-fold, while lowering MAP by 6%, in sodium-deprived animals, and indomethacin, which did not affect basal renin release, inhibited 82% of this drug-stimulated renin release. Indomethacin did not affect the hemodynamic changes seen in sodium-depleted rats after saralasin. Saralasin-stimulated renin release similarly was inhibited by indomethacin, propranolol, and the combination of indomethacin and propranolol by 79%, 93%, and 100%, respectively. Campbell et al. (181) concluded that the renin release caused by saralasin in conscious rats appeared to be intimately associated with renal beta-adrenergic receptors and possibly was mediated by renal prostaglandins.

Concerning the effects of AII antagonists on renin release in vitro, Vandongen et al. (1136) found that nonpressor derivatives of AII, including saralasin, increased perfusate renin activity by 4-fold in the isolated perfused rat kidney. A slight decrement in renal perfusion pressure occurred. Hofbauer et al. (488) noted that small doses of saralasin caused a slight amount of vasodilatation and renin release in the isolated perfused rat kidney, but larger doses, which completely blocked AII-induced vasoconstriction, elicited vasoconstriction and inhibition of renin release. Plasma saralasin levels of a similar magnitude were associated with increased renin release in vivo (572). If a high concentration of AII was used to depress renal perfusate flow and renin release in the isolated perfused rat kidney, saralasin reversed the vasoconstriction but not the inhibition of renin release. It was concluded that saralasin possessed a high degree of intrinsic activity at the AII receptors of granular JG cells. Even though saralasin reversed AII-mediated inhibition of renin release from rat renal cortical slices in vitro, saralasin by itself did not cause a significant elevation of renin release (782).

In normotensive (153, 321, 388, 511, 685, 777, 811, 994) and hypertensive (151, 153, 201, 874, 895, 898, 900, 901, 1138, 1139, 1142, 1223, 1245, 1246) humans, saralasin and other receptor antagonists of AII have been observed to elevate PRA, and the ability of these agents to stimulate renin release appeared to be a function of both the pretreatment level of PRA (153, 201, 659, 898, 900, 1223, 1245) and sodium intake (201, 388, 498, 511, 777, 994, 1139, 1142, 1216). As a general rule, those patients with higher than normal PRA values exhibited a rise in PRA during the administration of saralasin. In like fashion, when basal PRA was elevated by salt depletion in humans who had not previously shown a renin response to saralasin, this AII antagonist elicited renin release. Saralasin, and other AII antagonists such as 1-Sar-8-Ile-AII, are partial agonists at AII receptors located in the vasculature, adrenal gland, and granular JG cells, and the

expression of the agonistic and antagonistic properties of saralasin is dependent on the basal value of PRA (18, 153, 201, 498, 1142, 1245) and sodium intake (18, 201, 388, 498, 511, 685, 826, 1142, 1216). Thus, saralasin decreased PRA (498, 685, 1142, 1216, 1245) and increased blood pressure (18, 153, 201, 388, 498, 511, 685, 826, 1245) in normal humans on a high salt diet, in normal-renin hypertensive patients on a high salt diet, and in low-renin hypertensive patients on either a normal or low salt diet. Conversely, AII receptor blockade increased renin release and decreased blood pressure in patients with high-renin hypertension on a normal (153, 201, 1245) or low salt (153, 201) diet, in normal-renin hypertensive (153, 201, 1139, 1142) and normotensive (153, 388, 511, 685, 777, 811) humans on a salt-restricted diet, in hypertensive patients with coarctation of the thoracic aorta (932), in patients with renovascular hypertension (1139, 1223), in hypertensive patients being treated with vasodilators (895, 898, 900, 901), in some hypertensive patients on maintenance hemodialysis (659), in cases of pheochromocytoma (944, 1138), and in other hyperreninemic conditions not associated with an elevation of blood pressure. In the last category, normotensive patients with Bartter's syndrome (1245), renal tubular acidosis (1245), and cirrhosis with ascites (994, 1245) experienced a fall in blood pressure and a rise in PRA during the antagonism of AII receptors.

Although many investigators have reported saralasin-induced renin release in humans, there is a major disagreement concerning the mechanism by which this stimulation occurs. On the one hand, saralasin was thought to elicit renin release only in those situations in which it caused vasodepression (201, 659, 777, 811, 874, 932, 1142, 1223, 1245). On the other hand, many researchers (151–153, 388, 511, 895, 898, 900, 994, 1139) have voiced the opinion that the renin-releasing effects of saralasin were not dependent on the ability of this compound to lower blood pressure. In the former case, saralasin-induced hypotension was thought to stimulate renin release via activation of the renal baroreceptor and/or the renal sympathetic nerves, whereas in the latter case, saralasin was thought to increase renin release by blocking the negative feedback of AII on the secretory function of the granular JG cells.

With regard to the activation of the renal baroreceptor by saralasin-induced hypotension, several groups of researchers (498, 685, 1139) have studied the effects of saralasin on renal hemodynamics during alterations in sodium intake. Van Hoogdalem et al. (1139) found that sodium depletion enhanced the hypotensive effect of saralasin in supine patients with unilateral renovascular, bilateral renovascular, and essential hypertension, but effective RPF was decreased in all three groups regardless of their salt intake or blood pressure response. When the subjects were on a normal sodium diet, saralasin elevated PRA by 3-fold in patients with stenosis of a single renal artery but caused a 22% decrease in PRA in patients with essential hypertension. After these two groups of patients had been sodium-depleted, saralasin caused a 2- to 3-fold increase in PRA in all patients despite the fact that the fall in blood pressure was twice as large in the renal hypertensive group as compared to those patients with essential hypertension. These authors (1139) concluded that no relationship existed between the changes in PRA and the changes in renal hemodynamics caused by saralasin, and that the renal vasculature appeared to be extremely sensitive to the partial agonist activity of saralasin. Hollenberg et al. (498) came to a similar conclusion when they found that saralasin brought about a dose-related decrease in RBF in normotensive humans given a high salt diet. In these subjects, saralasin caused a small rise in blood pressure and a decrease in PRA, GFR, and the excretion of sodium and potassium. MacGregor and Dawes (685) also noted that saralasin decreased effective RPF, urine flow, and sodium excretion when given to normal humans on a high salt intake, but the effect of incremental doses of saralasin on urine flow and sodium excretion were variable after sodium depletion. Thus, the renal baroreceptor does not appear to play a crucial role in saralasin-induced renin release in humans.

The sympathetic nervous system appears to play a role in saralasin-induced renin release in humans. It is not unusual for hypotensive agents to stimulate renin release since the fall in blood pressure results in the reflex activation of the renal sympathetic nerves. However, this generalized increase in sympathetic discharge usually results in an increase in heart rate, and saralasin-induced hypotension is notable for its inconsistent effects on heart rate (811, 895, 900, 994). Despite this fact, Pettinger and Mitchell (898, 900, 901) have found that the infusion of saralasin into hypertensive patients receiving minoxidil caused a 3-fold rise in PRA that was clearly related to the fall in blood pressure. A single dose of propranolol that yielded an average plasma propranolol level of 150 ng/ml did not alter basal PRA or the hypotensive action of saralasin but did prevent the previously observed rise in PRA. Chronic therapy with propranolol decreased basal PRA and blood pressure; however, under these conditions, saralasin had little effect on blood pressure or renin release. It was suggested that PRA was elevated by saralasin as a result of blockade of the AII-mediated, "short-loop" inhibition of renin release and that the intrarenal AII receptors responsible for the suppression of renin release were closely related to the beta-adrenergic receptors located on the granular JG cells (898). These conclusions are in accord with the results obtained in animal studies (181, 572).

Saralasin has been demonstrated to increase the plasma concentration of norepinephrine, but not epinephrine, in both normotensive and normal- and low-renin hypertensive humans (717, 944, 1160), but this effect is usually associated with the transient pressor action of saralasin. On the other hand, Carey et al. (191) reported that the transient and sustained pressor action of saralasin in normal- and low-renin hypertensive pa-

tients, respectively, was not associated with a change in plasma catecholamine content. In agreement with this viewpoint, Fagard et al. (321, 322) observed that saralasin did not alter the plasma levels of catecholamines seen in the supine or upright position. In these normal volunteers, saralasin potentiated the rise in PRA seen during exercise and slightly attenuated the increase in plasma norepinephrine concentration occurring at maximal exercise (322). Saralasin has been reported to cause a large increase in PRA and the plasma levels of norepinephrine and epinephrine as it lowered blood pressure in patients with a pheochromocytoma (944, 1138). It is not known if the prolonged depressor effect of saralasin in high-renin hypertension leads to an increase in plasma norepinephrine content.

2. Inhibitors of angiotensin I converting enzyme. Both the nonapeptide teprotide (80) and the modified proline molecule captopril (840, 963, 964) have been shown to prevent the conversion of AI to AII and the degradation of bradykinin. Therefore, just as the partial agonist activity of the AII receptor antagonists was found to limit their use as pharmacologic tools in the study of physiologic and pathophysiologic phenomena, the dual effects of the former drugs on angiotensin and kinin metabolism also has presented problems of interpretation. For example, Thurston and Swales (1093) presented evidence that indicated that a portion of the vasodepressor effect of teprotide in anesthetized, two-kidney Goldblatt hypertensive rats was dependent on the renal production of kinins. Additionally, captopril has been demonstrated to lower blood pressure in conscious SH rats (625, 775), an animal model of hypertension that does not exhibit a hypotensive response to AII receptor antagonists (361, 871), and this action of captopril was thought to be mediated by renal kinins.

In the first report of the induction of renin release by the blockade of AI converting enzyme, Bing (84) discovered that teprotide caused a rapid rise in PRC in conscious normal and adrenalectomized rats. In a later study, Bing and Poulsen (86) found that a single i.v. injection of teprotide resulted in a 5-fold increase in PRC in conscious normotensive rats, and this stimulation of renin release had dissipated by 1 hr. The injection of a second dose of teprotide then caused an equal rise in PRC, but a constant infusion of the peptide over a 5-hr period did not result in prolonged stimulation of renin release. Blood pressure did not change after the bolus injection or continuous infusion of teprotide. Blood pressure was lowered when teprotide was administered to anesthetized normotensive rats, and the magnitude and duration of the renin response was greater than that observed in conscious animals. When AI converting enzyme was blocked in conscious adrenalectomized rats, blood pressure remained constant and the increase in PRC was the same as that seen in normal rats. Teprotide elicited a 7- to 10-fold elevation of PRC in both conscious and anesthetized SH rats. Lastly, pretreatment of conscious normotensive animals with saralasin, which did not alter basal PRC values, prevented teprotide from releasing renin, and the administration of saralasin after teprotide reversed the increase in PRC caused by the latter compound. Bing and Poulsen suggested that teprotide stimulated renin release in conscious rats by functionally blocking the "short-loop" feedback inhibition of renin release. In anesthetized rats, teprotide had an additional hypotensive effect that augmented renin release, and the partial agonist effect of saralasin at the AII receptors of the granular JG cells prevented the renin release caused by the blockade of AI converting enzyme. Other investigators have observed that teprotide stimulated renin release in conscious mice (87) and anesthetized rats (297).

The AI-converting enzyme inhibitor captopril, which is more potent than teprotide and has no direct effect on vascular smooth muscle (964), has been shown to elicit renin release in normotensive (962), two-kidney Goldblatt hypertensive (962), and SH rats (503). In normotensive rats, captopril did not affect blood pressure (503), and yet the chronic administration of this drug resulted in a continual elevation of PRA over a 6-month period (962). The chronic treatment of SH rats with captopril for 6 months caused a large decrement in blood pressure and a 15-fold increment in PRA. In contrast, a dose of hydralazine that produced a lesser degree of hypotension over a 6-month period caused only a 3-fold increase in PRC (503). These observations are similar to those obtained when saralasin and hydralazine were compared in sodium-depleted normotensive rats (572).

Although the renal effects of teprotide and captopril are still being characterized, it is unlikely that these compounds elicit renin release by activation of the renal baroreceptor, the macula densa, or the renal sympathetic nerves. Like saralasin, teprotide produced vasodilatation in the kidneys of salt-restricted rats (28), and yet, as seen in the aforementioned studies, PRA was increased in sodium-depleted rats treated with these drugs (86, 962). Captopril lowered blood pressure by 22% in SH rats but did not change cardiac output; therefore, the hypotensive action of the drug was attributed to a decrease in total peripheral resistance (775). No diuresis, natriuresis, or kaluresis was observed. Like saralasin, the vasodepressor effects of captopril in rats rarely elicited a reflex increase in heart rate (625, 775, 963). Thus, the ability of teprotide and captopril to bring about an increase in renin release appears to result from the blockade of the "short-loop," negative feedback mechanism.

Antonaccio et al. (21a) studied the effects of cotreatment with either propranolol or indomethacin on the renin release seen in SH and Wistar-Kyoto (normotensive) rats after 3 days of oral therapy with captopril. Captopril elevated PRA to a greater extent in SH rats (8-fold increase) as compared to the normotensive animals (3-fold increase). Indomethacin alone suppressed PRA by 60% to 70% in both SH and normal rats but did not block the stimulation of renin release caused by captopril. Propranolol alone lowered basal PRA by 70% and 40% in SH and normal rats, respectively. During the

combined administration of propranolol and captopril to SH rats, PRA rose 7-fold relative to the values seen with propranolol alone, but the absolute PRA values were significantly less than those observed after captopril alone. In like fashion, propranolol did not impair the ability of captopril to elicit renin release in normal rats. Neither propranolol nor indomethacin altered the 20% decrease in MAP caused by captopril in the two strains of rats. Conversely, Abe et al. (2a) reported that indomethacin blocked the increase in PRA seen after the chronic treatment of normotensive and hypertensive humans with captopril. Captopril lowered MAP by 18% in hypertensive patients but had no effect on blood pressure in the normotensive subjects. The hemodynamic responses to captopril were not affected by the addition of indomethacin. The urinary excretion of PGE increased by 48% during therapy with captopril, and the addition of indomethacin resulted in a 50% decrease in the urinary concentration of PGE. Abe et al. (2a) concluded that captopril elevated PRA by interrupting the inhibition of renin release by AII and that endogenous prostaglandins were involved in the "short-loop" feedback inhibition of renin release. The latter conclusion is consistent with the observation that indomethacin blocked saralasin-induced renin release in conscious rats (181).

Ayers et al. (39) reported that teprotide stimulated renin release and renal vasodilation in conscious uninephrectomized dogs. Although teprotide did not affect PRA or MAP in normal dogs, this peptide lowered MAP and elevated PRA in one-kidney Goldblatt hypertensive dogs (752). When the drug was administered periodically after renal arterial constriction, it was noted that the hypotensive and renin-releasing effects of teprotide gradually waned. The constant infusion of teprotide after stenosis of the renal artery prevented the development of hypertension and caused a constant elevation of PRA. Because plasma bradykinin levels did not change after teprotide, it was concluded that the rise in PRA resulted from blockade of the "short-loop" feedback mechanism controlling renin release. McCaa (705, 706) also found a persistent 6-fold increase in PRA when conscious sodium-deprived dogs were given a constant infusion of teprotide over a seven-day period. This increase in PRA was associated with a natriuresis and kaluresis.

Samuels et al. (977) observed that teprotide did not alter PRA or MAP in normal conscious dogs. Salt-deprivation elevated basal PRA in these animals, and treatment with teprotide lowered blood pressure and increased PRA by 4-fold. In adrenalectomized dogs that were given hormonal replacement therapy with DOCA and corticosterone the inhibition of AI converting enzyme had no effect on PRA or MAP during the ingestion of a normal salt diet, but a sharp fall in blood pressure and increase in renin release was seen when the animals had been ingesting a low salt diet. Because similar hemodynamic and hormonal responses followed the administration of saralasin, bradykinin was not considered to play a role in the actions of teprotide. When phenylephrine was used to maintain blood pressure at normal levels in sodium-depleted adrenalectomized dogs, teprotide elicited an increase in PRA similar to that when MAP was allowed to fall. This observation, combined with the facts that little reflex tachycardia occurred when teprotide lowered arterial pressure and that propranolol did not block the rise in PRA, led these researchers to conclude that the nonapeptide inhibitors of AI converting enzyme stimulated renin release by blockade of the "short-loop" feedback system.

As with saralasin (572), teprotide-induced renin release was potentiated by sodium depletion and blunted by sodium loading in conscious dogs (591). When infused directly into the kidney, teprotide increased RBF, GFR, and sodium excretion in sodium-deprived dogs but had no effect on these parameters after a high salt diet. The presence of elevated renin release in the face of an increase in sodium excretion (591, 705) makes it unlikely that teprotide stimulated renin release via the macula densa.

Captopril also has been shown to elicit renin release in anesthetized dogs (1170) and conscious dogs on a normal (445) and sodium-restricted (705, 707) diet. In conscious normotensive dogs, captopril caused a moderate dose-related decrease in MAP without affecting heart rate (445). In a parallel fashion, this drug elicited a dose-related elevation of PRA (up to 15-fold increase), and both the level of PRA achieved and the duration of the effect were dose-dependent. Plasma renin activity was thought to increase in response to the interruption of the "short-loop" feedback mechanism and the fall in arterial pressure. When given chronically to sodium-depleted dogs for 2 weeks, captopril raised PRA, sodium excretion, effective RPF, and blood kinin concentration while lowering MAP, GFR, and the level of urinary kallikrein (707). In related studies, chronic oral therapy with captopril increased PRA from 5.0 to 34.6 ng of AI/ml/hr, and in the presence of beta-adrenergic blockade, captopril caused PRA to rise to 5.9 ng of AI/ml/hr (R.E. McCaa, personal communication). Thus, in contrast to the lack of an effect of propranolol on teprotide-induced renin release in conscious sodium-depleted dogs (977), propranolol greatly attenuated the ability of captopril to stimulate renin release in sodium-depleted dogs. However, this point is in need of further clarification since the 5-fold elevation of PRA that followed the administration of captopril to conscious rabbits (780) was not altered by pretreatment with the beta-adrenergic antagonist nadolol (V. S. Murthy, personal communication).

The inhibition of AI converting enzyme by teprotide and captopril has been found to elevate PRA in humans. The nonapeptide teprotide has been reported to increase PRA in both normotensive (978, 1167, 1215, 1217) and hypertensive (202, 376, 381, 1167, 1215, 1217) humans. In

like fashion, treatment with captopril stimulated renin release in normotensive (326) and hypertensive (154, 156, 200, 223, 378) humans.

Concerning teprotide, Case et al. (202) reported that the i.v. administration of this compound increased PRA in normal- and high-renin hypertensive patients on either a low or normal salt diet but was without effect in patients with low-renin hypertension on either diet. A close relationship was noted between the hypotensive effect of teprotide and the subsequent rise in PRA. Gavras et al. (376, 381) suggested that the stimulation of renin release by teprotide resulted from a combination of blockade of the "short-loop" feedback controlling renin release and the fall in blood pressure. In these studies, PRA increased in supine hypertensive patients on a low or normal salt diet, and orthostasis-induced renin release also was potentiated by teprotide. Other investigators (978, 1167) have observed that teprotide potentiated the rise in PRA observed after the attainment of upright posture. Sancho et al. (978) observed a 2- to 3-fold elevation of PRA after teprotide was given to supine normotensive patients on a low or normal salt diet. Blood pressure fell slightly in the former case, but did not change in the latter case. Thus, the stimulation of renin release was felt to be due to a decrease in the concentration of AII at the granular JG cells (978, 1167). The ability of AII to suppress renin release was found to be impaired greatly in patients with essential hypertension, as compared to normotensive volunteers. When the normotensive and hypertensive subjects were placed on a sodium-restricted diet, an equivalent decrease in blood pressure after teprotide produced a smaller increase in PRA in the hypertensive patients (1217).

Williams and Hollenberg (1215) examined the effects of teprotide on RBF and plasma bradykinin levels in supine sodium-depleted normotensive and hypertensive patients. Renal blood flow was increased by the drug in both groups, but the plasma concentration of bradykinin was increased only in the hypertensive patients. A slight vasodepression and an equal increase in PRA, as compared to basal values, was noted in both groups. These data (1215) make it unlikely that teprotide stimulates renin release by increasing the renal production of kinins or activation of the renal baroreceptor.

In 1977, Ferguson et al. (326) reported that a single dose of captopril elicited a 2-fold increase in PRA in normotensive humans without lowering blood pressure. Because blood pressure did not fall, the rise in PRA was conjectured to be the result of blockade of the "short-loop" feedback of renin release. Case et al. (200) disagreed in a later study. The increase in PRA seen after the administration of a single oral dose of captopril to seated hypertensive patients was closely correlated with the decrement in arterial pressure and the pretreatment PRA value. During chronic oral therapy with captopril, PRA was elevated in both the supine and upright positions. In other clinical studies (378), chronic treatment of hypertensive patients with captopril lowered MAP by 21% and increased PRA by 5-fold. A greater stimulation of renin release was observed in patients with renovascular hypertension as compared to those with essential hypertension, and a slight elevation of pulse rate was seen in all patients. As a result, it was concluded that captopril stimulated renin release by blockade of the "short-loop" control system, by activation of the renal baroreceptor and by hypotensive activation of the renal sympathetic nerves.

However, tachycardia in association with captopril-induced hypotension is not a consistent observation (154, 223). For instance, Brunner et al. (154) found that 1 week of oral therapy with captopril lowered diastolic blood pressure by 16% and increased PRA by 4-fold but did not change heart rate. Because cardiac index was not changed, Cody et al. (223) concluded that the average 15% reduction in MAP caused by 3 days of oral therapy with captopril was the result of a diminution of total peripheral resistance. Despite the lack of activation of the sympathetic nervous system, PRA values tripled during drug treatment. The usual increase in heart rate and total peripheral resistance and decrease in cardiac index attendant to passive tilting were not altered by captopril; therefore, the lack of reflex cardiac stimulation was suggested to be because captopril caused a significant amount of venodilatation. It is hoped that the role of the sympathetic nervous system in the renin release brought about by captopril will be better defined in future studies.

To summarize, AII receptor antagonists and inhibitors of AI converting enzyme increase renin release in normotensive and hypertensive animals and humans. In general, the ability of these drugs to stimulate renin release is dependent on the pretreatment level of PRA, which is in turn affected by changes in salt intake. In situations in which PRA is increased by these agents, and yet blood pressure is unaltered, the stimulation of renin release is probably the result of blockade of the negative feedback effect of AII on the secretory function of the granular JG cells. The importance of this "short-loop" inhibition of renin release is amplified by sodium deprivation, but, in addition, the stimulation of renin release in sodium-depleted states is partly attributable to the hypotensive effect of these drugs. In certain situations, the partial agonist effect of saralasin actually causes a decrease in renin secretion. Beta-adrenergic receptor blockade prevents saralasin-induced renin release in rats and humans, and inhibition of prostaglandin synthesis prevents this drug action in rats. Saralasin causes a transient elevation of the circulating levels of norepinephrine in the blood, but it is not known if the drug actually alters the functional status of the peripheral sympathetic neuron during continued therapy. Several questions are still unanswered with regard to the renin release induced by AII receptor antagonists and inhibi-

tors of AI converting enzyme. Do saralasin, teprotide, and captopril stimulate renin release in conscious dogs with a single, denervated, nonfiltering kidney? Does the hypotensive action of these drugs result in a reflexly mediated increase in the plasma concentration of norepinephrine?

F. Lithium

Lithium is used as a psychoactive agent in the treatment of manic-depressive disorders (254, 992, 1018). The major route of elimination of lithium from the body is renal excretion (254, 992, 1018), and, like sodium, approximately 80% of the filtered lithium is reabsorbed in the proximal tubule (1087, 1088). In addition, factors known to increase or decrease the proximal tubular reabsorption of sodium similarly increase or decrease the reabsorption of lithium at this site (1087, 1088). Thus, the clearances of lithium and sodium have been found to be directly related. In contrast to sodium, lithium is not reabsorbed in the more distal segments of the nephron, and its excretion is not altered by mineralocorticoids or diuretics that act on these distal segments. Since lithium has physicochemical properties that are similar to those of sodium and potassium, and since the renal metabolism of lithium and sodium are closely related, it is not surprising that lithium alters renin release.

Gutman et al. (425) were the first to demonstrate an effect of lithium chloride on renin release. When rats were injected with lithium chloride (6 mmoles/kg/day) for 4 days, a 2- to 3-fold increase in PRA was observed. In a later study (427), lithium chloride elicited a biphasic change in renin release with small doses (3 mmoles/kg/day) reducing the PRA by 50% and large doses (16 mmoles/kg/day) causing a 2-fold increase in PRA. When a dose of sodium chloride equal to the largest dose of lithium was given, basal PRA fell by 75%, and the increase in PRA usually caused by lithium chloride was blocked. When 5 mM lithium was added to the perfusate of isolated perfused rat kidneys, renin release increased 4-fold. The authors (425, 427) conjectured that small doses of lithium suppressed the release of renin by acting on the macula densa in a manner similar to sodium whereas large doses stimulated renin release by causing sodium depletion. This latter suggestion is supported by the finding that the co-administration of sodium chloride blocked lithium-induced renin release. However, this suggested mechanism of action does not explain why lithium elicited renin release in the isolated perfused rat kidney. Considering the known role of chloride in the control of renin release by the macula densa (610), it would be of interest to determine whether a low dose of lithium carbonate suppressed PRA in vivo as much as a low dose of lithium chloride.

Kierkegaard-Hansen (583, 584) found that chronic treatment of rats with lithium chloride, sufficient to yield serum lithium levels of 0.44 mM, did not affect PRC, plasma renin substrate content, or blood pressure. A large dose of lithium chloride eventually resulted in an average serum lithium concentration of 1.29 mM and overt signs of lithium intoxication. In this situation, PRC increased by 10-fold, plasma renin substrate concentration dropped by 72%, and blood pressure remained constant. Neither dose was found to alter serum sodium concentration, total body sodium content, or the amount of exchangeable sodium (1086). A large dose of lithium chloride produced lithium intoxication, stimulated renin release, and suppressed plasma renin substrate levels in rats ingesting a low, but not a high, sodium diet (584). On the high sodium diet, however, PRC was increased if the dose of lithium chloride was increased. As before, the concentration of renin substrate in the plasma declined significantly. It was pointed out that the rise in PRC and the fall in plasma renin substrate content seen during lithium intoxication was similar to the situation encountered after sodium depletion or bilateral adrenalectomy (196). Again, it would be interesting to know whether large doses of lithium carbonate had the same effect as large doses of lithium chloride.

Beck et al. (66) studied the effects of lithium chloride on basal and isoproterenol-stimulated renin release in anesthetized dogs. After an oral dose of lithium chloride, which raised the plasma lithium concentration to 0.9 mM, PRA doubled and urinary cyclic AMP excretion fell by 66%. Mean arterial pressure, RPF, GRF, and sodium excretion were not changed. Furthermore, lithium did not affect the increase in PRA caused by isoproterenol. Because sodium excretion, RPF, and GRF were not altered by lithium in these experiments, the authors (66) felt that it was unlikely that lithium increased PRA by contraction of the extracellular volume or diminution of the amount of sodium reaching the macula densa; however, no alternative explanation for the action of lithium was proposed.

Several investigators (14, 265, 585, 1013) have noted the effects of lithium carbonate on renin release in psychiatric patients. Demers et al. (265) were the first to report that PRA was elevated approximately 2-fold in four of six agitated patients on either a normal or low sodium diet. In these patients, the serum lithium levels varied between 0.75 and 1.34 mM. Shopsin et al. (1013) observed that PRA increased 4- to 6-fold within the first 24 hr after the administration of lithium to three patients. However, during the second week of treatment, PRA returned to pretreatment values despite therapeutic levels of lithium in the blood. This finding prompted these clinicians (1013) to state that lithium did not directly stimulate the release of renin. A similar transient stimulation of renin release was reported by Altamura and Morganti (14). In addition, they noted that PRA increased more when lithium-treated patients were in the upright position (14). Kierkegaard-Hansen et al. (585) found that PRC was not elevated in nine patients treated with lithium for 3 months when compared to their pretreatment values. Also, in patients treated with lithium for periods of 2 to 20 years, PRC did not differ from a

control group of normal volunteers and manic-depressive patients not receiving the drug.

In summary, lithium in small doses appears to inhibit renin release but in large doses it stimulates its release. The stimulatory effect is transient with PRA levels returning to normal within 2 weeks. This observation plus the requirements for high plasma levels of lithium indicates that lithium does not tonically affect the release of renin. The mechanisms by which lithium stimulates or inhibits renin release have not been studied adequately. Therefore, from the available data, we can only suggest that these effects are due to an action of lithium on the proximal reabsorption of sodium since: 1) the co-administration of sodium blocked the stimulatory effect of lithium on renin release; 2) lithium does not alter sodium reabsorption in more distal segments of the nephron; and 3) systemic and renal hemodynamics are not affected by lithium.

G. Nonsteroidal Anti-Inflammatory Drugs (Prostaglandin Synthesis Inhibitors)

Since the discovery by Vane (1137) in 1971 that nonsteroidal anti-inflammatory drugs such as aspirin and indomethacin inhibited the synthesis of prostaglandins, a monumental number of studies have been performed with these drugs in an attempt to delineate the contribution of endogenous prostaglandins to various physiologic phenomena. Along these lines, a number of investigators have used these prostaglandin synthesis inhibitors to probe the involvement of renal prostaglandins in the control of renin release. In reviewing these studies, however, the reader must bear in mind that these drugs have a number of actions, in addition to inhibiting prostaglandin synthesis, that may alter the release of renin (341). For instance, various inhibitors of prostaglandin synthesis have been shown to antagonize the actions of calcium (810), elicit salt and water retention (127), and inhibit the enzymes phosphodiesterase and l-aromatic amino acid decarboxylase (341). Thus, even in studies in which suppression of prostaglandin synthesis has been clearly demonstrated, the evidence for a prostaglandin-mediated mechanism of action is indirect and the conclusions should be viewed with appropriate caution.

A number of studies (127, 286, 364, 807, 877, 966) have examined the effect of inhibition of prostaglandin synthesis on basal PRA values. Rumpf et al. (966) found that either single or multiple doses of indomethacin reduced PRA by 49% in normal subjects in the recumbent position. Furthermore, a single dose of indomethacin continued to suppress PRA over a 12-hr period. After a single dose of indomethacin, this suppression of renin release occurred in the absence of any change in sodium balance since sodium and potassium excretion and urine volume were unchanged. The authors, however, failed to mention if changes in blood pressure or heart rate occurred. The same year, Patak et al. (877) reported a 75% suppression of PRA by indomethacin in normal subjects and hypertensive patients. Urinary sodium excretion did not change, but blood pressure increased significantly by approximately 5 mm Hg. Norbiato et al. (807), in studies with normal humans in the supine position, observed a 16% suppression of PRA with aspirin and a 62% suppression with diclofenac sodium after 2 days of treatment with each drug. It should be mentioned that these investigators (807, 877, 966) did not measure the degree of suppression of prostaglandin synthesis.

In contrast, Frolich et al. (364) reported that indomethacin suppressed PRA by 48% in association with a 33% decrease in sodium excretion and a 55% decrease in the urinary excretion of PGE. Since indomethacin did not alter either the generation of AI in vitro or the radioimmunoassay procedure used in their PRA determinations, the authors concluded that the fall in PRA was due to a decrease in the release of renin. Donker et al. (286) also observed a 58% suppression of PRA, in association with a 36% decrease in the excretion of sodium, when indomethacin was administered to a group of normal subjects and patients with renal disease.

Indomethacin, in doses that suppressed the renal synthesis of prostaglandins, decreased the release of renin in conscious and anesthetized rabbits (635, 948, 951). In one such study, Romero and Strong (951) observed a 85% suppression of PRA by indomethacin in conscious rabbits. This fall in PRA was associated with a slight fall in blood pressure, a 16% decrease in RBF, and an approximately 85% suppression of PGE concentration in arterial blood. Changes in salt and water excretion were not determined. Similar changes in renin release were reported for anesthetized rats after indomethacin (656) and for conscious rats after indomethacin or meclofenemate (21a, 179, 180). Leyssac et al. (656) found that indomethacin, in doses that lowered renal venous PGE_2 levels by 61%, suppressed renal venous PRA by 30% and RPF by 18%. The proximal reabsorption of sodium increased by 8%, and MAP rose 7 mm Hg. Campbell et al. (179, 180) observed a 43% to 50% suppression of SRA after indomethacin and a 27% to 38% suppression of SRA after meclofenamate in conscious rats. The urinary excretion of both PGE_2 and $PGF_{2\alpha}$ was lowered by 75%. These prostaglandin synthesis inhibitors failed to alter systemic blood pressure. In like fashion, 3 days of oral therapy with indomethacin, which has no effect on MAP, lowered basal PRA by 60% to 70% in conscious SH and normal rats.

Yun et al. (1256) found that indomethacin decreased renal venous PRA and renin secretion by 46% and 68%, respectively, in sodium-depleted anesthetized dogs. This change in renin secretion was accompanied by a 68% decrease in RPF, a 36 mm Hg increase in MAP, a 28% decrease in heart rate, a 79% decrease in urinary volume, and no change in sodium excretion. Since indomethacin increased blood pressure, the same experiments were repeated in dogs in which renal perfusion pressure was held constant by means of a suprarenal aortic clamp. As

in the previous series of studies, indomethacin suppressed renin secretion by 54% while decreasing RPF by 48% and urinary volume by 57%. In a later report (1257), however, indomethacin failed to alter the PRA of conscious dogs on a high salt diet. Since indomethacin also failed to affect the basal PRA of these same dogs after the induction of pentobarbital anesthesia, but suppressed PRA in anesthetized, laparotomized dogs (1256), the authors suggested that laparotomy per se stimulated renin release by a prostaglandin-mediated mechanism that was blocked by indomethacin (1257). In support of this hypothesis, Terragno et al. (1080) found that anesthesia alone did not change the renal venous concentrations of these hormones. Other investigators (45, 246) also have reported a fall in PRA in anesthetized, surgically stressed dogs. For instance, Bailie et al. (45) noted a 58% reduction of arterial PRA and renin secretion after treatment with indomethacin. This decrement in renin secretion was accompanied by a 21 mm Hg increase in MAP, an 18% decrease in RBF, and complete suppression of PGE secretion from the kidney. In anesthetized dogs with a single denervated, nonfiltering kidney, Data et al. (246) found that indomethacin did not reduce the renal venous PRA significantly.

Thus, indomethacin and other nonsteroidal anti-inflammatory drugs suppress the basal release of renin in humans and animals by a mechanism that may be related to their ability to suppress renal prostaglandin synthesis. However, it should be noted that inhibitors of prostaglandin synthetase may suppress renin release by either a direct action on the granular JG cells or by an indirect action that may involve salt and water retention, renal vasoconstriction, or increased blood pressure. However, the studies cited above suggest that renal prostaglandins exert a tonic stimulatory influence on the release of renin from the kidney.

In addition to altering basal renin release, these drugs inhibit renin release that has been elevated by a number of physiologic, pharmacologic, and pathologic stimuli. In normal humans, Rumpf et al. (966) observed that the 2-fold increment in PRA associated with upright posture was blocked completely by pretreatment with indomethacin. These results obtained with indomethacin were confirmed by other workers (286). In addition, Norbiato et al. (807) performed similar studies with the prostaglandin synthetase inhibitors aspirin and diclofenac sodium. In subjects on a normal sodium diet, upright posture caused a 3-fold increase in PRA. Aspirin and diclofenac sodium reduced this orthostasis-induced renin release by 73% and 79%, respectively. When the same subjects were placed on a low sodium diet containing 15 to 30 mEq of sodium/day, PRA was increased 4-fold in the supine position, and upright posture caused a further 2-fold increase in PRA. Treatment with diclofenac sodium reduced supine PRA by 83% and standing PRA by 65%. Further sodium restriction (less than 15 mEq of sodium/day) produced an additional increment in supine and standing PRA values; however, under these conditions, diclofenac sodium did not affect the elevated PRA in either the supine or standing position. The authors suggested that severe sodium depletion might directly stimulate renin release by a mechanism not mediated by prostaglandins. It would appear, however, that prostaglandins are involved in the renin response to postural changes in humans. In agreement with the findings in humans, indomethacin, in doses that decreased the urinary excretion of PGE and PGF by 68% and 52%, respectively, reduced SRA by 43% in rats on a normal sodium diet but failed to alter SRA in rats ingesting a low sodium diet (179).

Galvez et al. (371) examined the effects of indomethacin on the increased renin release associated with potassium deficiency in dogs. Following 3 weeks of potassium depletion, PRA increased by 43-fold and urinary PGE excretion by 8-fold whereas RPF, GFR, and MAP were unchanged. Indomethacin reduced the urinary excretion of PGE to levels below the values before potassium depletion and suppressed PRA by 96%. Plasma renin activity remained suppressed during the 3 days of therapy with indomethacin, but no change in sodium or potassium balance occurred despite a 3-fold decrease in urinary volume during the period. These researchers suggested that the effect of potassium on renin secretion was not due to changes in sodium transport or delivery to the macula densa unless these factors were in some way related to the synthesis of renal prostaglandins.

The role of renal prostaglandins in macula densa-mediated renin release has received little attention to date. Williams et al. (1218), with a stop-flow technique in anesthetized dogs, found the peak concentrations of urinary PGE to be located in the portion of the tubular fluid that would correspond to a nephron segment located between the proximal and distal tubule. Therefore PGE, and possibly other renal prostaglandins, enter the renal tubular fluid at a site proximal to the macula densa. If the PGE reaching the macula densa inhibits the active reabsorption of sodium and chloride, as it does in the ascending limb of the loop of Henle (1052) and the collecting duct (1051), then the rate of renin release would be enhanced. It is hoped that the knowledge that prostaglandins are present in the tubular urine bathing the macula densa and the observation that furosemide- and sodium depletion-induced renin release are impaired by inhibitors of prostaglandin synthesis will stimulate interest in this worthwhile area of research.

As discussed previously, prostaglandins appear to be involved in the mediation of renal baroreceptor-stimulated renin release. Since ureteral occlusion in anesthetized dogs was thought to elevate renin release by activation of the renal baroreceptor mechanism (301), and since this maneuver increased RBF and the urinary excretion of PGE_2 in anesthetized dogs (836), Blackshear and Wathen (95) tested the effects of indomethacin on PRA and RBF during ureteral occlusion in anesthetized,

hydropenic dogs. Blockade of renal prostaglandin synthesis prevented the increase in RBF and markedly blunted the increase in renin secretion normally observed during ureteral clamping. After ureteral occlusion had increased renin secretion and RBF in untreated animals, an intrarenal arterial infusion of PGE_2 did not further elevate RBF or renin secretion. However, the infusion of PGE_2 in indomethacin-treated dogs after ureteral occlusion resulted in renal vasodilatation and increased renin secretion. It was concluded that renal prostaglandins caused the increase in RBF seen during ureteral occlusion. Furthermore, these prostaglandins, either directly, or indirectly through vasodilatation, appeared to stimulate renin secretion during an increase in ureteral pressure (95). Although indomethacin may inhibit renal vasodilatation and renin secretion by actions (810) that do not involve the inhibition of prostaglandin synthesis, it does appear that these inhibitors have the potential to alter baroreceptor-mediated renin secretion. Orthostasis-induced renin release in humans is thought to be due to activation of the renal sympathetic nerves (846) and renal baroreceptor (69). Concerning the latter mechanism, 2 hr of ambulation in 19 recipients of renal allografts was found to result in a 3-fold increase in PRA (69). It would be of interest to determine whether indomethacin can prevent orthostasis-induced renin release in patients with functioning renal allografts.

Indomethacin also has been found to inhibit furosemide-induced renin release in humans and animals (45, 364, 830, 877, 948, 966, 1074, 1191). Furosemide-induced renin release is biphasic with the first increase in PRA occurring within 10 min followed by another larger increase in PRA occurring 60 to 120 min later (364, 830, 1191). In the most comprehensive study, Frolich et al. (364) found in normal humans that i.v. furosemide produced a 2.6-fold increase in PRA that reached its peak level at 10 min. Indomethacin, in doses that caused a 55% suppression of the urinary excretion of PGE, completely inhibited the initial increase in PRA caused by furosemide. Indomethacin also reduced the natriuretic effect of furosemide by 28% but did not alter the urinary excretion or plasma levels of furosemide. Abe et al. (3) observed a 2.5-fold increase in the urinary excretion of PGE in normal and hypertensive humans within the first 2 hr after i.v. furosemide. These changes in PGE excretion were accompanied by a 4.5-fold increase in PRA and a 6-fold increase in sodium excretion. Therefore, the initial elevation of PRA caused by furosemide appeared to result from the increased production of prostaglandins, possibly PGE, and indomethacin prevented this initial increase in PRA. In addition, pretreatment with indomethacin inhibited by 50% to 80% the second, later rise in PRA caused by furosemide in humans and animals (830, 877, 966, 1074, 1191). As a result, indomethacin can modify the results obtained with the furosemide stimulation test used to identify low-renin hypertensive patients (364, 1074). For instance, Tan and Mulrow (1074) administered furosemide orally to 12 normotensive humans the night before and the morning of the test, followed by 4 hr of ambulation to elevate PRA further. Indomethacin, in doses that suppressed the urinary excretion of PGE_2 by 97%, prevented 78% of the stimulated renin release. Thus, it is clear that indomethacin inhibited the late rise in PRA elicited by furosemide; however, in the absence of studies in which the urinary losses of salt and water caused by furosemide were replaced, it is not known whether indomethacin reduced the late rise in PRA by inhibiting furosemide-induced natriuresis and/or renal prostaglandin synthesis.

Inhibitors of prostaglandin synthesis have been shown to block orthostasis-induced renin release (286, 807, 966), which is known to involve activation of the sympathetic nervous system (846) and renal baroreceptor (69). Thus, prostaglandins also may be involved in the elevation of renin release by the sympathetic nerves. In order to explore this possibility, Frolich et al. (365) infused isoproterenol i.v. into normal humans on a 150 mEq/day sodium diet and observed a 20 beat/min increase in heart rate and a 5-fold increase in PRA. Pretreatment with indomethacin, in a dose that decreased the urinary excretion of the major urinary metabolite of PGE_2 by 50%, suppressed the isoproterenol-induced increase in PRA by 91%. Interestingly, in subjects ingesting a 10 mEq/day diet, isoproterenol increased PRA only 2-fold and indomethacin failed to reduce basal or isoproterenol-stimulated renin levels. Campbell et al. (180), in conscious rats, found that the vasodilator hydralazine caused a 10-fold increase in SRA whereas a equidepressor dose of chlorisondamine, a ganglionic blocker, caused only a 2-fold increase in SRA. The renal baroreceptor stimulation produced by the two drugs was similar, and the difference in the renin responses to chlorisondamine and hydralazine was thought to be due to the presence of a functional sympathetic nervous system in the hydralazine-treated rats. In support of this hypothesis, the rise in SRA caused by hydralazine, but not that caused by chlorisondamine, was inhibited by pretreatment with propranolol (180a). However, the elevation of SRA caused by chlorisondamine, which has been shown to be the result of activation of the renal baroreceptor (571), was completely blocked by pretreatment with indomethacin. The hypotension following chlorisondamine was not affected by indomethacin (180). In addition, indomethacin and meclofenamate, in doses that reduced the urinary excretion of PGE_2 and $PGF_{2\alpha}$ by 65% and 89%, respectively, inhibited hydralazine-induced renin release by 100% and 77%, respectively. Since pretreatment with a combination of indomethacin and propranolol did not inhibit hydralazine-induced renin release to a greater extent than did either blocker alone, the authors concluded that indomethacin and propranolol inhibited hydralazine-induced renin release by a common mechanism that involved the sympathetic nervous system (180a).

This contention was supported further by the obser-

vation that indomethacin prevented 70% of the 4-fold increase in renin release elicited by the beta-adrenergic agonist isoproterenol (180). Indomethacin did not alter isoproterenol-induced hypotension and tachycardia; therefore, the inhibitory effect of indomethacin was not due to beta-adrenergic receptor blockade, but rather was thought to be due to inhibition of a mechanism distal to renal beta-adrenergic receptors. In addition, beta-adrenergically mediated renin release was stimulated with intraarterial infusions of isoproterenol and the selective $beta_1$-adrenergic agonist H133/22. Blood pressure did not change with either drug. Indomethacin inhibited the renin release, caused by these two drugs by 67% and 80%, respectively. This belief was further substantiated by the observation that pretreatment with indomethacin totally prevented the 5-fold increase in SRA produced by the infusion of dibutyryl cyclic AMP into the aorta above the kidneys. Based on these findings with hydralazine, isoproterenol, H133/22, and dibutyryl cyclic AMP, Campbell et al. (180) concluded that renal prostaglandins, by acting at a site distal to the beta-adrenergic receptors of the granular JG cells, serve as mediators of sympathetically-induced renin release in the conscious rat.

Other researchers have also investigated the effects of indomethacin on isoproterenol-stimulated renin release. Seymour and Zehr (1006a) reported a 3-fold increase in PRA after an i.v. infusion of isoproterenol into anesthetized, unilaterally nephrectomized dogs. An intrarenal infusion of indomethacin decreased the basal PRA by 56% and inhibited isoproterenol-stimulated renin release by 66%. Feuerstein and Feuerstein (331a) also reported that indomethacin inhibited by 91% the 5-fold increase in PRC that accompanied an intrarenal infusion of isoproterenol into anesthetized cats. In contrast to these reports, Berl et al. (75a), in anesthetized dogs, observed a 5-fold increase in PRA, an increase in heart rate and a decrease in MAP after an i.v. infusion of isoproterenol. Indomethacin did not change the increment in PRA that followed isoproterenol infusion. A similar lack of effect was obtained with indomethacin when renal perfusion pressure was maintained constant (by adjusting a suprarenal aortic clamp) during the isoproterenol infusion.

Campbell et al. (182) found that hydralazine caused a 10-fold increase in PRA and a 3-fold increase in the plasma concentration of norepinephrine and epinephrine in conscious rabbits. Indomethacin, in a dose that lowered renal venous PGE_2 levels by 56%, blocked hydralazine-elicited renin release but not catecholamine release. Indomethacin did not affect the fall in blood pressure brought about by hydralazine, but the reflex increase in heart rate was attenuated. Thus, in the rabbit, as in the rat, indomethacin inhibited the renin release that accompanied reflex activation of the renal sympathetic nerves.

Subsequently, the same investigators (187) administered insulin to conscious rats to activate the sympathetic nervous system and stimulate renin release. Insulin increased PRA, plasma epinephrine, and plasma norepinephrine by 3-, 9.6-, and 1.6-fold, respectively. The urinary excretion of PGE_2 and $PGF_{2\alpha}$ doubled. Indomethacin inhibited insulin-induced renin release by 67% and blocked the insulin-induced increment in urinary PGE_2 and $PGF_{2\alpha}$. The changes in the plasma glucose and plasma catecholamine concentrations seen after insulin were not changed by indomethacin.

In closely related studies, bilateral adrenalectomy of rats resulted in a progressive rise in PRC over a 72-hr period. Up to 48 hr after adrenalectomy, neither propranolol or indomethacin affected PRC, but 60 hr after adrenalectomy, both propranolol and indomethacin lowered renin release by about 50% (731a). Combined treatment with propranolol and indomethacin did not show additive effects in the suppression of adrenalectomy-induced renin release.

A number of studies (180, 182, 187, 286, 331a, 366, 731a, 807, 966, 1006a) suggest that renal prostaglandins may be involved in the stimulation of renin release by the sympathetic nervous system. Furthermore, these hormones appear to act distal to the beta-adrenergic receptors of the granular JG cells. However, additional studies are necessary to clarify this relationship. In particular, it is of cardinal importance to determine the effects of inhibitors of prostaglandin synthesis on 1) the renin release elicited by direct stimulation of the renal nerves in vivo and 2) the renin release induced by isoproterenol and dibutyryl cyclic AMP in renal cortical slices in vitro.

Inhibitors of prostaglandin synthetase also have been shown to reduce hemorrhage-induced renin release, which is probably mediated by the renal baroreceptor and renal sympathetic nerves. For example, Romero et al. (948) found that the rapid removal of 24 ml of blood caused a 5-fold increase in PRA in conscious rabbits. Indomethacin, in a dose that completely suppressed the renal synthesis of PGE, prevented the elevation of PRA that followed hemorrhage. Aspirin and meclofenamate, in doses that reduced the renal synthesis of PGE by 90%, also suppressed hemorrhage-induced renin release by 56% and 25%, respectively. Unfortunately, the changes in RBF or MAP after hemorrhage were not reported so interpretation of the data is difficult. However, McKenzie et al. (719) found that MAP did not fall below 77 mm Hg when conscious rabbits were rapidly hemorrhaged to a similar extent. Thus, blockade of prostaglandin synthesis prevented the increase in PRA (948) brought about by nonhypotensive hemorrhage (719) in rabbits. In contrast, Henrich et al. (472) hemorrhaged anesthetized dogs such that MAP was reduced by 30% (from 150 to 104 mm Hg). This degree of hemorrhage resulted in a 3.5-fold increase in PRA, a 33% decrease in RBF, and a 23% reduction in GFR. In the presence of indomethacin, this same degree of hypotensive hemorrhage still elevated PRA by 3.8-fold, but now both RBF and GFR were reduced by 80%. The renal concentration of prostaglandins was suppressed by 94% of control values. Similar results were obtained when the competitive inhibitor of prostaglandin

synthetase, RO 20-5720, was given prior to hemorrhage. The disparate results reported in these two studies (472, 948) can be reconciled by assuming that renal prostaglandins mediate the release of renin that occurs following nonhypotensive hemorrhage in which RBF and GFR are maintained. However, following hypotensive hemorrhage, in which RBF and GFR are significantly reduced, the release of renin is controlled by factors other than the prostaglandins. This situation would be analogous to that observed with baroreceptor-mediated renin release in which renal prostaglandins mediate the renin release only within the autoregulatory range of RBF (vide supra).

Isakson et al. (520) observed the hemodynamic and endocrine effects of endotoxic shock in the presence and absence of indomethacin. The i.v. injection of *Escherichia coli* endotoxin into anesthetized dogs resulted in a 70 mm Hg fall in MAP and a 12-fold increase in PRA. When indomethacin was administered 60 min after endotoxin, there was a 40 mm Hg rise in MAP, a 55% suppression of the elevated PRA levels, and a large drop in the plasma concentration of prostaglandin-like material. Similarly, if indomethacin was administered prior to the endotoxin, the fall in MAP and the rise in PRA were attenuated. The authors concluded that the suppression of the endotoxin-induced renin release by indomethacin could have been due to: 1)an indirect effect of the drug; 2) the indomethacin-induced rise in MAP; or 3) the ability of indomethacin to prevent the increase in renin-stimulating prostaglandins normally caused by endotoxin. Since the precipitious fall in MAP caused by endotoxin would be expected to stimulate the renin release by reflex activation of the sympathetic nervous system as well as stimulation of the intrarenal baroreceptor, indomethacin appears to exert an inhibitory action on both of these mechanisms.

The effect of prostaglandin synthesis inhibitors on renin release was examined in rabbits with one- and two-kidney renovascular hypertension (949, 951). Larsson et al. (635) and Romero et al. (949) observed a 35 mm Hg rise in MAP within 5 weeks in rabbits with one-kidney Goldblatt hypertension, and although no change in PRA or arterial plasma PGE concentration was noted, RBF was reduced by 29%. The administration of indomethacin at this point reduced PRA by approximately 80% and RBF by 20% whereas MAP was slightly increased. In two-kidney Goldblatt hypertensive rabbits (951) with normal PRA values, indomethacin reduced PRA by approximately 50% and lowered plasma PGE levels to almost undetectable levels. Mean arterial pressure was not altered. Thus, the changes in PRA, plasma PGE concentration, and MAP seen after indomethacin were similar to those observed in normal rabbits. In contrast, when indomethacin was given to two-kidney Goldblatt hypertensive rabbits with elevated PRA values, renal failure and malignant hypertension ensued. As before, PRA values dropped by 50%. In each of the three hypertensive models, treatment with indomethacin was associated with a fall in PRA, a reduction in renal function, and suppression of arterial plasma PGE concentrations (635, 949, 951). Along these lines, Tores et al. (1099) reported that indomethacin prevented the rise in PRA associated with glycerol-induced failure even though it enhanced the severity of the renal failure.

In patients with postmalignant hypertension, indomethacin decreased PRA by 59% and the urinary excretion of PGE by 67% (364). This decrement in renin release was associated with a 50% drop in urinary sodium excretion and an average weight gain of 0.8 kg. Patak et al. (877) found that furosemide produced similar increments in PRA in normal and hypertensive humans, and this stimulated renin release was inhibited by 75% by pretreatment with indomethacin. Thus, in hypertensive patients, as in normal subjects, inhibition of prostaglandin synthesis reduced both basal and stimulated renin release. Based on the observation that both the basal and furosemide-stimulated excretion of PGE in the urine was approximately 50% less in hypertensive patients than in normotensive subjects, several groups of researchers have suggested that a deficiency in renal prostaglandin production exists in hypertensive humans (3, 178, 1073, 1075). Other investigators, however, have failed to observe these differences (1247). If such an abnormality in fact does exist, its relationship to the release of renin in these patients is unknown.

Perhaps the disease in which the effect of prostaglandin synthesis inhibitors has been studied most extensively is Bartter's syndrome, a condition characterized by hyperreninemia, hyperaldosteronism, normotension, hypokalemia, juxtaglomerular hyperplasia, insensitivity to the pressor effects of AII, and an increased production of renal prostaglandins (714). In 1976 Verberckmoes et al. (1148) reported that indomethacin reversed the hypokalemia, hyperreninemia, hyperaldosteronism, and angiotensin insensitivity of Bartter's syndrome. Since that time, a number of reports, involving 12 patients of various ages, have revealed that the administration of the prostaglandin synthesis inhibitors indomethacin, aspirin, or ibuprofen resulted in reversal of the abnormalities observed in Bartter's syndrome (287, 335, 395, 437, 808, 1015, 1148). McGiff (714) recently has reviewed the role of prostaglandins in Bartter's syndrome and the treatment of this disease with inhibitors of prostaglandin synthetase. Gill et al. (385) observed that the urinary excretion of PGE_2 was greatly increased in three patients with Bartter's syndrome. Furthermore, indomethacin reduced the urinary excretion of PGE_2 in each of the patients and lowered both the supine and standing PRA values. Thus, it would appear that the enhanced renal production of prostaglandins is responsible for the hyperreninemia observed in this pathologic state. Whether this enhanced prostaglandin synthesis is a primary event or secondary to the hypokalemia (371) or other unknown factors remains to be determined.

Finally, Kochar and Itskovitz (598) studied the effects of indomethacin in four patients with idiopathic orthostatic hypotension (Shy-Drager syndrome). Upon standing, patients with this condition, which is characterized by an autonomic nervous system insufficiency of unknown origin, develop hypotension without a reflex increase in heart rate. They found that PRA levels were low in each of the patients and failed to increase in response to sodium depletion; however, indomethacin produced a slight reduction in PRA, particularly in those patients with the higher initial PRA values. More importantly, all four of the patients had higher systolic and diastolic blood pressure in the upright position during treatment with indomethacin and thus obtained symptomatic relief from their orthostatic hypotension. The authors (598) suggested that the orthostatic hypotension observed in Shy-Drager syndrome may result from a relative excess of a vasodilator prostaglandin as well as autonomic insufficiency. Since this syndrome is characterized by low PRA levels, whereas Bartter's syndrome is characterized by high PRA levels, the authors felt that the enhanced prostaglandin production must not be of renal origin.

In summary, these studies indicate that nonsteroidal anti-inflammatory drugs inhibit the release of renin by a mechanism most likely related to inhibition of the synthesis of renal prostaglandins. Furthermore, it would appear that endogenous renal prostaglandins are involved in baroreceptor- and sympathetically-mediated renin release. Their involvement in the renin release mediated by the macula densa is not known at present. An overproduction of renal prostaglandins seems to mediate the hyperreninemia of Bartter's syndrome, and inhibitors of prostaglandin synthesis have been shown to lessen the biochemical changes that characterize this disease. Although renal prostaglandins appear to mediate the elevated PRA values observed in other pathologic conditions, there is no evidence to date that this mediation is related to an underlying abnormality of the renal prostaglandin system.

H. Steroids

Based on both clinical and experimental observations, researchers realized many years ago that steroids, particularly those from the adrenal gland, have the ability to alter the release of renin. In fact, it is now appreciated that aldosterone is one of the principal long-term physiologic regulators of renin release. Therefore, we will consider the effects of the various classes of steroids on the release of renin.

1. Mineralocorticoids. In 1953, Hartroft and Hartroft (449) published one of the first studies concerned with the mechanism by which DOCA altered renin release. They administered DOCA to rats on a low, normal, or high sodium intake for 2 to 3 weeks and then examined the kidneys histologically for granular JG cells. In rats ingesting a low sodium diet, DOCA failed to affect the JG cell index whereas DOCA reduced the JG cell index in rats on a normal or high sodium diet. The greatest reduction in the number of granular JG cells occurred in the rats on a high salt diet. The authors concluded that the effects of DOCA on JG cell granularity was secondary to its effects on salt metabolism.

In a subsequent study of similar design, Goodwin et al. (398) noted that 6 weeks of treatment with DOCA did not change blood pressure, plasma electrolytes, or PRA in rats that had been ingesting a low sodium diet. However, in rats ingesting a high sodium diet, DOCA suppressed PRA by 84% but also increased blood pressure by 64 mm Hg. Blood for the measurement of PRA was taken after ether-induced anesthesia. Since DOCA lowered PRA only when dietary sodium was available, it was concluded that the suppression of renin release by DOCA was sodium-dependent and not due to a direct inhibitory effect of the steroid. It is not known whether the rise in blood pressure in the rats given DOCA and a high salt diet contributed to the suppression of renin release. The ability of DOCA to suppress renin release in rats ingesting a normal or high sodium intake was subsequently confirmed by several investigators (36, 183, 245, 377, 784, 896). In anesthetized rats, Nasjletti and Masson (784) found that adrenalectomy increased PRA 24-fold and that this rise in PRA was reversed by administering steroids. The descending order or potency in reversing adrenalectomy-induced renin release was DOCA, aldosterone, cortisol, and corticosterone. Pettinger et al. (896) found PRA to be lowered by 86% after 1 day and by 95% after 3 days of treatment in conscious rats with DOCA. The addition of sodium chloride to the drinking water accelerated the rate of suppression of renin release but did not affect the maximal inhibition observed with DOCA alone. In a subsequent study, Czyzewski and Pettinger (245) reported that DOCA plus sodium chloride suppressed renin release in 4-, 8-, and 16-week old Sprague-Dawley, Wistar, and SH rats. However, at 40 weeks of age, the same regimen was inhibitory to renin release in the Sprague-Dawley and Wistar rats, but was without effect in SH rats. Thus, at least one step in the mechanism responsible for the inhibition of renin release by mineralocorticoids and sodium chloride appeared to become inoperative in SH rats as the disease progressed. Unfortunately, sodium and potassium balances were not determined in these experiments, so it is not known whether DOCA has the same mineralocorticoid potency in young and old SH rats.

To determine whether DOCA suppressed renin release via its effects on salt metabolism or by a direct action on the granular JG cells, deJong (262) examined the effect of DOCA treatment on the release of renin in vivo and in vitro. He found that rats treated with DOCA and sodium chloride for four days exhibited a 50% reduction in PRA. Furthermore, when the kidneys from these same rats were incubated in vitro, the release of renin into the medium was reduced by 50% even though the renin

content of the kidneys was unchanged. However, DeVito et al. (276) found that DOCA did not alter the release of renin in vitro when added to the incubation media of rat renal slices. These findings suggest that 1) DOCA does not exert a direct effect on renin release when added to renal cortical slices and 2) DOCA exerts a prolonged effect on renin release such that treatment in vivo alters the subsequent release of this enzyme in vitro. In a study of DOCA-salt hypertension in rats, Mohring et al. (761) noted that PRC was suppressed by 88% after 4 weeks of treatment. In the animals with nonmalignant hypertension, the plasma levels of AVP were increased 3-fold but plasma sodium concentration and the hematocrit were essentially unchanged. As mentioned previously, AVP has a direct inhibitory effect on renin release, but the role of increased circulating levels of AVP in the inhibition of renin release caused by long-term treatment with DOCA and saline is unknown.

Haynes et al. (458) were among the first to study the effects of DOCA on renin release in the unanesthetized dog. In three dogs given DOCA for 3 to 5 days, no change in blood pressure, PRA, or plasma renin substrate concentration was observed. In a subsequent study, Robb et al. (937) observed a 60% decrease in PRA in conscious dogs treated with DOCA for 2 weeks; however, if the dogs were placed on a low sodium diet, DOCA failed to suppress renin release. The authors concluded that DOCA did not inhibit renin release in the absence of plasma volume expansion and thus excluded a direct action of the steroid on the granular JG cells. When Marks et al. (696) increased the endogenous levels of DOC by administering metyrapone to conscious dogs, they observed an increase in MAP and a decrease in PRA. In addition, neither furosemide nor furosemide combined with a low sodium diet increased PRA in dogs treated with metyrapone. It was conjectured that metyrapone suppressed basal and stimulated renin release either through a direct action on the granular JG cells or by elevating the circulating levels of DOC.

Starting with normal humans that had been sodium-depleted and patients with renal disease, Warren and Ferris (1173) determined the renin response of both groups to DOCA and a normal sodium diet. In normal sodium-depleted subjects, PRA levels were suppressed to undetectable levels by the administration of DOCA. These changes in PRA were accompanied by a marked increase in body weight and ECF volume. In contrast, DOCA reduced but failed to suppress completely PRA in patients wth chronic renal disease and renal artery stenosis despite an attendant increase in body weight similar to that observed in the normal subjects. Thus, it appeared that DOCA suppressed renin release in normal subjects by expansion of the extracellular fluid volume; however, in patients with renal disease, this control mechanism for renin release appeared to be defective. After administering small doses of DOCA to normal humans, Shade and Grim (1009) observed a fall in PRA within 48 hr, and PRA continued to fall during the next four days. Similar decrements in PRA were observed whether the subjects were ingesting a high or low sodium diet. At either level of sodium intake, the fall in PRA was accompanied by an increase in the cumulative sodium balance and the ECF volume. In agreement with previous studies (1173), these investigators (1009) concluded that the most probable mechanism by which DOCA suppressed renin release was through expansion of the extracellular fluid volume.

Geelhoed and Vander (382) assessed the effects of aldosterone on renin release in both conscious and anesthetized dogs. When renal perfusion pressure was held constant, the acute administration of aldosterone to anesthetized dogs resulted in an increase in renal venous PRA in one dog and a decrease in two other animals. When renal perfusion pressure was decreased in order to stimulate renin release, an infusion of aldosterone did not affect the changes in renin release, GFR, RPF, or sodium excretion that accompanied this maneuver. In chronic studies in conscious sodium-depleted dogs, aldosterone reduced arterial PRA values slightly. In addition, the administration of aldosterone to adrenalectomized dogs reduced the rate of rise of arterial PRA that occurred during dietary sodium restriction. Unfortunately, the effects of chronic aldosterone administration on renin release in dogs on a normal or high sodium intake were not studied. Despite this fact, the authors decided that the aldosterone-induced changes in renin release were a function of sodium balance rather than the elevated levels of plasma aldosterone per se. This conclusion, however, is supported by the studies of several investigators (276, 961, 1154) who found that aldosterone failed to alter the release of renin from rat renal cortical slices in vitro.

The most comprehensive study of the effects of plasma aldosterone concentration on renin release is that of Young and Guyton (1248), who measured PRA, the plasma concentrations of sodium and potassium, sodium space, and MAP in conscious, adrenalectomized dogs infused at four different levels of aldosterone concentration over a 13-week period. The animals also received a constant infusion of the synthetic glucocorticoid methylprednisolone at a dose that had no mineralocorticoid activity. Plasma renin activity rose very rapidly when aldosterone was infused at a level below the normal secretory rate despite the fact that plasma potassium concentration increased. However, both ECF volume and plasma sodium content decreased significantly at this subnormal plasma concentration of aldosterone. Renin release fell off to undetectable levels at aldosterone infusion rates slightly above normal, and this suppression of renin release by aldosterone was accompanied by an increase in ECF volume, a decrease in plasma potassium concentration, and a 10 mm Hg rise in MAP. Therefore, changes in PRA correlated inversely with changes in ECF volume as the steady-state plasma levels of aldos-

terone were altered. It is interesting to note that changes in plasma potassium concentration did not have their normal effects on PRA in these experiments. However, it should be remembered that an increase in plasma potassium concentration appears to inhibit renin release by increasing sodium excretion, and it is probable that the marked antinatriuretic effects of aldosterone exceeded the mild natriuretic effect of potassium in these experiments.

DeChamplain et al. (261) observed a 35% decrease in PRA when a short-term infusion of aldosterone was given to sodium-depleted humans, and this fall in PRA was accompanied by a decrease in sodium excretion and blood pressure. The suppression of PRA to low or undetectable levels in most patients with Conn's syndrome is felt to be the result of the salt retention caused by the large increase in the circulating levels of aldosterone (226).

Finally, the effect of several other mineralocorticoids on renin release have been explored. Gomez-Sanchez et al. (36,395) compared 16-beta-hydroxy-dehydroepiandrosterone (16-β-hydroxy-DHEA) and DOCA in conscious rats, and found that the two steroids, when given in doses that had equal renal mineralocorticoid activity, had markedly different effects on renin release. Whereas long-term administration of DOCA increased blood pressure and suppressed PRA, 16-β-hydroxy-DHEA failed to alter either of these parameters. Licorice also has been reported to have mineralocorticoid activity, and Epstein et al. (306, 307) found that the ingestion of confectionery licorice reduced PRA by 85% and increased plasma potassium by as much as 1.5 mEq/l in normal humans.

In summary, mineralocorticoids appear to suppress renin release through their action on the distal tubule, which increases the reabsorption of sodium and water and thus expands extracellular fluid volume. In those states in which mineralocorticoids cannot exert this effect, e.g. severe sodium depletion, these compounds do not affect renin release. The importance of the tubular effects of mineralocorticoids in the suppression of renin release is emphasized by the fact that DOCA and aldosterone have no effect on renin release from renal cortical slices in vitro. Although the presence of sodium ions in the tubular fluid appears to be a prerequisite for the suppression of renin release by mineralocorticoids, the role of other ions is unknown. Presumably the increase in ECF volume elicited by mineralocorticoids suppresses renin release by activation of the renal baroreceptor and/or reflexly mediated withdrawal of renal sympathetic tone. The role of AVP in the inhibition of renin release by mineralocorticoids also needs to be clarified.

2. Glucocorticoids. As discussed previously, Nasjletti and Masson (784) found that the administration of steroids to rats decreased the elevated PRA that occurred secondary to adrenalectomy. They found that corticosterone and cortisol decreased PRA and increased plasma renin substrate levels; however, these glucocorticoids were less than 1/100th as potent as the mineralocorticoids in the suppression of renin release. Hauger-Klevene et al. (456) examined the effects of dexamethasone and cortisol on PRA in conscious intact rats. As in the previous study (784), they (456) found that large doses of steroids decreased PRA by 54%. However, in a subsequent study (452) the same authors reported that the same dose of dexamethasone did not change PRA in conscious rats. The reason for this discrepancy was not mentioned.

Krakoff et al. (616) compared the effects of 2 weeks of treatment with DOCA and methylprednisolone in rats. Blood samples were obtained after anesthesia. Methylprednisolone caused a significant 37 mm Hg increase in MAP whereas DOCA was without effect. Furthermore, methylprednisolone increased PRA by 2-fold and plasma renin substrate by 42%, but PRC was not increased significantly. None of these parameters were changed significantly by DOCA. Since the plasma angiotensinogen concentration was increased by 42%, the increase in PRA could have been due to this factor rather than an increase in renin release per se. However, when the control, methylprednisolone- and DOCA-treated animals were placed on a high sodium diet, PRC and PRA decreased to a similar level in all three groups of rats, but plasma renin substrate content remained elevated in the methylprednisolone group. From these studies, the authors suggested that the rise in PRA caused by methylprednisolone may have been due to the mild sodium depletion produced by this agent since no rise in PRA was observed in similarly treated rats on a high sodium diet. Such a conclusion is consistent with other reports in which it was shown that methylprednisolone (260) and prednisolone (912) increased the urinary excretion of sodium either by increasing GFR (260) or by decreasing the proximal reabsorption of sodium (912). Furthermore, one of the latter studies (260) indicated that methylprednisolone increased RPF by 42% and that this increase occurred mainly in the inner cortical nephrons. Thus, it would appear that the increase in renin release caused by methylprednisolone must have been due to mild sodium depletion since an increase in inner cortical renal blood flow and an increase in MAP would both tend to decrease, rather than increase, the release of renin.

It should be pointed out that other glucocorticoids beside methylprednisolone have been shown to elevate the plasma concentration of renin substrate in animals; among them are cortisone (466) and hydrocortisone (638). These observations explain the ability of adrenalectomy to prevent the increase in plasma renin substrate caused by ACTH (458) and the ability of ACTH to reverse hypophysectomy-induced depression of plasma angiotensinogen concentration (466).

Newton and Laragh (792) examined the effects of glucocorticoids on renin release in normal subjects and patients with essential hypertension. When they administered either dexamethasone or hydrocortisone chroni-

cally to normal subjects on a low sodium diet, the changes in PRA were variable with a decrease occurring in seven subjects, an increase in two and no change in one. A similar pattern was observed in patients with essential hypertension. The net mean change in PRA was a decrease; however, this change was not statistically significant. When a single dose of hydrocortisone was administered to normal subjects, PRA was not changed. It was concluded that these steroids had no direct effects on renin release. Furthermore, it was suggested that the decrease in renin release caused by chronic treatment with glucocorticoids may have resulted from a shift of sodium from the intracellular compartment into the extracellular compartment with an accompanying increase in blood volume.

Kelsch et al. (576) studied the effects of prednisone on renin and norepinephrine release in normotensive sodium-depleted subjects. They noted that prednisone had no significant effect on PRA, whereas plasma norepinephrine concentration was decreased by 54%. Plasma volume was increased by 1.6 ml/kg. Katz et al. (565) assessed the effects of i.v. infusions of large doses of prednisolone on PRA in normal subjects and patients with renal homografts. Prednisolone decreased PRA by 36% in normal subjects and by 48% in the patients with renal transplants. The authors (565) suggested that renin release was suppressed by the glucocorticoid-induced increase in extracellular fluid volume and cardiac output. The rapidity of the response seemed to rule out any effect of prednisolone on renal salt and water metabolism. The fact that prednisolone also lowered PRA in subjects with renal homografts tends to eliminate the involvement of the sympathetic nervous system in this effect.

Finally, Krakoff (614) measured PRA and renin substrate levels in patients treated with glucocorticoids for various pathologic conditions. In this heterogenous group, glucocorticoids increased renin substrate levels by 2-fold and PRA by 3.3-fold. A similar effect was observed in patients with Cushing's syndrome (614), but other investigators (693) have reported that upright PRA values are suppressed slightly in some patients with Cushing's syndrome.

In summary, the effects of glucocorticoids on renin release appear to be slight and variable. In the absence of studies designed to compare the effects of the various glucocorticoids on renin release over a range of doses and to correlate these findings with changes in sodium excretion, blood pressure, RBF, and plasma volume, little can be said concerning the mechanism by which these steroids modify renin release.

3. Androgens. Nasjletti et al. (785) were the first to study the effects of testosterone on the renin-angiotensin system. In ovariectomized rats, they found that administration of testosterone for 21 days had no effect on plasma renin substrate concentration, renal renin content, or PRC. Furthermore, castration of male rats did not change these parameters. Finally, testosterone did not alter the velocity of the renin-renin substrate reaction in vitro (785). Subsequently, Katz et al. (567) gauged the effects of testosterone on the renin-angiotensin system in conscious ovariectomized and orchidectomized rats. As in the experiments of Nasjletti et al. (785), testosterone treatment for 21 days did not affect PRA, PRC, or renin substrate production in ovariectomized female rats (567). However, in orchidectomized male rats, testosterone increased PRA by 83% and PRC by 52% without significantly altering the plasma levels of renin substrate. The authors concluded that testosterone increased the rate of renin release in young castrated male rats but not in female rats. The mechanism by which this increase in PRA occurs is unknown.

4. Estrogens. In 1952, diethylstilbestrol was shown to elevate the concentration of angiotensinogen in rat plasma (466). Later it was observed that PRA was increased during the luteal phase of the human menstrual cycle (146) and during human pregnancy (145). These observations coupled with the fact that estrogens were known to decrease the excretion of salt and water (213, 918, 1089) prompted Crane et al. (241) to investigate the effect of estrogens on the renin-angiotensin system in normal female humans. After 3 weeks of treatment with ethinyl estradiol, PRA was increased by 12-fold and 3-fold in subjects on an unrestricted or low sodium diet, respectively. In a subsequent study, the same researchers (238) found that 1 week of therapy with ethinyl estradiol caused no change in PRA in normal volunteers on a restricted or unrestricted sodium intake. However, in agreement with their previous findings (241), 3 weeks of treatment with this estrogen elevated PRA 5-fold and 2-fold in both male and female humans on an ad libitum and low sodium diet, respectively (238). Since ethinyl estradiol increased PRA during either a normal or low sodium diet, and since the sodium-retaining effects of estrogens would be expected to suppress renin release, it appeared that estrogens elevated PRA by another mechanism.

In 1967, Helmer and Judson (467) measured PRA and plasma renin substrate levels during pregnancy and therapy with estrogens. During pregnancy, PRA increased 6-fold, and the concentration of angiotensinogen tripled. In a similar fashion, treatment with estrogens increased the amount of renin substrate in plasma by 4-fold, but PRA did not increase above the normal range. Thus, the increments in PRA observed during pregnancy and in some estrogen-treated subjects may have been the result of an increase in the plasma concentration of renin substrate rather than an increase in the release of renin. In later years, other researchers obtained similar findings in humans (240, 821, 868) and experimental animals (726, 785, 983). For example, Oelkers et al. (821) found that ethinyl estradiol raised the plasma levels of renin substrate more in women than in men but increased PRA only in women. Pallas et al. (868) noted that conjugated estrogens increased plasma renin substrate levels and

PRA without altering PRC. The latter report emphasized that 1) PRA measurements were dependent on the concentration of renin substrate in the plasma, 2) estrogens increased PRA by increasing the production of renin substrate, and 3) the level of renin in blood was not affected by estrogens since PRC did not change. Discontinuation of therapy with conjugated estrogens or diethylstilbestrol led to the following biochemical changes in patients who had developed hypertension during therapy: 1) total exchangeable sodium fell by 60 mEq; 2) plasma renin substrate content decreased by 65% but was still above the normal limits; and 3) PRA decreased by 20% to 25% on a normal or low sodium diet (240).

In rats killed during anesthesia, the chronic administration of stilbestrol caused a dose-related rise in the concentration of renin substrate in the plasma (785). Plasma renin activity was elevated slightly by stilbestrol but PRC was suppressed by 90%. Based on these results, Nasjletti et al. (785) concluded that estrogens stimulated the production of angiotensinogen, which in turn led to a rise in PRA. The increased genesis of AII then led to the inhibition of renin release via the "short-loop" negative feedback system. Menard et al. (726) also found that diethylstilbestrol increased plasma renin substrate levels and decreased PRC. Similar results were obtained in adrenalectomized rats even though adrenalectomy per se decreased the plasma concentration of renin substrate. Finally, Saruta et al. (983) clearly demonstrated that the administration of estrogen to conscious rats elevated PRA by 2-fold, plasma renin substrate content by 3-fold, and MAP by 17 mm Hg. Plasma renin concentration was unchanged. However, if the rats were given saline along with estrogen, plasma renin substrate levels increased to the same extent as seen with estrogen alone, but PRA, PRC, and MAP were not affected.

5. Progestins. The effect of five progestins on the renin-angiotensin system was studied by Oelkers et al. (825). In normal male subjects, progesterone caused an increase in sodium excretion during the first 2 days of treatment. After 3 days, PRA was increased 2-fold in both the supine and standing positions when compared to pretreatment values, and plasma renin substrate levels were unchanged. Megestrol acetate also increased PRA without altering the plasma concentration of renin substrate; however, unlike progesterone, this steroid did not change sodium excretion. Neither dydrogesterone nor D-norgestrol affected PRA or plasma renin substrate content even through D-norgestrol increased sodium excretion. Norethisterone acetate increased PRA 2-fold in the upright position but did not affect supine PRA values. Plasma renin substrate levels were increased slightly by this compound, an effect apparently due to its slight estrogenic properties. Sodium excretion also was increased. These findings with norethisterone acetate were subsequently confirmed by the same group of investigators (824). The authors concluded that progesterone stimulated renin release secondary to the induction of a natriuresis and, unlike the estrogenic steroids, progesterone did not alter the amount of renin substrate in the plasma. In contrast, the fact that megestrol acetate stimulated renin release in the absence of increased sodium excretion suggested a direct effect of this steroid on renin release. Finally, the increase in PRA seen with norethisterone acetate appeared to be the result of an increase in the production of plasma renin substrate rather than an increase in the release of renin per se.

In addition to dydrogesterone and D-norgestrol, other progestins have been found to have no effect on renin release (238, 563, 785, 844, 1031). Crane and Harris (238) saw no change in PRA in normal subjects on an unrestricted or low sodium diet after 1 and 3 weeks of treatment with medroxyprogesterone acetate. Plasma renin substrate levels remained constant. A similar lack of activity was reported with chlormadinone acetate (563) and lynestrenol (1031).

In a comprehensive study, Oparil et al. (844) examined the effects of progesterone on renin release and renal function in normal men. They found that the acute administration of progesterone during the ingestion of a low or high sodium diet increased RPF, sodium excretion, and the percentage of filtered sodium delivered distally without altering GFR. In subjects on a low sodium diet, PRA was decreased by 25% and the plasma concentration of renin substrate remained constant. Neither PRA or plasma angiotensinogen content changed when progesterone was given to volunteers receiving a high salt diet. Chronic treatment with progesterone did not elicit changes in sodium excretion and renal function of the same magnitude as those seen after a single dose of the steroid. However, the chronic administration of progesterone increased PRA by 4-fold and 6-fold in subjects on a low and high sodium diet, respectively. Again, plasma renin substrate levels were unchanged. Thus, a single dose of progesterone appeared to suppress renin release by increasing the delivery of sodium to the macula densa. However, the increase in renin release after chronic treatment with progesterone appeared to be secondary to the increase in sodium excretion and the negative sodium balance.

6. Oral contraceptives. Because oral contraceptives consist of a combination of an estrogenic and a progestatic steroid, their effects on the renin-angiotensin system are the sum of the effects of these two types of steroids. However, because most of the commonly used synthetic progestins fail to alter the renin system (vide supra), the effects of the oral contraceptives on PRA usually result from an action of their estrogenic component. The effects of the oral contraceptives on the release of renin has been studied widely in normotensive and hypertensive humans (68, 175, 203, 239–241, 467, 496, 563, 566, 570, 614, 632, 821, 984, 1022, 1031, 1198, 1200).

Laragh et al. (632) reported a 2- to 9-fold increase in plasma renin substrate levels with variable changes in PRA in nine of the 10 hypertensive women taking a

variety of different oral contraceptives. Several years later, Skinner et al. (1022) found a 2-fold increase in PRA and plasma renin substrate concentration in conjunction with a 50% suppression of PRC in women taking oral contraceptives. This led the authors to conclude that oral contraceptives increased PRA by elevating the concentration of renin substrate in the blood. The decrease in PRC was thought to result from the suppression of renin release by the increased circulating levels of AII. Furthermore, they suggested that a failure of the increase in PRA and plasma AII content to suppress renin release might mediate or aggravate the hypertension occasionally resulting from therapy with oral contraceptives. These findings were subsequently confirmed by a number of investigators (68, 175, 203, 984). Similar changes in PRA and plasma angiotensinogen content during the ingestion of oral contraceptives were observed in women ingesting a low, normal, or high sodium diet (1198). Incidentally, a normal increase in PRA was seen when patients on oral contraceptives assumed the upright position (1198).

Renal blood flow and the response of the renal vasculature to AII were found to be reduced when women on a high or low salt diet took oral contraceptives over an extended period of time (496). These alterations in renal hemodynamics were accompanied by an increase in PRA and a 3-fold rise in plasma renin substrate levels. Hollenberg et al. (496) suggested that oral contraceptives modified the relationship between sodium balance and the vascular responsiveness to AII, and thereby contributed to the sodium retention and hypertension occasionally attendant to the chronic ingestion of oral contraceptives.

Thus, the effects of the oral contraceptives on PRA appear to reflect the activity of the estrogenic component of the steroid mixture. Oral contraceptives increase renin substrate and PRA but suppress PRC.

In summary, both naturally occurring and synthetic steroids have an effect on the renin-angiotensin system, but the different classes of steroids elicit these changes in PRA by different mechanisms. For instance, mineralocorticoids, by virtue of their action on renal sodium metabolism, appear to suppress renin release by expansion of the ECF and plasma volumes. Aldosterone is one of the major factors controlling renin release on a long-term basis. In contrast, glucocorticoids have been found to cause an increase, decrease, or no change in PRA. The increase in PRA occasionally observed after glucocorticoids has been attributed to sodium depletion or an increase in the plasma concentration of renin substrate whereas the decrease in PRA was supposedly due to an increase in ECF volume. Like mineralocorticoids, glucocorticoids do not seem to have any direct effects on renin release, but the effects of glucocorticoids on renin release are in need of systematic investigation. Androgens have little effect on PRA or PRC, but, again, the effects of this class of steroids on renin release has not been studied widely. Estrogens increase PRA by elevating the concentration of renin substrate in the plasma. However, PRC often does not change or even decreases because the rise in PRA increases the production of AII, which in turn directly inhibits renin release via the "short-loop" negative feedback system. This is one of the few cases in which PRA and PRC do not change in concert after a pharmacologic intervention. Progesterone appears to stimulate renin release by causing sodium depletion, but other progestins may elevate PRA by a direct effect on the granular JG cells (megestrol) or increasing the hepatic synthesis of renin substrate (norethisterone). Many of the other synthetic progestins do not change PRA. The increase in PRA elicited by oral contraceptives reflects the effect of the estrogenic component of this steroid mixture on plasma renin substrate levels.

I. Vasodilators

The peripheral vasodilating drugs are used widely in the treatment of hypertension, and the increase in renin release caused by these agents has proved to be of great clinical significance since the resulting increase in the blood levels of AII has been shown to antagonize the antihypertensive effect of these drugs (892, 898, 899). Hydralazine (37, 86, 122, 124, 180, 182, 185, 407, 509, 692, 701, 737, 809, 884, 887, 891–893, 909, 936, 1107, 1144, 1238), minoxidil (185, 407, 781, 837, 838, 891, 897, 899, 1145), diazoxide (41, 404, 408, 569, 620, 1045, 1049, 1065, 1228), sodium nitroprusside (8, 551, 553, 749), bupicomide (1144), and nifedipine (26, 27) have been shown to increase renin release in animals and humans and appear to stimulate renin release by reflex activation of the sympathetic nervous system.

1. Hydralazine. Hydralazine has been shown to increase renin release in rats (86, 124, 180, 185, 737, 887, 891–893, 909, 936), rabbits (182), hypertensive dogs (37, 701, 1238), and normotensive (122, 1108) and hypertensive humans (407, 509, 692, 809, 1107, 1108, 1144). Originally, hydralazine was believed to elicit renin release only under conditions in which RBF was reduced (509, 1166, 1238), as in dogs with coarctation of the thoracic aorta and patients with renal artery stenosis (509). Based on these reports (509, 1238) and the known ability of hydralazine to increase RBF without altering GFR (243, 772, 931, 1214), Voudoukis (1166) suggested that in circumstances in which renal perfusion pressure was below normal, hydralazine altered renal hemodynamics such that medullary blood flow rose whereas cortical blood flow was reduced further. The relative cortical ischemia then lead to an underdistention of the afferent arteriole, triggering an increase in renin release. Later, Mannick et al. (692) published an anecdotal report supporting the idea that hydralazine stimulated renin release only from the affected kidney in patients with unilateral renovascular hypertension. They claimed that hydralazine increased renin release from both kidneys in patients with essential hypertension, even if pyelonephritis was present; however, no data were presented to support these

contentions. These observers (692) also claimed that hydralazine produced a fall in RBF distal to the renal arterial lesion and thus induced renin release by exaggerating the physiologic defect produced by stenosis of the renal artery. In the subsequent years, Norman et al. (809) found that dihydralazine produced a significant renin response from the contralateral kidney in patients with unilateral renovascular hypertension even though renin release from the affected kidney was stimulated to a greater extent. Effective RPF was measured with radioactive orthoiodohippurate in 10 of these patients and decreased by 10% in the affected kidney but rose by 6% in the contralateral kidney (891). In light of the fact that hippurate extraction is decreased by hydralazine (243, 772), it is difficult to make any definite statement concerning the effect of hydralazine on RBF in renovascular hypertension. Ayers et al. (37), who found that i.v. hydralazine elevated PRA by 2- to 3-fold in conscious dogs with established renal hypertension, also believed that hydralazine-induced renal vasodilatation was the stimulus to renin release.

In 1967, Bozovic and Castenfors (122, 124) first suggested that hydralazine stimulated renin release via the reflex activation of the renal sympathetic nerves. The administration of hydralazine to anesthetized rats with bilateral occlusion of the carotid arteries resulted in a 2.5-fold increase in PRA and potentiated the rise in PRA caused by hemorrhage. The ganglionic blocker pentolinium lowered basal PRA by 15% and significantly lessened the increase in PRA elicited by hydralazine both before and after hemorrhage. Exercise-induced renin release in supine normotensive humans also was potentiated by a single i.v. dose of dihydralazine, and this treatment maintained PRA at seven times the control value during the post-exercise period when renin release normally dropped back to the pre-exercise level. Dihydralazine lowered blood pressure, increased heart rate, and lessened the decrease in RPF and the increase in filtration fraction that normally accompanied exercise. Despite its effects on renal hemodynamics, dihydralazine was thought to elevate PRA by reflex activation of the renal sympathetic nerves (122). In support of this theory was the observation that the peripheral vasodilatation caused by hydralazine increased the firing rate of the peripheral sympathetic nerves (7, 163, 772, 931).

Soon thereafter, Ueda et al. (1107, 1108) performed an extensive study of hydralazine-induced renin release in recumbent humans. Thirty minutes after i.v. hydralazine, PRA was increased by 3.5-fold in five of seven normotensive humans and by 3-fold in 10 of 20 hypertensive patients. The control PRA values were the same in both groups. In seven patients with renovascular hypertension, basal PRA values were five times higher than the normotensive and essential hypertensive patients and PRA rose 5-fold after hydralazine. After 3 days of salt restriction, PRA tripled in normotensive and essential hypertensive subjects and doubled in the renal hypertensive patients. Hydralazine then elicited an approximate 3-fold elevation of renin release in each patient in all three groups. Plasma renin activity in patients with primary aldosteronism was undetectable both before and after hydralazine.

In a later study, Ueda et al. (1107) found that the i.v. administration of hydralazine to 20 hypertensive patients lowered MAP by 16%, increased heart rate by 16%, and elevated renin secretion by 6.5-fold. Renal blood flow rose by 34% as renal vascular resistance dropped by 37%, but GFR was unchanged. Sodium excretion fell by 20%, and medullary RBF increased. These changes in renal hemodynamics and function after the administration of hydralazine were similar to those previously reported by other clinical investigators (243, 931, 1214). The increase in renin secretion did not correlate with changes in MAP, RBF, renal medullary blood flow, renal vascular resistance, filtration fraction, or sodium excretion, but a strong correlation with the increase in heart rate was noted. In order to test the hypothesis that hydralazine elicited renin release via the sympathetic nervous system, hydralazine was injected into the kidneys of three patients followed by i.v. hydralazine some 10 min later. Intrarenally administered hydralazine did not alter the renal venous PRA of the injected kidneys but the subsequent i.v. dose of hydralazine resulted in a significant rise in renal venous PRA from both kidneys. In addition, hydralazine failed to stimulate renin release in a patient with a functioning renal allograft. Therefore, Ueda et al. (1107, 1108) proposed that the reflexly induced increase in sympathetic tone precipitated by the vasodilatory properties of hydralazine was the stimulus to renin release.

When patients with hypertension were treated with hydralazine, Velasco and McNay (1144) found that a good correlation existed between: 1) basal PRA and the increase in PRA after hydralazine; 2) the increase in PRA and the tachycardia after hydralazine; and 3) the rise in PRA and the fall in blood pressure caused by hydralazine. Therefore, they suggested that the stimulation of renin release by this vasodilator was due both to a fall in renal perfusion, as a result of the fall in MAP, and to an increase in activity of the peripheral sympathetic nerves.

The importance of the renal sympathetic nerves in hydralazine-induced renin release became more apparent when it was determined that beta-adrenergic antagonists inhibited this renin release (737, 884, 891, 892, 909, 936). In the first experiments of this type, Meyer et al. (737) discovered that pretreatment with propranolol blocked 85% of the 9-fold increase in renin release seen when a large dose of hydralazine was given to anesthetized rats. Blood pressure and heart rate were not measured in these studies, and the inhibition by propranolol was thought to be due to the blockade of renal beta-adrenergic receptors.

In a more comprehensive series of studies conducted

with conscious and normotensive and hypertensive rats, Pettinger and coworkers (891–893) found that hydralazine elicited a dose-related elevation of SRA. The peak increase (5-fold) in SRA after 1 mg/kg of hydralazine occurred at 20 min, and SRA remained elevated (2- to 3-fold) for the next 5 hr. Pretreatment of normal rats with 0.3 and 1.5 mg/kg of propranolol, which resulted in serum propranolol levels of 50 and 220 ng/ml, respectively, inhibited this rise in SRA by 85% and 91%, respectively. In concert with earlier investigators (122, 124, 737, 1107, 1108), Pettinger et al. (891) concluded that hydralazine-induced hypotension reflexly activated the noradrenergic nerves innervating the granular JG cells. These same researchers also demonstrated that hydralazine caused a 4.5-fold rise in SRA in conscious SH rats, which was blocked by 95% when the animals were pretreated with propranolol (892, 893). When the ability of propranolol to prevent the rise in SRA caused by hydralazine was examined in greater detail, it was discovered that pretreatment with a higher dose of propranolol (15 mg/kg), which gave plasma propranolol concentrations of 750 ng/ml, resulted in less impairment of renin release than did lower doses of propranolol (892). Furthermore, higher doses of hydralazine were capable of overriding the inhibition of renin release by propranolol. In both normotensive and hypertensive rats, propranolol potentiated the hypotensive effects of hydralazine and blocked the reflex tachycardia. For instance, in normotensive rats hydralazine and propranolol lowered blood pressure by 21% and 5%, respectively, but the combination of these two drugs lowered blood pressure by 39%. Thus, propranolol inhibited hydralazine-induced renin release even though systemic blood was lowered to a greater extent than with hydralazine alone. These observations in conscious animals again emphasize the importance of the renal sympathetic nerves, rather than the afferent arteriolar baroreceptor, in the stimulation of renin release by hydralazine.

Riley et al. (936) compared hydralazine-induced renin release and its modification by beta-adrenergic blockade in conscious, SH, Sprague-Dawley, and Wistar-Kyoto rats. The administration of a single oral dose of hydralazine to SH rats was followed by a peak increase in PRA at 30 min after which PRA declined and stabilized at an elevated level during the next 6 hr. Timolol prevented 60% of the renin release caused by this single dose of hydralazine. Continued therapy of SH and Wistar-Kyoto rats with hydralazine for 4 days resulted in a 3- to 4-fold elevation of PRA that was inhibited 100% by co-treatment with timolol. Timolol alone lowered PRA by 60% to 75% in these animals. Although timolol had no effect on basal PRA when given to Sprague-Dawley rats for 4 days, it prevented 70% of the 4-fold elevation in renin release brought about by hydralazine. In addition, propranolol was more efficacious than timolol in mitigating the renin-releasing effects of hydralazine in Sprague-Dawley rats. Therefore, although strain differences might be noted in the beta-adrenergic antagonist-hydralazine drug interaction, the same general pattern of inhibition emerged in all three strains. The beta-adrenergic antagonist bupranolol also has been found to blunt dihydralazine-stimulated renin release in anesthetized, normotensive rats (909). Bupranolol was found to be about twice as potent as propranolol in this system. Lastly, alprenolol has been shown to prevent the increase in PRA caused by hydralazine in hypertensive patients (884).

More recently, Campbell et al. (180, 180a, 182) discovered that inhibitors of prostaglandin synthesis prevented the 10-fold increase in renin release elicited by hydralazine in rats (180, 180a) and rabbits (182). Pretreatment of conscious rats with indomethacin or meclofenamate, in doses that reduced the urinary excretion of PGE_2 and $PGF_{2\alpha}$ by 89% and 74%, respectively, inhibited hydralazine-induced renin release by 100% and 77%, respectively. Since pretreatment with a combination of indomethacin and propranolol did not inhibit hydralazine-induced renin release to a greater extent than did either blocker alone, the authors concluded that indomethacin and propranolol inhibited hydralazine-induced renin release by a common mechanism that involved the sympathetic nervous system. These same investigators also found that hydralazine caused a 2-fold increase in PRA, which was accompanied by a 3-fold elevation of plasma norepinephrine concentration, in conscious rabbits (182). Indomethacin, in a dose that lowered renal venous PGE_2 levels by 56%, blocked hydralazine-elicited renin release but not the increment in plasma norepinephrine concentration. Indomethacin did not affect the fall in blood pressure brought about by hydralazine, but the reflex increase in heart rate was attenuated. Thus, in the rabbit and the rat, renal prostaglandins appear to be involved in the renin release that accompanies the reflex activation of the renal sympathetic nerves by hydralazine.

Because both renal nerve stimulation (626, 1082a) and an intrarenal arterial infusion of isoproterenol (302, 1157) have been demonstrated to elicit a greater renin response at a low renal perfusion pressure than at a normal renal perfusion pressure, the fall in renal perfusion pressure, which results from the decrease in systemic blood pressure after hydralazine, may serve to potentiate the renin-releasing effects of the reflex increase in noradrenergic nerve activity at the granular JG cells. Such an interaction between these mechanisms controlling renin release also might explain the greater stimulation of renin release from the affected kidney in patients with unilateral renal artery stenosis after therapy with hydralazine. However, since beta-adrenergic blockade inhibited hydralazine-induced renin release (892) while potentiating hydralazine-induced hypotension (386, 892, 1258), the amplifying effects of the renal baroreceptor on vasodilatory drug-induced renin release may be of importance only in patients with unilateral renal artery stenosis.

2. Minoxidil. The newly released peripheral vasodilator minoxidil has been reported to elevate PRA in con-

scious rats (185, 891, 892) and hypertensive humans (407, 781, 837, 838, 897, 899, 1145) and, as with hydralazine, this stimulation of renin release by minoxidil has been found to be blocked by propranolol (185, 781, 837, 838, 891, 899, 1145).

After the initial reports of minoxidil-induced renin release in patients (407, 897), Pettinger and colleagues (185, 891, 892) demonstrated that minoxidil elicited a dose-related elevation of SRA in normotensive rats. At higher doses, minoxidil was much more potent than hydralazine in increasing renin release. The peak increase in SRA occurred at 45 min and renin release remained stimulated over the next 5 hr. Pretreatment with 0.3 and 1.5 mg/kg of propranolol inhibited minoxidil-induced renin release by 78% and 89%, respectively. As with hydralazine, the ability of propranolol to mitigate the elevation of SRA caused by minoxidil waned as the dose of propranolol was increased, but, unlike hydralazine, higher doses of minoxidil did not override the inhibition of renin release produced by propranolol. Concerning hemodynamic changes in normal rats, propranolol and minoxidil reduced blood pressure by 3% and 15%, respectively, whereas propranolol decreased heart rate and minoxidil, when given alone, markedly increased heart rate. Propranolol potentiated the hypotensive effect of minoxidil (a 24% decrement in blood pressure) and prevented the associated tachycardia.

Campbell et al. (185) discovered that the dose-related increase in SRA brought about by treatment of normotensive rats with minoxidil was accompanied by a dose-related elevation of serum aldosterone concentration, and the stimulation of both endocrine systems by minoxidil was prevented by propranolol. In order to prove that minoxidil elicited an increase in mineralocorticoid production via stimulation of the renin-angiotensin system, animals were pretreated with saralasin, a receptor antagonist of AII, prior to minoxidil. Saralasin, even in large doses, was not able to prevent the rise in serum aldosterone concentration, but this lack of effect was found to be due to a huge increase in SRA after the combination of saralasin and minoxidil. Whereas minoxidil (1 mg/kg) alone elevated SRA by 5-fold, the addition of saralasin (1 mg/kg) resulted in 25-fold rise in SRA. In fact, saralasin caused a dose-related potentiation of minoxidil-induced renin release with SRA reaching 1000 ng of ml per hr at the highest dose of saralasin. Several factors may account for the enhancement of renin release during combined treatment with saralasin and minoxidil. For instance, Pettinger and Keeton (892) have shown that saralasin potentiated the decrease in blood pressure, but not the increase in heart rate, caused by minoxidil; therefore, the greater degree of hypotension may have resulted in further activation of the renal baroreceptor. Activation of the renal baroreceptor by itself would increase renin release as well as amplify the effect of the renal nerves on renin release. In addition, the feedback inhibition of renin release by AII has been found to be enhanced when renin release is stimulated (572), and it is likely that saralasin potentiated minoxidil-induced renin release by preventing the inhibitory action of AII on renin release.

Minoxidil-induced renin release also has been studied extensively in hypertensive patients (407, 781, 837, 838, 897, 899, 1145). Pettinger and Mitchell (897, 899) found PRA to be elevated in severely hypertensive patients during long-term therapy with minoxidil. When propranolol was withdrawn from patients receiving propranolol and minoxidil, both supine and upright PRA increased. In another study of patients with malignant hypertension, it was noted that propranolol lowered supine and upright PRA by 80%, and the addition of minoxidil resulted in a 2-fold rise in PRA (781). However, even though minoxidil stimulated renin release in the presence of propranolol, the supine and upright PRA values were still 60% to 70% lower than the predrug levels (781).

When O'Malley and co-workers (837, 838, 1145) used minoxidil to lower blood pressure in patients with essential hypertension, PRA rose to six to seven times the control values, and the addition of propranolol to the drug regimen blocked 60% to 75% of the stimulatory effect of minoxidil. Minoxidil lowered MAP (−27%) and total peripheral resistance (−45%) and raised heart rate (+31%) and cardiac index (+47%). The addition of propranolol further lowered blood pressure, and heart rate and cardiac index returned to the control levels. Total peripheral resistance rose after propranolol but remained significantly lower (−25%) than the value observed during the predrug period. Sodium excretion fell by 16% after minoxidil alone and propranolol caused no further change in renal function. Velasco et al. (1145) noted a good correlation between plasma propranolol concentration and the lessening of minoxidil-induced tachycardia, but no such relationship was apparent between plasma propranolol content and the blockade of minoxidil-induced renin release. However, at plasma propranolol levels below 60 ng/ml, a good correlation existed between the drug level and the suppression of renin release. A positive relationship was found between the change in PRA and the change in heart rate during therapy with minoxidil alone and between control PRA and PRA after minoxidil. It was concluded that: 1) maximal blockade of minoxidil-induced renin release occurred at much lower plasma levels of propranolol than those necessary for maximal suppression of minoxidil- induced tachycardia; 2) control PRA was a major determinant of the magnitude of the change in PRA after treatment with minoxidil; and 3) minoxidil stimulated renin release by increasing sympathetic tone, which was sensitive to propranolol, and by decreasing renal perfusion pressure, which was not sensitive to propranolol.

In a conflicting report, Werning (1204) reported that minoxidil actually lowered PRA in 21 hypertensive patients, nine of whom were diagnosed as having renal hypertension. He attributed the 20% fall in PRA to the improvement of tubular sodium metabolism as a result

of the renal vasodilatation. However, it is important to point out that these patients also were being treated simultaneously with propranolol and chlorthalidone, and the presence of the renin-suppressing drug propranolol makes such an interpretation less plausible.

Even though the hypotensive effect of minoxidil was not accompanied by a change in RPF or GFR (386), sodium retention is a problem during continued therapy with all peripheral vasodilatory drugs (795), including minoxidil (836, 897). Zins (1273) has suggested that these vasodilators increase sodium reabsorption in the proximal tubule; however, since plasma (185) and urinary (386) aldosterone levels are elevated by minoxidil, the antinatriuretic effect of this vasodilator may be mediated by aldosterone. On the other hand, propranolol blocked the rise in plasma (185) and urinary (386) aldosterone concentration caused by minoxidil, so the antinatriuretic effect of vasodilatory drugs in the presence of propranolol may result from a direct renal action. Whatever the mechanism involved, the continued retention of sodium and the attendant expansion of plasma volume during continued therapy with minoxidil (386) would be expected to act as a negative stimulus to renin release, and yet PRA remains elevated (407, 781, 837, 838, 897, 899).

3. Diazoxide. Diazoxide is effective in causing a rapid fall in blood pressure and is used in the treatment of hypertensive crisis (713). Treatment with diazoxide has been demonstrated to elevate PRA in rats (569), dogs (408), and normotensive (404, 1228) and hypertensive (41, 620, 1045, 1049, 1065) humans.

Kuchel et al. (620) investigated the renin response to i.v. diazoxide in a group of hypertensive patients. Diazoxide elicited a 5-fold increase in PRA when patients on a normal sodium diet were in a recumbent position. Supine blood pressure fell and heart rate increased. Whereas the attainment of upright posture brought about a 2-fold rise in PRA, orthostasis after diazoxide resulted in little additional increment in renin release. Salt depletion raised supine PRA values by 5-fold, and PRA increased another 56% when the patients stood up. The injection of diazoxide at this point caused an additional 3-fold increase in PRA; therefore, sodium depletion potentiated the renin-releasing effects of diazoxide. In some patients, diazoxide lowered blood pressure and increased heart rate, but renin release was not stimulated. A marked depression of sodium excretion and an increase in plasma glucose concentration were noted in both the renin responders and nonresponders. It was concluded that diazoxide elicited renin release via activation of the sympathetic nervous system, and this conclusion was supported by the previous observation that diazoxide increased the circulating level of catecholamines in rats (1262). In addition, since some of the patients who did not exhibit a renin response to diazoxide and low basal PRA values and normal aldosterone secretion rates, and since these patients developed less tachycardia and more prolonged hypotension after the drug, these patients were believed to have suffered a loss of normal sympathetic responses (620).

Consistent with the belief that diazoxide stimulated renin release via the sympathetic nervous system (620), Winer et al. (1228) found that propranolol prevented diazoxide-induced renin release in normal humans. Plasma renin activity increased within 30 min of injecting diazoxide, and, as in other studies (41, 620), the peak renin response occurred at 2 hr (1228). Propranolol prevented both the renin release and tachycardia, but not the hypotension, caused by diazoxide. The alpha-adrenergic antagonist phentolamine also was reported to inhibit diazoxide-induced renin release even though this drug potentiated the tachycardia seen after diazoxide. These authors suggested that treatment with diazoxide elicited renin release by enhancing renal nerve activity. In addition, they felt that either both alpha- and beta-adrenergic receptors mediated renin release or these blockers acted at a site distal to these receptor sites. However, considering what is now known about the neural regulation of renin release (vide supra), it is difficult to envisage a mechanism by which phentolamine might block sympathetically mediated renin release.

When Baer et al. (41) gave an i.v. bolus of diazoxide to patients with essential hypertension, PRA was doubled some 2 to 3 hr later and sodium excretion declined. The change in renin release was not related to changes in plasma volume or ECF volume, but rather was attributed to the decrease in sodium excretion. As in previous studies (620), some patients showed no increase in renin release after diazoxide even though blood pressure fell (41). Swales and Thurston (1065) found that treatment of severely hypertensive subjects with orally administered diazoxide for 1 week resulted in an elevation of both PRA and plasma AII concentration.

Like hydralazine, diazoxide has been used to accentuate the ratio of renal venous PRA values in patients with renovascular hypertension (1045, 1049). In the most complete study of this type, Stokes et al. (1049) discovered that i.v. diazoxide elicited a rapid increase in renal venous PRA from both the affected and contralateral kidney in humans with unilateral renal artery stenosis. However, the response of the affected kidney (a 4.6-fold increase) was significantly greater than that of the unaffected kidney (a 2-fold increase). Patients with bilateral renal artery stenosis exhibited a 3-fold increase in renin release from the kidney with the greatest impairment of blood flow, and, rather surprisingly, the contralateral kidney, although also suffering from ischemia, showed no response. An equal increase in renal venous PRA occurred from both kidneys in subjects with bilateral renal parenchymal disease. Considering the patients collectively, no relationship was noted between the hypotensive effect of diazoxide and its ability to elevate renin release.

Unlike the other peripheral vasodilatory drugs, the effect of diazoxide on renin release in animals has not

been studied extensively. Graham et al. (408) found that diazoxide elicited a 3-fold rise in PRA in anesthetized dogs as blood pressure dropped by 24%. However, it should be pointed out that these animals had been treated with prazosin [which lowered MAP (−27%) and PRA (−18%)] 1 hr before the administration of diazoxide. Kaul and Grewal (569) determined that a large dose of diazoxide brought about a 11-fold increase in PRA in anesthetized rats, and this stimulatory effect was reduced by one-half by prior adrenal demedullation or treatment with oxprenolol. Although a single dose of guanethidine and multiple doses of reserpine and 6-hydroxydopamine had essentially no effect on basal renin release, each of these treatments blocked the renin response to diazoxide by approximately 50%. These data further support the belief that diazoxide-stimulated renin release results from activation of the sympathetic nervous system in response to a decrease in blood pressure.

On the other hand, Vandongen and Greenwood (1130) detected an increase in renin release when diazoxide was injected into the isolated, perfused rat kidney, but this drug was a comparatively weak stimulus when compared to isoproterenol . Since the decrease in renal perfusion pressure, which occurred with time, was similar in control and diazoxide-treated kidneys, it was believed that diazoxide had a direct action on the granular JG cells that might involve a competition for calcium binding sites.

4. Sodium nitroprusside. Like diazoxide, sodium nitroprusside rapidly lowers blood pressure and has been used in hypertensive emergency (1104). Since the hypotensive effect of sodium nitroprusside is short-lived, this drug must be given by continuous i.v. infusion in order to lower blood pressure to an acceptable level. In a recent collaborative study, no significant increase in heart rate was observed during sodium nitroprusside-induced hypotensive (1104), but some clinicians (285, 552, 553) found that the drug produced a tachycardia. Because a standardized preparation of sodium nitroprusside has become available only recently, the number of studies concerning the effects of sodium nitroprusside on renin release is small. However, sodium nitroprusside has been shown to increase PRA in conscious (8, 749) and anesthetized (749) rats and in normotensive (553) and hypertensive (552) humans.

As early as 1967 Kaneko et al. (553) discovered that renin secretion increased 6.3-fold in supine, normotensive humans after lowering MAP from 93 to 68 mm Hg with sodium nitroprusside. Mean heart rate rose from 75 to 96 beats/min, and effective RPF was reduced by 23%. Sodium nitroprusside elicited an equal increase in renin release from both kidneys, and renal venous PRA values returned to normal within 15 to 30 min after the infusion of drug was halted. No change in renin secretion occurred at a MAP above 75 mm Hg. A positive relationship between the decrement in blood pressure and the increment in renal venous PRA was found. Sodium nitroprusside, in doses that elicited vasodepression and tachycardia, stimulated renin release at an MAP of 90 mm Hg in patients with renovascular hypertension. The rise in renal venous PRA was significantly greater from the affected kidney as compared to the contralateral kidney.

In a subsequent study, the same investigators (552) found that the threshold MAP necessary for the stimulation of renin release in patients with essential hypertension was higher than that observed in normotensive humans, but lower than that determined in patients with renovascular hypertension. When the MAP of these supine patients with essential hypertension was lowered from 122 to 88 mm Hg, renin secretion increased 5-fold, and RPF fell and heart rate increased. The increase in renal venous PRA was reciprocally related to the fall in RPF. Some of the patients exhibited no stimulation of renin secretion despite an equal decrease in blood pressure and sodium excretion and an equal increase in heart rate as compared to the renin responders. However, the nonresponders showed no change in RPF and a slight decrease in renal vascular resistance. In addition, the basal rates of renin secretion in the nonresponders was only 15% of that measured in those patients who showed a renin response. The difference in renin responsiveness in these two groups of patients was not related to the severity of the hypertension. The authors felt that the fall in RPF and rise in renin secretion and renal vascular resistance in the responders was a manifestation of an increase in renal sympathetic nerve activity reflexly induced by the vasodepressor effect of sodium nitroprusside. This activation apparently did not occur in the nonresponding subjects. At first glance this conclusion might seem paradoxical since treatment with sodium nitroprusside precipitated an equal increase in heart rate in both groups, but tachycardia is a relatively poor index of changes in adrenergic nerve activity in supine humans since the reflexly-induced tachycardia is predominantly due to the withdrawal of parasympathetic tone (941). However, sodium nitroprusside-induced hypotension does appear to elevate peripheral adrenergic neurotransmission since Dollery et al. (285) found plasma norepinephrine concentration to be doubled by this drug.

Miller et al. (749) found that hypotensive doses of sodium nitroprusside raised PRA by 4- and 8-fold in conscious and anesthetized rats, respectively. Similarly, Abukhres et al. (8) observed that sodium nitroprusside, in a dose that lowered MAP by 27% and increased heart rate by 32%, caused a 5-fold increase in PRA in conscious rats.

The ability of sodium nitroprusside to release renin by a strictly intrarenal action appears unlikely. The infusion of sodium nitroprusside into the isolated rat kidney, which was perfused with an electrolyte solution containing protein and washed bovine red blood cells, resulted in a 2-fold increase in renin release that developed slowly (490). By way of contrast, an infusion of isoproterenol, in

a dose that elicited changes in RPF, GFR, and sodium excretion similar to those observed with sodium nitroprusside, caused a rapid 6-fold elevation of renin release.

Thus, sodium nitroprusside appears to stimulate renin release via reflex activation of the renal sympathetic nerves (8,552), with a possible minor contribution via the renal baroreceptor (490). However, additional pharmacologic studies of sodium nitroprusside-induced renin release need to be performed.

5. Other vasodilators. Bupicomide, a compound with systemic hemodynamic effects similar to those of hydralazine (1143), has been shown to elevate PRA in hypertensive patients (1144). This stimulation of renin release was thought to occur as a result of an increase in sympathetic nerve activity and a decrease in renal perfusion pressure (1144).

Aoki et al. (27) found that the coronary vasodilator nifedipine, which is a calcium antagonist, lowered diastolic blood pressure by 26% when given sublingually to hypertensive patients. Heart rate increased and PRA doubled. The renin responses of two patients with malignant hypertension and one patient with renovascular hypertension did not differ from the patients with essential hypertension, but two patients with primary aldosteronism failed to exhibit a rise in PRA. In the latter case, a marked fall in blood pressure was not accompanied by an increase in heart rate. Later, propranolol was shown to prevent the increase in PRA and heart rate caused by nifedipine (26). On the other hand, the inhalation of amyl nitrite by recumbent, normal humans lowered blood pressure and raised heart rate, but no perceptible change in PRA was observed (504). However, after PRA had been elevated by treatment with phentolamine, amyl nitrite caused a further increase in PRA (504). Since the various coronary vasodilators, when given systemically to anesthetized dogs, had differing effects on RBF, with some compounds causing a vasodilatation and others causing a dose-related vasoconstriction (827), it would be interesting to know if their effects on RBF could be related to their ability or inability to alter renin release.

The effects of substance P, a naturally occurring undecapeptide with hypotensive and vasodilator properties, on renin release has been studied in anesthetized dogs. Gullner et al. (419) found that an i.v. infusion of 5 ng/kg/min, which increased the plasma concentration of substance P from 140 to 152 ng/ml, suppressed renin secretion by 75%. When the dose was increased to 50 ng/kg/min, renin secretion rose to 3.6 times the control level. The small i.v. dose of substance P lowered MAP by 11%, without affecting RBF, GFR, or electrolyte excretion. When the same small dose of substance P was infused directly into the renal artery, renin secretion fell by 82% and MAP decreased by 7%. Glomerular filtration rate was unchanged, but urinary volume, sodium and potassium excretion, and RBF were increased markedly. At an intrarenal dose of 50 ng/kg/min, renin secretion rose 5-fold, as compared to the control values, and blood pressure was lowered by 16%. At this point, RBF remained elevated, GFR fell to below control values, urinary volume returned to the control level, and sodium and potassium excretion remained elevated. Thus, substance P suppressed renin release in both the presence and absence of diuresis, natriuresis, and renal and systemic vasodilatation.

The suppression of renin secretion by small doses of substance P was thought to be the result of activation of the renal baroreceptor, by afferent arteriolar vasodilatation, and/or increasing the sodium load at the macula densa. However, since a very small i.v. dose of substance P (0.5 ng/kg/min) suppressed renin secretion as much as did 5 ng/kg/min, but did not alter systemic or renal hemodynamics or renal function, it was suggested that substance P might have a direct inhibitory action on the granular JG cells. The renin release caused by the i.v. and intrarenal infusion of the highest dose of substance P was thought to be due to the reflex activation of the renal sympathetic nerves (419).

In summary, the peripheral vasodilating drugs elicit renin release in animals and humans, and, for the most part, this stimulation appears to be due to a reflexly induced increase in renal sympathetic nerve activity. When challenged with these drugs, patients with unilateral renovascular hypertension exhibit an exaggerated release of renin from the affected kidney, and the renal baroreceptor may play a larger role in the stimulation of renin release in this situation. The increment in the plasma concentration of AII that results from vasodilatatory drug-induced renin release limits the hypotension caused by these agents, and the blockade of this drug-elicited renin release potentiates the hypotensive effect of the vasodilators. Drugs that interfere with beta-adrenergic neurotransmission, such as propranolol, inhibit the renin release caused by the systemic vasodilators. The relationship between the direct and indirect effects of these vasodilators of renal function and their ability to elevate renin release is not known. The ability of coronary vasodilators to elicit renin release remains essentially untested.

J. Other Hormones

1. *Adrenocorticotrophic hormone (ACTH).* Haynes et al. (458) originally reported a transitory increase in PRA after the administration of ACTH to anesthetized dogs. Later studies in rats demonstrated that the administration of ACTH increased the granular JG cell index (697). This effect was observed in intact, adrenalectomized and hypophysectomized-adrenalectomized rats. Early attempts to alter renin secretion in humans with a single dose of ACTH proved fruitless (791), but the hormone was able to induce an increase in PRA in patients with hypopituitarism (457).

Working with conscious rats, Hauger-Klevene et al. (456) provided the first clear-cut evidence of ACTH-induced renin release. ACTH resulted in a 4-fold elevation of PRA at 30 min, and this increase had dissipated by one hour after the injection. Tachyphylaxis developed quickly to ACTH, and this tachyphylaxis was related to a progressive increase in the plasma levels of corticosterone. In fact, exogenously supplied cortisol prevented ACTH-induced renin release, and adrenalectomy or the inhibition of steroid synthesis with aminoglutethimide increased both the magnitude and duration of the renin response to ACTH. Other investigators (125) also have found that ACTH caused a short-lived stimulation of renin release in adrenalectomized rats. The rate of renin release in vitro from renal cortical slices obtained from rats pretreated with ACTH also was increased (125). Due to the short periods of time involved in vivo and ACTH stimulation of renin release in vitro, the sodium retention and volume expansion normally caused by a rise in the plasma levels of glucocorticoids could not have been the cause of the tachyphylaxis. These data provided a good explanation for the lack of a renin response to ACTH in normal humans as opposed to those patients with hypopituitarism.

In later work, Hauger-Klevene (452) demonstrated that ACTH possibly increased renin release by activation of an adenylate cyclase system. ACTH-stimulated renin release again was blocked by the glucocorticoid dexamethasone but also was potentiated by a dose of theophylline that had no affect on PRA by itself. The inhibition of ACTH-induced renin release by dexamethasone was blocked by actinomycin D. Actinomycin D did not prevent the elevation of PRA caused by ACTH. Ganglionic blockade with pentolinium markedly attenuated the rise in PRA caused by ACTH in conscious rats, but the mechanism involved is unknown (455). The addition of dexamethasone to pentolinium completely abolished the elevation of PRA elicited by ACTH. It was concluded that ACTH, like glucagon and the catecholamines, stimulated an adenylate cyclase system in the granular JG cells to increase renin release but that dexamethasone inhibited the renin response to ACTH by a mechanism that involved DNA-dependent RNA synthesis (452). Incidentally, growth hormone, oxytocin, and thyroid stimulating hormone had no effect on PRA in conscious rats, but alpha-melanocyte stimulating hormone, which contains part of the structure of ACTH, mimicked the effect of ACTH on renin release (452).

Ganong (372) noted a decrease in PRA in dogs during three days of treatment with ACTH even though a decline in plasma potassium occurred. However, the decrease in PRA was attributed to the stimulation of aldosterone release from the adrenal cortex and thus secondary to the salt- and water-retaining properties of the steroid.

In more recent clinical studies, the infusion of ACTH into patients pretreated with dexamethasone, to suppress the endogenous levels of ACTH, did not alter PRA unless the patients were on a sodium-deficient diet (577). The extremely brief increase in PRA in response to ACTH previously reported in normal, supine humans (125) was not confirmed (577). In like fashion, ACTH did not affect PRA, although it did increase the production of aldosterone, in patients with congestive heart failure (794).

ACTH also may cause an apparent elevation of PRA, but not PRC, by increasing the concentration of plasma renin substrate. Haynes et al. (458) reported that ACTH increased the plasma levels of renin substrate in normal dogs, and this effect was abolished by adrenalectomy. The same results with ACTH were obtained in the rat (465), and hypophysectomy led to a 50% reduction in the concentration of renin substrate in the plasma (398, 465). The effect of hypophysectomy on the plasma content of renin substrate was reversed by the administration of ACTH (465).

The measurement of PRA in chronically hypophysectomized rats has produced confusing and conflicting results. Hypophysectomy alone has been reported both to decrease (697) and to increase (295, 946) the granular JG cell index. Despite an increase in the density of the granules in JG cells and an elevation of renal renin content, PRA was not increased in rats 2 months after hypophysectomy (946). Other researchers had previously reported that hypophysectomy alone caused no significant change in PRA (398) and did not prevent the increase in PRA induced by a sodium-deficient diet (398, 867) or renal arterial hypotension (855). The administration of ACTH to anesthetized, hypophysectomized rats on a low or normal sodium diet was reported to cause no increase in PRA (867), and similar results were obtained in conscious dogs (323). No reports have been forthcoming during recent years to reconcile and clarify these previous findings.

2. Growth hormone. Growth hormone (GH), a polypeptide originating from the anterior pituitary, elicits growth in all tissues of the body, including the kidney. In fact, radiolabeled growth hormone has been found to localize in the kidney after its administration to young hypophysectomized rats (704).

Despite the fact that a short-term infusion of GH caused a slight increase in PRA in anesthetized, chronically hypophysectomized rats (468), the treatment of chronically hypophysectomized rats, on a normal or low salt diet, with GH for a week did not alter PRA (867). GH also had no effect on PRA in hypophysectomized dogs (374). When rat renal cortical slices were studied in vitro, GH slightly suppressed renin release and the renin content of the slices (453).

Highly purified human GH, which was free of antidiuretic hormone, increased the plasma levels of free fatty acids, indicating the potency of its biologic activity, but had no effect on PRA in normal humans (309). In like

fashion, the continued administration of GH to patients with isolated GH deficiency did not affect the renin response to furosemide (228).

Variable changes in PRA have been reported in patients with acromegaly, a disease associated with elevated levels of GH in the blood. In normotensive patients with acromegaly, basal PRA and the renin response to orthostasis or sodium depletion appeared to be normal (174, 1056). However, basal PRA and its response to upright posture were suppressed in hypertensive acromegalic patients (174, 454, 1056). After a reduction in plasma volume by furosemide-induced diruesis, the normal renin response to the attainment of upright posture was restored in the latter group. Therefore, the original lack of response was believed to be due to an expansion of the ECF volume (174, 1056) possibly due to an elevation of aldosterone.

GH originally was believed to exert an antinatriuretic effect in animals (674) and humans (470), and such an action was felt to be responsible for the elevation of plasma volume observed in patients with acromegaly (174, 1056). However, carefully controlled studies with highly purified GH revealed that this hormone had no effect on sodium excretion or urinary volume in normal rats and humans (374, 921). In addition, the depression of renal function seen by earlier investigators appeared to be the result of the preparations of GH being contaminated with antidiuretic hormone and/or prolactin (374). Thus, the increase in plasma volume, and subsequent suppression of PRA in hypertensive, acromegalic patients cannot be attributed to an effect of GH on renal function. In short, GH appears to play little part in the control of renin release.

3. Somatostatin. Somatostatin, a tetradecapeptide formed in many areas of the brain, inhibits the secretion of many polypeptides including GH, insulin, glucagon, gastrin, thyroid stimulating hormone, and ACTH (418). The i.v. infusion of somatostatin has been shown to inhibit furosemide-induced renin release in normal humans even though basal PRA, blood pressure, and heart rate were not affected (394, 959). In later studies, the increase in renin release, heart rate, and blood pressure elicited by the administration of orciprenaline to normal subjects was attenuated by somatostatin (956). The inhibition of beta-adrenergic receptor-mediated renin release and tachycardia led to the suggestion that this peptide was capable of blocking beta-adrenergic receptors (956).

Rosenthal et al. (960) extended these studies when they monitored PRA and hemodynamic parameters during the administration of somatostatin and/or furosemide to patients with low-, normal-, and high-renin hypertension. Somatostatin lowered basal PRA, without affecting the cardiovascular measurements, in high- and normal-renin hypertension but had no effect on renin release in low-renin hypertension or normal subjects. The renin-releasing effects of furosemide were significantly attenuated by somatostatin in all individuals, except the low-renin hypertensive patients, which did not exhibit a renin response to furosemide. Furosemide alone had no effect on blood pressure, but the combination of furosemide and somatostatin significantly lowered MAP, by decreasing cardiac index and stroke index, in normal- and high-renin hypertension. As before, it was suggested that somatostatin altered renin release by interfering with the function of beta-adrenergic receptors.

Somatostatin was found to lower blood pressure and triple PRA values in anesthetized, normotensive rats (991). Despite these findings (394, 956, 959, 960, 991), the importance of somatostatin in the control of renin release in normal and diseased states is unknown.

4. Glucagon. Glucagon, a polypeptide with anti-insulin-like effects, has been shown to stimulate renin release in the isolated perfused rat kidney (1135, 1136), anesthetized dogs (1112), and some normal humans (329). In the isolated perfused rat kidney, the elevation of renin release brought about by glucagon was inhibited by the simultaneous administration of AII or AIII (1136) but was not affected by saralasin (1136) or propranolol (1135).

In anesthetized dogs, Olsen (833) found that the i.v. infusion of glucagon elevated heart rate, RBF, urinary flow, the urinary excretion of cyclic AMP and PGE_2 but did not have a consistent effect on PRA. Pretreatment with indomethacin attenuated the natriuresis caused by glucagon, but the increases in RBF, heart rate, cardiac output, and urinary cyclic AMP were not affected. Plasma renin activity decreased when glucagon was given in the presence of indomethacin. However, when Ueda et al. (1112) infused glucagon directly into the renal arteries of anesthetized dogs, renin secretion increased 11-fold in association with a rise in heart rate, RBF, GFR, and urinary flow. The prior infusion of theophylline caused renin secretion to double and potentiated the stimulation of renin secretion by glucagon even though the renal hemodynamic and hydrodynamic actions of glucagon were not changed. Beta-adrenergic receptor blockade with propranolol did not suppress the renin secretion induced by the combination of theophylline and glucagon.

It is well known that glucagon exerts its lipolytic, glycogenolytic, and cardiac effects by increasing the production of cyclic AMP in the target tissues (1028). In addition, an adenylate cyclase system specific for glucagon has been shown to exist in the renal medulla (778), and the effects of glucagon on renal function are similar to those of dibutyryl cyclic AMP (1113). Based on these facts and the effects of propranolol and theophylline on glucagon-stimulated renin release, Ueda et al. (1112) concluded that glucagon elicited renin secretion by increasing the concentration of cyclic AMP in the granular JG cells. This is probably the case since afferent arteriolar vasodilatation without a change in renal perfusion

pressure and the natriuretic effect of glucagon (1113) constitute negative stimuli to renin release. Prostaglandins also may be involved in glucagon-induced renin release since Olsen (833) found that glucagon actually lowered PRA in the presence of indomethacin.

5. Parathyroid hormone. Originally, the renin release caused by the injection of parathyroid extract into anesthetized dogs was believed to be due to the presence of a vasoactive impurity (710). A purer preparation of parathyroid hormone (PTH) elevated PRA in only two of four animals. Similarly, the bolus injection of PTH into normal humans did not alter PRA (310). However, when the synthetic amino-terminal 34 amino acid peptide of bovine (PTH 1–34) was infused into anesthetized saline-loaded dogs, a dose-related increase in PRA was observed (917). Blood pressure did not change during these experiments. It should be pointed out that the PTH (1–34) fragment has the same physiologic effects on calcium and phosphorous metabolism and cyclic AMP production as does PTH (914).

Smith et al. (1027) recently published a comprehensive study demonstrating that an i.v. infusion of PTH (1–34) increased PRA by 60% in anesthetized dogs. The urinary excretion of sodium and phosphate also increased, but blood pressure did not change. The stimulation of the release of endogenous PTH, induced by localized hypocalcemia in the parathyroid glands, also elicited renin release. As before, sodium and phosphate excretion rose and the magnitude of the natriuresis appeared to modulate PTH-induced renin release. That is, the well-documented natriuretic effect of PTH (10), which results from a decrease in the reabsorption of sodium in the proximal tubule, increased the sodium load at the macula densa, which attenuated the renin-releasing effects of PTH. Thyrocalcitonin had no effect on PRA. Smith et al. (1027) felt it unlikely that PTH affected renin release via the renal baroreceptor or macula densa, but the exact mechanism of action of PTH was not determined. Lindner et al. (662) noted that a single injection of PTH or PTH (1–34) elevated PRA and RBF in conscious dogs without affecting blood pressure.

Lastly, the removal of adenomas of the parathyroid gland from hyperparathyroid patients with hypertension and hyperreninemia has been observed to return PRA values to normal (139). It is unlikely that the hypercalcemia usually found in patients with hyperparathyroidism contributes to the elevation of PRA, since calcium tends to suppress renin release, but the increased circulating levels of PTH may contribute to the rise in PRA. The importance of PTH in modulating renin release needs to be clarified.

6. Insulin. The hypoglycemia produced by insulin has been found to lead to an increase in PRA in anesthetized dogs (29, 856), conscious rats (187), and normotensive (461, 670) and hypertensive (461, 671) humans. Several lines of evidence indicate that this increase in renin release is the result of stimulation of intrarenal beta-adrenergic receptors by neuronally released or circulating catecholamines. In anesthetized dogs, insulin evoked a 3- to 5-fold increase in the plasma concentration of epinephrine whereas plasma norepinephrine did not change. This in turn led to a 2- to 3-fold elevation of PRA (856). Unilateral adrenalectomy and denervation of the remaining adrenal gland reduced the renin response to hypoglycemia, whereas renal denervation was without effect. In addition, insulin-induced renin release was blocked by propranolol and potentiated by phentolamine (29). Hedeland et al. (461) found a good correlation between the increase in PRA and the increase in the urinary excretion of catecholamines during insulin-induced hypoglycemia in normotensive and hypertensive patients. Pretreatment with clonidine prevented the elevation of PRA and urinary norepinephrine content caused by insulin. A significant elevation of the urinary concentration of epinephrine still occurred. Because insulin elicited renin release in adrenalectomized humans, Lowder et al. (670) concluded that reflex stimulation of the peripheral sympathetic nerves was responsible for the increase in PRA. In normal- and low-renin hypertensive patients, insulin induced the same degree of hypoglycemia and the same increase in the plasma levels of cyclic AMP and cortisol, but only the patients with normal PRA values exhibited an elevation of renin release after insulin (671). The increase in plasma epinephrine concentration observed after the administration of 2-deoxyglucose to normal humans also was associated with a rise in PRA and heart rate (904).

More recently, Campbell and Zimmer (187) discovered that prostaglandins appeared to be involved in insulin-induced renin release in conscious rats. After a dose of insulin sufficient to lower plasma glucose levels by 50%, plasma epinephrine and norepinephrine increased by 9.6- and 1.6-fold, respectively. Plasma renin activity tripled and the urinary excretion of PGE_2 and $PGF_{2\alpha}$ doubled. Indomethacin inhibited insulin-induced renin release by 67% and blocked the insulin-induced increments in urinary PGE_2 and $PGF_{2\alpha}$. The changes in the concentrations of plasma catecholamines, potassium, and glucose seen after insulin were unaltered by indomethacin.

K. Miscellaneous Drugs

Apomorphine, a dopaminergic agonist, caused a 4-fold elevation of renin secretion when given into the renal arteries of anesthetized dogs, and this effect was blocked by pretreatment with the dopaminergic antagonist haloperidol (515). Renal blood flow, sodium excretion, and urinary flow were not changed by apomorphine. On the other hand, pimozide, another agent that blocks dopaminergic receptors in the brain, did not attenuate the increase in renin secretion or RBF caused by an intrarenal infusion of dopamine. The results were taken to indicate that renal dopaminergic receptors are different

from the dopamine receptors in the brain. Ergometrine, an alkaloid of ergot, has been used as an oxytocic to control postpartum hemorrhage, but the compound is also a specific antagonist of dopamine in the canine kidney (72). Although ergometrine was shown to increase PRA in conscious rabbits (655), this compound blocked the rise in circulating AII levels caused by hemorrhage, renal ischemia, and intrarenally infused dopamine in anesthetized dogs. The elevation of AII concentration in the blood stream after furosemide was not affected. Even though PRA was not measured in these experiments, these data were taken to mean that dopaminergic nerves in the kidney (71) were important mediators of the renin release caused by hemorrhage and a decreased renal perfusion pressure (72).

The long-acting dopamine agonist bromocriptine suppressed plasma prolactin concentrations to undetectable levels but did not change PRA or plasma aldosterone in normal subjects (190a). Similar results were obtained by Semple and Mason (1002a) in five normal subjects. Along the same lines, metoclopramide, a dopamine receptor antagonist, increased plasma prolactin and aldosterone levels by 5- and 3-fold, respectively, but did not change PRA (190a). Neither bromocriptine nor metoclopramide altered the ability of exogenous AII to suppress PRA. In a subsequent study, Noth et al. (810a) also noted that i.v. metoclopramide increased plasma prolactin levels by 10-fold and plasma aldosterone levels by 2-fold. Plasma renin activity was unchanged. Orally administered metoclopramide increased plasma aldosterone concentrations in two of five subjects, increased plasma prolactin levels by 12-fold, but did not alter PRA.

The antihyperglycemic drugs phenformin and chlorpropamide suppressed PRA by 60% in rats (423) but tolbutamide had no such effect (1011). The mechanism involved in this inhibition of renin release is not known.

Histamine has been found to cause a 2-fold rise in PRA and dipsogenesis in rats (426). The antihistamine diphenhydramine abolished the effect of histamine on drinking, but the effect of histamine-induced renin release was not reported. Dextran also elicited renin release and drinking. Pretreatment with either diphenhydramine or propranolol blocked the drinking response but did not alter the stimulation of renin release caused by dextran.

Puromycin and cycloheximide inhibit the final stages of protein synthesis at the ribosomes. The renin release caused by a decrease in renal perfusion (166) or the application of a clip to the renal arteries of dogs (684) was attenuated by puromycin. Cycloheximide lowered basal renin release and the stimulation of renin release caused by isoproterenol and glucagon in the isolated perfused rat kidney (1127). The mechanism responsible for this suppression of renin release is not known.

Because intracellular microtubules seemed to play a role in many secretory processes, the effects of several inhibitors of the microtubular system on renin release have been studied. Vincristine was shown to inhibit isoproterenol-stimulated renin release, but not basal renin release, from rat renal cortical slices in vitro (189). However, Hackenthal et al. (430) found that vinblastine and colchicine had a variable influence on basal and stimulated renin release. Both compounds attenuated the increase in PRC seen after the administration of furosemide to rats. Vinblastine, when added to rat renal cortical slices in vitro, lessened basal renin release and that release caused by isobutylmethylxanthine and isoproterenol. Colchicine was without effect. Conversely, vinblastine and colchicine increased renin release by 2- to 3-fold when injected into the isolated perfused rat kidney and did not affect the renin response to isoproterenol in this system. While the authors conceded that renin release might involve microtubules, the usefulness of vinblastine and colchicine in studying this relationship was judged to be limited (430).

In an attempt to delve into the role of calcium in renin release, two calcium ionophores were injected into the isolated, perfused rat kidney in the presence and absence of calcium (996). The ionophore X537A stimulated renin release in the presence and absence of calcium. In the absence of calcium, A23187 had no effect on renin release, and in the presence of calcium this ionophore both increased and decreased renin release. Harada et al. (443a) found that A23187 evoked a dose-related increase in renin release from the isolated perfused feline kidney. Because this stimulation of renin release was inhibited by calcium deprivation, propranolol, or the prior treatment of the cats with reserpine, it was concluded that A23187 induced renin release in the intact kidney by the release of norepinephrine. However, A23187 also enhanced the secretion of renin from superfused feline glomeruli in vitro, and this stimulation was not impaired by the removal of calcium from the superfusate. In the latter case, A23187 was believed to stimulate renin secretion by mobilizing intracellular calcium. As mentioned in the section on calcium and renin release, the elevation of the intracellular concentration of calcium in the granular JG cells appears to inhibit renin release.

In epileptic patients treated with anticonvulsant doses of phenobarbital, an inverse correlation was noted between PRC and the plasma concentration of phenobarbital (115a). Conversely, treatment with phenobarbital elevated the concentration of renin substrate in the plasma. Phenobarbital did not inhibit the renin-renin substrate reaction in vitro. Another anticonvulsant, phenytoin, was observed to elicit a dose-related stimulation of renin secretion from rat renal cortical slices in vitro (218a). Both basal and phenytoin-induced renin secretion were inhibited by removing potassium from the medium and adding ouabain or by reducing the sodium concentration of the medium. Churchill et al. (218a) suggested that renin secretion was a function of the transmembrane sodium gradient of the granular JG cells

and that phenytoin increased this gradient, causing an increase in calcium efflux and/or a decrease in calcium influx that led to the enhanced secretion of renin.

L. Inactive Renin and Its Alteration by Drugs.

One of the original techniques developed for the measurement of PRC involved the prior destruction of plasma angiotensinases and endogenous renin substrate by lowering the plasma to less than pH 4. Exogenous renin substrate was then added, and PRC was calculated from the amount of AI generated at pH 7.4 (1020). However, recent studies (1001, 1021) have indicated that human plasma contains both an active and an inactive form of renin, and the latter can be converted into an enzymatically active form by acid-activation or cryoactivation. Thus, prior acidification followed by neutralization may artificially increase the activity of renin in plasma from humans (1001, 1021), dogs (524), and pigs

TABLE 3

*The alteration of active renin (PRA), total plasma renin activity (TPRA), and inactive renin (TPRA-PRA) by physiologic and pharmacologic interventions**

Experimental Subjects	Intervention	PRA	TPRA	Inactive Renin	Comments	References
Anesthetized dogs	Hemorrhage	↑	↑	↑		524
	Furosemide, single dose	↑	↑	↓		
Anesthetized pigs	Isoproterenol, infusion, i.v.	↑	↑	↑	Renal venous blood in all cases	47
	Furosemide, single dose	↑	↑	↑		
	Propranolol, single dose	↓	↓	↓	After furosemide	
	Indomethacin, single dose	↓	↓	↓	After propranolol	
Anesthetized pigs	Intravenous infusion of saline	↓	↓	↓	Renal venous blood in all cases	47
	Furosemide, single dose	↑	↑	↑	After i.v. saline	
	Propranolol, single dose	↓	↓	↓	After furosemide	
NT humans	Head-up tilting	↑	N.C.	↓		269
HT humans, seated	Sodium restriction, 5 days	↑	↑	↑		33
NT and HT humans, upright	Saline infusion, i.v.	↓	N.C.	N.C.		1196
HT humans, seated	Chlorthalidone, 3–8 wk	↑	↑	↑		33
HT humans, seated	Spironolactone, 3–6 wk	↑	↑	↑		33
NT humans, supine	Hydrochlorothiazide, 5 days	↑	↑	↑		557
	Saralasin infusion, i.v.	↑	↑	N.C.	Given after hydrochlorothiazide, 5 days	
HT humans, supine	Hydrochlorothiazide, 3 mo	↑	↑	↑		557
HT humans (low renin), upright	Hydrochlorothiazide, 1 wk	↑	↑	N.C.		720
	Low salt diet, 1 wk	↑	↑	N.C.	Added to hydrochlorothiazide	
	Propranolol, 1 wk	N.C.	N.C.	N.C.	Added to hydrochlorothiazide and low salt diet	
	Indomethacin, 1 wk	↓	↓	N.C.	Added to hydrochlorothiazide and low salt diet	
NT and HT humans, upright	Furosemide, single dose	↑	↑	N.C. or ↑		557
NT humans	Orthostasis	↑	↑	N.C.		967
	Furosemide, single dose	↑	N.C.	N.C.	Furosemide given after orthostasis	
NT and HT humans, upright	Furosemide, 1 day	↑	↑	↑		1196
NT humans	Indomethacin, 3 days	↓	↓	N.C.	Supine position	967
	Orthostasis	N.C.	N.C.	N.C.	After indomethacin	
	Furosemide, single dose	N.C.	N.C.	N.C.	After indomethacin and orthostasis	
NT humans, supine	Isoproterenol infusion, i.v.	↑	N.C.	↓		269
HT humans, seated	Propranolol, 8 wk	↓	N.C.	↑	Blood pressure decreased	33
		↓	↓	N.C.	No change in blood pressure	
HT humans, supine	propranolol, 2 wk	↓	↓	N.C.	Measured renin secretion during angiographic studies	91
HT humans, supine	Propranolol, 1–4 wk	↓	N.C.	↑		269
HT humans, supine	Diazoxide, single dose	↑	N.C.	N.C.	Renal venous blood, normal renal arteries	267
		↑	↓	↓	Renal venous blood, stenotic renal arteries	
HT humans, supine	Diazoxide, single dose	↑	N.C.	↓		269
HT humans, supine	Clonidine, 2–5 wk	↓	N.C.	↑		33

* ↑, increase; ↓, decrease; N.C., no change.

(47). Inactive renin also has been reported to be present in renal tissue from humans (270), rabbits (639), pigs (120), and rats (271). In fact, it has been suggested that the inactive form of renin may be the intrarenal storage form of this enzyme (271).

At this time, many questions concerning the physicochemical characteristics and pathophysiologic significance of the inactive renin in the blood are unanswered. Nevertheless, the following facts have been established: 1) the increase in the enzymatic activity of plasma renin after acid treatment does indeed appear to be due to the activation of a proenzyme rather than the removal of an inhibitor (270); 2) the values determined for inactive renin in human (270, 557) and porcine (47) plasma are considerably greater than those of active renin; 3) the values of active and inactive renin in human plasma are well-correlated under steady-state conditions (269, 270); 4) bilateral nephrectomy causes a marked decrease in both active and inactive renin in the blood (270); 5) the half-life of inactive renin in the circulation is much longer than the half-life of active renin (270); 6) the reaction of acid-activated human plasma renin and renal renin with either homologous or heterologous renin substrate revealed identical K_m values (270); 7) plasma AII levels are well correlated with active renin (PRA) but not with inactive renin (557); 8) the kidney may play a role in the activation of inactive renin in the blood (267, 270); 9) under basal conditions, renin is secreted from the human kidney mainly in the active form (91); 10) the renal release of active and inactive renin in response to various stimuli can be dissociated (33, 47, 91, 267, 270, 557, 720, 967, 1196); and 11) changes in the release of active renin in response to stimuli occur rapidly whereas changes in inactive renin release occur more slowly (1196).

With these observations in mind, we will briefly summarize the physiologic and pharmacologic alteration of the release of inactive renin from the kidney. As mentioned previously, the beta-adrenergic antagonists propranolol (269) and metoprolol (16) lowered PRA without affecting PRC [measured as "total plasma renin" by the method of Skinner et al. (1021)] in hypertensive patients. In like fashion, atenolol did not lower "total plasma renin activity" (TPRA) in hypertensive humans (319). In more recent studies, researchers have measured active renin (PRA), total renin (TPRA), and inactive renin (TPRA-PRA) after physiologic perturbations or the administration of various drugs to healthy and hypertensive humans and experimental animals. These studies are summarized in table 3. In many cases (33, 267, 269), the stimulation of the release of active renin (PRA) is accompanied by a decrease in the circulating level of inactive renin. On the other hand, certain interventions, sodium depletion in particular (33, 47, 557, 1196), tend to elicit an increase in PRA, TPRA, and inactive renin. Some species differences also may occur. For example, isoproterenol increases PRA and decreases inactive renin in humans (269), whereas this drug elevates both active and inactive renin in pigs (47). Until the exact importance of inactive renin in health and disease is determined, the significance of these drug-induced changes in the release of inactive renin cannot be stated with any certainty.

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