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INTRODUCTION

The most widely adhered to theory of the control of renin release is the so-called "stretch" hypothesis proposed by Tobian (423, 424, 425, 427, 435). According to this theory, renin is secreted in response to a decreased pressure differential across the juxtaglomerular cells, and secretion is inhibited by an increase in the pressure differential. There is abundant evidence supporting an augmentation of renin secretion when the transmural pressure is lowered by decreasing the intramural hydrostatic pressure (see Table I). To further test this hypothesis, experiments were designed to lower transmural pressure by raising the extravascular renal interstitial pressure. This was done by measuring the change in aldosterone output in hypophysectomized dogs after partial obstruction of the renal vein or elevation of the ureteral pressure.

EXPERIMENTAL METHODS

Unilaterally nephrectomized male mongrel dogs were anesthetized with pentobarbital after having been fasted for 24 hours. A femoral vein and artery were cannulated for the reinfusion of donor blood and for constant monitoring of arterial pressure, respectively. A lumboadrenal vein was then cannulated by the method of Hume and Nelson (245). The ureter was cannulated in experiments in which the ureteral pressure was elevated. In experiments in which the renal venous pressure was raised, the left testicular vein was cannulated to measure renal venous pressure, which was altered by means of an adjustable loop of umbilical tape around the left renal vein next to the inferior vena cava. Renal interstitial pressure was estimated by plunging a size 24 needle into the parenchyma of the renal cortex, according to a modification of the method of Bush and associates (58). The needle was connected to a strain gauge by a fine polyethylene tubing filled with heparinized saline.

After the dogs were hypophysectomized by the transbuccal route, collections were not begun for at least one hour. Control readings of intrarenal pressure (IRP), renal venous pressure (RVP), or ureteral pressure (UP), femoral arterial blood pressure, and adrenal venous collections for aldosterone and 17-hydroxycorticoids were taken at 30 and 15 minutes before either raising the renal venous pressure or raising the ureteral pressure. These same parameters were monitored and adrenal venous collections were again taken at 10, 30, 60, and 90 minutes. The renal venous or ureteral pressures were then reduced to

control levels, and collection and measurements were made at 150 minutes. To test adrenal responsiveness, one IU of ACTH was injected into the femoral vein, and adrenal effluent was collected after 4 minutes.

All pressures were monitored via Statham strain gauges connected to a Grass model 5 polygraph. Adrenal venous blood was quickly centrifuged and the plasma frozen. Aldosterone was measured by the double isotope derivative method of Kliman and Peterson (262) and the 17-hydroxycorticoids by the method of Silber and Porter (395). The output of both hormones was calculated by multiplying concentrations per ml. of plasma times the plasma flow per minute. Completeness of hypophysectomy was judged by the level of 17-hydroxycorticoids from one to two hours following hypophysectomy in relation to maximal 17-hydroxycorticoid output after administration of one IU of ACTH, according to the criteria of Ganong and Lowe (142).

EXPERIMENTAL RESULTS

As one increases the renal venous pressure, the renal interstitial pressure (IRP) rises in direct proportion, such that the interstitial pressure is about one mm Hg above the renal venous pressure at any one time. In contradistinction, when the ureteral pressure is raised, the IRP follows only to a level of about 40 mm Hg. A further increase in ureteral pressure is not accompanied by an increase in the IRP. In both situations the renal capsule becomes very tense, and the kidney assumes a bluish color. These observations are not different from those made by other investigators (171, 172, 233, 236, 307, 413, 414).

The IRP rose from 11 to 32 mm Hg when the renal vein was compressed and from a mean of 12 to 41 mm Hg when the ureteral pressure was increased to approximately 70 mm Hg. in all experiments. Changes in the IRP were not accompanied by changes in either the mean arterial blood pressure or pulse pressure, except for small fluctuations in any one experiment. An average of the mean arterial blood pressure at all time intervals shows no statistically significant deviation from the control level.

Adrenal plasma flow rates remained relatively constant in any one experiment. The mean control adrenal venous plasma flow rate was 1.55 ml per minute in dogs in which the ureteral pressure was raised and 1.18 ml per minute in dogs in which the venous pressure was raised. There was no significant change in mean flow rate in either of the two types of experiments at all time intervals. Furthermore, there was no necessary

correlation between adrenal flow and steroid secretion in any experiment in which there were minor fluctuations of adrenal venous plasma flow rates.

Control 17-hydroxycorticoid outputs in all except one animal were less than 15% of the maximal output produced by ACTH. In the remaining animal the control secretion rate was 27% of the maximal response, a value still well within a range indicating completeness of hypophysectomy (142). There was no significant rise in Silber-Porter chromogens in comparison to control levels at all time intervals throughout the experiment. The rise after administration of one IU of ACTH was highly significant.

Figure 1 shows that as one raises the IRP by constricting the renal vein there is an average small, insignificant, increase in aldosterone secretion from 15.9 to 20.9 mug/ml/min. at 60 minutes. In three of six dogs there was essentially no increase in aldosterone secretion. In one animal there was a slight increase in secretion (from 25 to 35 mug/ml/min.) and in the remaining two there was a gradual rise in aldosterone secretion, with two-fold increases in secretion persisting to the 150 minute collection, at which time the IRP had been at control levels for one hour.

Figure 2 illustrates that a similar result was observed in six dogs in which the ureteral pressure was increased. Aldosterone secretion increased from a control level of 15.6 to a maximum rise of 19 mug/ml/min. at 90 minutes, a rise which is not statistically significant. The secretion of aldosterone remained essentially unchanged in five of six experiments. In the remaining animal, aldosterone secretion increased

gradually with a maximum two-fold increase at 90 minutes, which persisted to 150 minutes when the IRP had been at control levels for one hour.

In all twelve experiments the adrenal glands were shown to be normally responsive to one unit of ACTH by secreting aldosterone and 17-hydroxycorticoids in the range of maximal secretion rates.

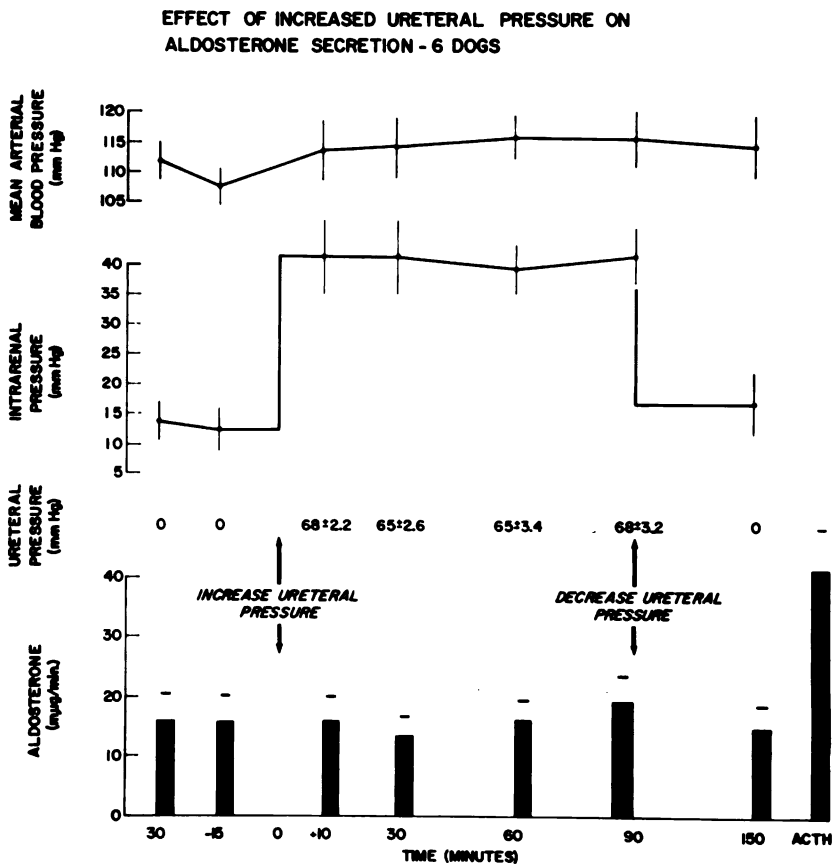

Figure 2. Effect of increased ureteral pressure on aldosterone secretion in 6 hypophysectomized dogs. Values are means ± standard errors. In the case of mean arterial pressure and intrarenal pressure, the vertical lines represent ± one standard error. In the case of aldosterone secretion, the horizontal lines are one standard error above each bar. The bar labeled ACTH represents aldosterone secretion 4 minutes after injection of 1 I.U. of ACTH.

DISCUSSION

The following is a general discussion of the various factors which have been suggested to play a role in renin secretion. Because any theory of the mechanism of renin secretion is dependant upon the anatomical origin of renin, the pertinent evidence is reviewed. The reader is referred to the section on the role of the renal interstitial pressure in renin secretion for a specific discussion of the above experiments.

I. Site of Renin Production

There is overwhelming evidence in favor of the juxtaglomerular apparatus as the site of renin secretion. The juxtaglomerular apparatus consists of three components: (1) granular epitheliod cells (J-G cells), (2) macula densa, and (3) small agranular cells referred to as the cells of Goormaghtigh, the polkissen cells of Zimmerman, or the lacis cells of Oberling and Hatt. Ruyter is given credit for having discovered the juxtaglomerular cells in 1925 (372). In the late thirties Goormightigh found hyperplasia, hypertrophy, and sometimes granulation of the juxtaglomerular cells in patients with scarlet fever and hypertension, in dogs made hypertensive by hypervitaminosis D, and in dogs and rabbits in which the renal arteries were constricted (165-168). On the basis of this evidence, he suggested that the J-G cells acted as an endocrine organ and were related to the hypertensive principle of the ischemic kidney. Kauffman observed hyperplasia and hypertrophy of the J-G cells in some humans with hypertension and with pyelonephritis (259). Dunihue confirmed the findings of Goormaghtigh in the rabbit subjected to renal artery stenosis and observed similar changes in the J-G cells acutely

in rabbits with cellophane perinephritis (104 & 105).

Regardless of evidence suggesting the J-G cells as the site of renin production, this hypothesis was, in general, temporarily rejected in favor of a tubular source of renin. Weeks et al showed that spleno-reno-plexy lowered the blood pressure of dogs made hypertensive by renal artery constriction (458). This procedure was accompanied by collateral circulation between the splenic sinusoids and tubular capillaries, but vascular connections were not seen with the glomeruli. This suggested to these authors that the tubular circulation was inhibiting a hypertensive principle. Friedman and Kaplan studied the renin content in various types of fish. They first thought that renin was found in only fish with glomeruli (133), but later modified this to fresh water fish with glomeruli (134), since all marine fish that had been tested had no renin, regardless of the presence of glomeruli. It is interesting that mention was not made of the possible ramifications of the very significant observation that renin was found only in fresh water fish who need to conserve sodium.

Since marine fish with glomeruli contained no renin in their kidneys, further evidence for a tubular source of renin was sought. It was found that renin content in embryonic pig kidneys correlated well with tubular content but not with arterioglomerular content (135). These authors next treated rabbits with sodium tartrate to produce selective necrosis of the proximal tubules and found a greatly diminished pressor response of renal extracts when injected into donor dogs (136). These findings, however, have not been confirmed; sodium tartrate does not seem to specifically necrose the proximal convoluted tubule, and the renal pressor activity in kidneys of animals treated with this agent has been shown to be normal by several investigators (472). After noting mitoses of

tubular epithelial cells kidneys with renal artery stenosis, Selye supported the idea of a proximal tubular source of renin (389). In 1950, Taquini found renal pressor activity only in the subcapsular, aglomerular zone of the cortex in the cat, dog, ox, and pig, suggesting a tubular site of renin secretion (417).

Whereas many investigators have confirmed Tigerstaedt and Bergman's original finding that renin is found in the cortex and not in the medulla (49, 75, 407, 422), most investigators have found little renin in the subcapsular, tubular portion of the cortex (22, 24, 70). In addition, below the subcapsular zone, the extractable renin increases proportionately with the distance from the surface until the deep cortex is reached, where there is no renin in spite of many large glomeruli (49, 70, 354). Bing and Wiberg isolated glomerular tufts by microdissection and found no renin in them (24-27). They also showed that the renin content was not altered by destruction of the glomeruli alone by means of a minute thermocautery, but if the burn was made more extensive to include the periglomerular area, the renin content diminished (24). Cook and Pickering passed magnetic iron oxide particles through the renal circulation, such that they became lodged in the glomeruli. The kidneys were fragmented, seived, and the glomeruli were isolated magnetically. A large amount of renin was found in the glomeruli with attached fragments of tubule and/or arteriole, but little renin was found in the "clean" glomeruli (71, 72, 354). These workers then bisected the glomeruli and found renin to be located on the half of the glomerulus that contains the juxtaglomerular apparatus (73).

Evidence for the location of renin in the J-G cells by microdissection techniques ceases at this point, and further support is dependent on morphological studies relating to the secretory nature of the J-G granules, the correlation of granularity with other indices of renin secretion, and studies with antirenin antibodies.

Most of the J-G cells are found in the media of the preglomerular afferent arteriole where they replace the smooth muscle cells. They have also been found in the media of the efferent arteriole, the interlobar arteries, and possibly even in the macula densa occasionally (116). Numerous mitochondria, a golgi apparatus, endoplasmic reticulum, and two types of granules suggest that these are metabolically very active cells with abundant synthetic machinery. Goormaghtigh noted changes in the J-G granules of rabbits with constriction of a renal artery that were suggestive of a secretory cycle. He found that the granules tend to disappear in the first 24 hours and then they reappear with strong granulation which persists for about 6 months (72, 168, 169). Miller and Hartroft found degranulation followed by hypergranulation in weanling rats subjected to acute dietary salt deficiency (308). The changes in granulation were accompanied by parallel changes in renin content. Electron microscope studies have been consistent with a secretory cycle but definitive work has not been published (9-11, 215, 334).

Since the early work of Goormaghtigh and Dunihue, a large number of observations in experimental animals and in clinical conditions have shown a close correlation between J-G granulation and other indices of renin secretion. These changes are detailed in Tables I-III; the

various stimuli producing these changes will be considered in a later section.

The most convincing evidence thus far that the J-G cells are the source of renin secretion has come from antirenin studies of Edelman and Hartroft. Dog antirenin antibodies to hog and rabbit renin were tagged with fluorescein and incubated with frozen sections of kidneys of salt deficient rats, rabbits, dogs, and pigs. The antibody was seen to localize in the J-G granules in all species except the rat (112, 212, 216). They were able to repeat this observation using the "sandwich" technique by which Nairn et al had found the fluoresence to localize in the glomeruli (328). It was also found that the amount of extractable renin correlated with the degree of fluorescence. Many investigators have noticed hyperplasia, hypertrophy, and hypergranularity of the J-G cells in animals actively or passively immunized with renin (140, 216, 379).

The role of the macula densa in the formation, storage, or secretion of renin is a perplexing problem and will be discussed in a later section.

II. Stimuli Associated with Changes in Renin Secretion

A large number of experimental situations and clinical conditions have been shown to be associated with changes in renin secretion. Conditions that have been associated with an increase, decrease, or no change in renin secretion have been listed with the references in Tables I, II, and III respectively. Criteria that are used to detect an increase in renin secretion are: (1) the level of renin in the blood or lymph; (2) the level of angiotensin in the blood; (3) the level of aldosterone in the blood or urine; (4) the degree of hypertrophy,

hyperplasia, or granularity of the juxtaglomerular cells; or (5) the amount of extractable pressor substance in the kidneys. Renin-like pressor substances have been demonstrated in some situations, and these findings are also listed. Although not necessarily indicative of changes in renin secretion, enzymes in the juxtaglomerular cells and macula densa have been measured in a few instances, and these data are included.

Each criterion used has its limitations, but, when there is general agreement among all criteria, the evidence for a change in renin secretion is considerably strengthened. The measurement of renin and angiotensin is based on bioassay and is thereby subject to biological variability and a certain subjectivity. A wide variety of methods is used to extract renin. Some methods yield very crude renin preparations, but a few of the more recent extraction procedures permit a fairly accurate and reproducible bioassay of renin. Many of the discrepancies in results can probably be explained by differences in the assay of renin. Genest has pointed out that the level of angiotensin depends not only on the level of renin, but on factors promoting or inhibiting fixation of angiotensin at arteriolar receptor sites, and on factors that may inhibit or promote the inactivation of this substance (152).

A chemical measurement of aldosterone has been developed, so that biological variability in the assay technique and a lack of objectivity is circumvented. However, in order to use aldosterone as an index of renin secretion, factors known to affect aldosterone secretion by means other than the renin-angiotensin system must be controlled. ACTH

release can be controlled by hypophysectomy, and there must be no large change in serum sodium or potassium. Electrolytes were not measured in the experiments presented above, but it is highly unlikely that shifts of potassium or sodium large enough to affect aldosterone secretion could have occurred (31, 32, 91). In addition, there may still be as yet unknown factors that influence aldosterone secretion. A less exact method of minimizing the role of ACTH in some experiments listed on Tables I, II, and III has been to compare aldosterone secretion in the experimental animal with the level in a surgically stressed control. A problem with this technique is that the control animal may have a very high aldosterone secretion rate.

Changes in juxtaglomerular granularity have provided a useful index of renin secretion as judged by a good correlation with other indices of renin release. The amount of extractable renin-like substance is determined by the pressor activity when crude kidney extracts are injected into assay animals. The amount of renal pressor substance correlates well with renin secretion.

Renin-like pressor substances have occasionally been demonstrated. They are called renin-like because the assay involves no extraction procedure and amounts to direct humoral transfer of the pressor substance to the donor animal.

TABLE I

SOME CONDITIONS IN WHICH THERE IS EVIDENCE FOR AN INCREASE IN RENIN SECRETION

Condition	Increased levels of renin in blood or lymph	Increased levels of angiotensin	Increased secretion or excretion of aldosterone	Increase in J-G Granulation	Increase in renal pressor substance	Other
Acute Constriction of the Renal Artery in Normal Animals	42-44, 119, 221, 263, 264, 280, 284, 297, 341, in dogs. 363 in dog & man. But see: 118 in dogs & 130 in rats.	12, 43, 164, 313 342, 381, 382, 399, 400, 406 in dogs.	405 in hypophysectomized dogs.	45, 104, 183 211, 228, 379, 418, 430, 435, 436 in rats. 96 in rat & rabbits.	55, 124, 195, 197, 368, 369, 430 in rats. But see: 35, 461, 37, 204, 362, 379, 461 in dogs. 356, 448 in rabbits, 204 in man.	Increased pressor activity in blood of dogs (20, 103, 179, 180, 242) & rats (266 & 277). But see: 36, 375 & 434 in the rat. Hypertrophy of the zona glomerulosa in the rat (344). Increase in macula densa glucose-6-phosphate dehydrogenase (227, 228).
Acute Constriction of the Aorta above the Renal Arteries.	56, 83, 87, 401-403, 444-446 in dogs.	56, 402, 404 in dogs. But see: 382.	83, 87, 143 in hypophysectomized dogs. 140 in dogs actively immunized with hog renin.	But see: 332 in rats.	298 in rats.	
Decrease in Renal Arterial Perfusion Pressure	56, 265, 401-404 in dogs. But see: 244 in dogs treated with amytal.	Trimethaphan camphor but not arfonad (342).		211, 238, 295 with hydralazine in rats.		

Table I (continued)

Condition	Increased levels of renin in blood or lymph	Increased levels of angiotensin	Increased secretion or excretion of aldosterone	Increase in J-G Granulation	Increase in renal pressor substance	Other
Hemorrhage	56, 98, 244, 374 in dogs and 197 in rats. But see: 371 in rabbits, and 451 in dogs.	342 & 382 in dogs.	77, 79, 83, 85, 143 316, 318, 319, 320, 405 in hypophysectomized dogs.	147, 188, 238 in rats.	But see: 197, 451, 474, 478.	Increased pressor activity in blood of dogs (68, 208, 209) and rats (306, 478).
Renal Artery Stenosis in Man	51, 118, 224, 252, 449, 453, 473.	273, 312, 313. 398 & sometimes with standing (243). But see: 95, 150, 151, 152, 315, 381, 382.	161, 181, 270.	39, 75, 95, 100, 152, 161, 183, 212, 312, 439. But see 11.	155, 204, 268	Increased pressor activity in plasma (186).
Malignant Hypertension	1, 51, 121, 129 224, 254, 341, 438, 473 in man.	253, 254, 398, 400 in man. But see: 95, 150, 312.	63 in non-hyped dogs, 150, 273 in man.	100, 212, 259, 303 in man.	63 in dogs.	
Thoracic Inferior Vena Cava or Hepatic Vein Constriction A. Acute			30, 31 in non-hypophysectomized sheep. 13, 16, 17 88, 137, 309, 335-337 in non-hypophysectomized dogs. 31 in decerebrate sheep. But see: 94, 137 in hypophysectomized dogs.			
B. Chronic	53, 87, 94, 230 231 in dogs.	230 in dogs	13, 62, 78, 82-84, 86, 90, 92, 94, 335-337 in non-hypophysectomized dogs. 6, 82, 94 in hypophysectomized dogs.	6, 87 in dogs.		

Table I (continued)

Condition	Increased levels of renin in blood or lymph	Increased levels of angiotensin	Increased secretion or excretion of aldosterone	Increase in J-G Granulation	Increase in renal pressor substance	Other
			in hypophysectomized dogs. But see: 84, 94 in hypophysectomized dogs.			
Some Patients with Cirrhosis and Ascites.	51, 118, 152, 231, 449, 473	95, 152, 153.	5, 270, 289.	212, 303, 343, 366.		Increased height of macula densa cells (303).
Heart Failure A. By constriction of the pulmonary artery			86, 90 in non-hypophysectomized dogs.		87 in dogs.	
B. By producing an A-V fistula distal to the kidneys			92, 93, 229 in normal and hypophysectomized dogs.	427 in rats.		
C. In some humans with edema	153, 231, 225, 305, 327, 449.	95, 152, 153, 231.	5, 289.	212, 427.		
Pregnancy	48, 51, 118, 426 in man.		251, 269, 296, 333, 370, 447, 471 in man.	183, 426 in man and 452 in rats.		
Nephrotic Syndrome with Ascites A. Aminonucleoside in rats			76, 396.	433.	But see: 192.	No change in glucose-6-phosphate dehydrogenase & 6-phosphogluconic dehydrogenase in the macula densa (125).

Table I (continued)

Condition	Increased levels of renin in blood or lymph	Increased levels of angiotensin	Increased secretion or excretion of aldosterone	Increase in J-G Granulation	Increase in renal pressor substance	Other
B. In humans	152, 449, 473.	95, 153.	270, 288, 289-291.	285, 303.		
Low Salt Diet in Normal Animals	59 in rats. 1, 50, 51, 118, 153, 190, 347, 358, 359, 449, 465 in man. 13, 29, 53 in dogs.	12, 152, 382 in dogs. But see: 323 in dogs.	189, 294 in rats. 12, 13, 81 in non-hypophysectomized dogs. 29, 81, 405 in hypophysectomized dogs. But see: 94 in hypophysectomized dogs. 5, 14 153, 286, 449 in humans.	110, 126, 213, 308, 418, 452, 459, in rats 1, 131, 366, in man. 331 in cats.	150, 189, 421 in rats. 358, 359 in dogs.	
Adrenal Insufficiency	190 in rats. 51, 473 in man.			10, 19, 106 435 in rats. 106, 107 in monkeys. 106 in dogs. 107-109, 331 in cats. 107 in rabbits. 131, 303 in man. But see: 377 in rats.	189, 190, 201, 375, 406 in rats.	Dilation of the efferent arteriole & change in the macula densa (10). Increase in glucose-6-phosphate dehydrogenase (193, 226) & α glycerol phosphate (227) in the macula densa. Increase in pressor substance in plasma (375).
Chronic treatment with Chlorthiazide	1, 464, 465 in man.		14 in man.	429 in rats.		

Table I (continued)

Condition	Increased levels of renin in blood or lymph	Increased levels of angiotensin	Increased secretion or excretion of aldosterone	Increase in J-G Granulation	Increase in renal pressor substance	Other
Decrease Plasma Sodium Concentration during the last week of Life	1 in man			1, 357 in man		
Salt losing form of the Adrenogenital Syndrome				61.		
Exercise in Normotensive & hypertensive Humans	224					
Standing in Humans	69		69			Increase in plasma pressor substance (60).
Cellophane Perinephritis or Renal Encapsulation	339-341 in dogs. But see: 46 in rats.			212 in rats 105 in rabbits. 39 in one human	37 in dogs. 187, 195 in rats.	
Figure-of-eight Ligature about the Kidney				211 in rats.	124 in rats.	Increase in glucose-6-phosphate dehydrogenase, 6-phosphogluconic dehydrogenase in macula densa of rat (124). Increase in Pressor substance in plasma in rat (266).
Hydronephrosis				39 in one human. 211 in	124 in rats.	

Table I (continued)

Condition	Increased levels of renin in blood or lymph	Increased levels of angiotensin	Increased secretion or excretion of aldosterone	Increase in J-G Granulation	Increase in renal pressor substance	Other
				rats. But see: 168 in rats & dogs.		
Oncometer applied to Kidney Surface	403 in dogs					
Acute Tubular Necrosis	252 & 438 in man.			169, 170 in man.		
Manipulation of the Kidney	224 in dog.					
Idiopathic Hypertrophy of the Juxta-glomerular cells			18	18		

TABLE II

SOME CONDITIONS IN WHICH THERE IS EVIDENCE FOR A DECREASE IN RENIN SECRETION

Condition	Decreased levels of renin in blood or lymph	Decreased levels of angiotensin	Decreased secretion or excretion of aldosterone	Decrease in J-G Granulation	Decrease in renal pressor substance	Other
Contralateral Kidney of an Animal with A. Constriction of the Homolateral Renal Artery				211, 228, 377 430, 431, 435 in rats.	36, 55, 125, 126, 190, 194, 195, 211, 226, 228, 290, 367, 368, 418, 430, 431 in rats. 20, 37 in dogs 204 in dogs & man.	Decrease in glucose-6-phosphate dehydrogenase (125, 126, 189, 193, 226, 228). 6-Phosphogluconic dehydrogenase (125, 126, 226) & α-glycerol phosphate dehydrogenase (227) in the macula densa.
B. Perinephritis of Homolateral Kidney					37 in dogs. 194 in rats.	
C. Figure-of-eight Ligature about the Homolateral Kidney				211 in rats.	125, 126 in rats.	Decrease in glucose-6-phosphate dehydrogenase & 6-phosphogluconic dehydrogenase in the macula densa (125, 126).
Increased Renal Perfusion Pressure A. Isolated Kidney				427, 436 in rats.		

Table II (continued)

Condition	Decreased levels of renin in blood or lymph	Decreased levels of angiotensin	Decreased secretion or excretion of aldosterone	Decrease in J-G Granulation	Decrease in renal pressor substance	Other
B. Pharmacologic Agents				211, 212 in rats		
C. Metacorticoid hypertension				425, 427 in rats.	55, 188 in rats	
D. Adrenal Regeneration Hypertension				425, 427 in rats.	188, 189 in rats.	
High Salt Diet	50, 51, 449 in man		189 in rats.	423, 427, 437 459 in rats. 449 in man.	187, 189, 421 423, 427 in rats. But see: 190, 299.	
Administration of Mineralocorticoids	391 in dogs.			108, 431 in rats. 107-109, 459 in cats. 107 in monkeys & rabbits. But see: 102 in mice.	125, 126, 215 299, 409, 423 435 in rats. But see: 187, 222, 391, in dogs. 448 in rabbits.	Decreased glucose-6-phosphate dehydrogenase & 6-phosphogluconic dehydrogenase in the macula densa (125, 126).
Administration of Mineralocorticoids plus sodium chloride	197 in rats.			19, 215, 423 459 in rats. 108, 459 in cats. 488 in rabbits.	19, 23, 109 187, 197, 200 in rats. 199, 488 in rabbits	Decrease in glucose-6-phosphate dehydrogenase (189, 193, 225) & α-glycerol phosphate dehydrogenase (227) in the macula densa.

TABLE III

SOME CONDITIONS IN WHICH THERE IS EVIDENCE FOR NO CHANGE IN RENIN SECRETION

Condition	No change in levels of renin in blood or lymph	No change in levels of angiotensin	No change in secretion or excretion of aldosterone	No change in J-G granulation	No change in renal pressor substance	Other
Renal Artery Constriction in Dogs on a Low Salt Diet	53		12 in non-hypophysectomized dogs.			
Decrease in Renal Blood Flow	263, 264, 403 in dogs.					
Increase in Renal Venous Pressure in Dogs.	8, 230, 403.		64. But see: 31 in sheep.			
Constriction of the Abdominal Inferior Vena Cava in Dogs.	8, 230.		64. But see: 31 in sheep.			
Stimulation of the Renal Nerve	451 in dogs. But see: 443.		279 in hypophysectomized dogs.			
Most Patients with Essential Hypertension	1, 99, 150, 449, 473 in man.	95, 150, 151 254, 399 in man.	63 in dogs. 273 in man. But see: 154 in man.	63 in dogs, 100, 439 in man.		
Patients with a Phaeochromocytoma		312				
Cushing's Syndrome in Man	473	243				
Chronic Glomerulonephritis in Man	438, 473			100, 439		
Primary Hyperaldosteronism	69, but see: 473.	243				
Adrenalectomy plus Administration of Mineralocorticoids				107 in cats & monkeys.		

Table III (continued)

Condition	No change in levels of renin in blood or lymph	No change in levels of angiotensin	No change in secretion or excretion of aldosterone	No change in J-G granulation	No change in renal pressor substance	Other
Low Salt Diet plus Mineralocorticoids				19 in rats	19, 187 in rats	
Aminonucleoside Nephrosis without Ascites				433 in rats		
Cirrhosis without Ascites	473					
Hypercapnia, Anoxic Anoxia, Histotoxic Anoxia	244, 403 in dogs.			109, 162, 163 in rats.		
Alteration in Atmospheric Pressure				162, 163 in rats.		
Bilateral Carotid Constriction			21 in hypophysectomized dogs.			
Administration of Potassium				212 in rats.		

III. Control of Renin Secretion

Theories that have attempted to explain how a large variety of stimuli could be construed to act by a single common mechanism have, in part, awaited the discovery of the J-G cells as a specific site of renin production in the last decade. In earlier experiments in which the kidney was rendered "ischemic" by constriction of its arterial supply, it was difficult to tell whether a reduction in pressure, flow, pulse pressure, or development of anoxia was the essential stimulus for renin release. This dilemma, which seems to be at least partially solved at present, serves to emphasize the continuing difficulty in interpreting much of the recent investigation in the field of the mechanism of renin secretion. Few experiments have been designed to effectively sort out the many mechanisms which have been suggested to play a role in renin release. Thus, evidence marshalled in support of or against a specific hypothesis is largely of an indirect nature. The following paragraphs are designed to examine the many routes by which the juxtaglomerular apparatus might possibly be signalled to secrete renin.

A. The Role of Arterial Pulse Pressure. In 1940, Kohlstaedt and Page perfused an isolated dog kidney and were able to show an increase in renin production by decreasing the pulse pressure, without necessarily lowering the blood flow or mean blood pressure (263, 264). Corcoran and Page demonstrated that hypertension could be produced by perinephritis without altering the renal blood flow (74), and Hawthorne et al produced hypertension in dogs by constricting the aorta so that the pulse pressure decreased but the mean blood pressure did not change (220). Kolff showed in 1958 that a diminution of pulse pressure did not

increase renin secretion in the dog, but a drop in the mean arterial pressure did (265). Skinner et al confirmed this finding and were unable to lower renin secretion by increasing the pulse pressure in the face of a lowered mean arterial blood pressure (401, 403). Higgins and Davis have reported an increase in aldosterone secretion in hypophysectomized dogs in which a large arteriovenous fistula had been made below the renal arteries (229). The resultant large pulse pressure did not block the hyperaldosteronism in these animals. One must conclude that a decrease in pulse pressure is not necessary for renin release and data presented thus far tend to negate a primary role for the pulse pressure.

B. The Role of Mean Arterial Blood Pressure. Since renin, angiotensin and aldosterone secretion are elevated with renal artery constriction or suprarenal aortic constriction (see Table I), many investigators have postulated that a diminution in blood pressure stimulates the production of renin. But evidence that the mean arterial blood pressure per se produces renin release has been lacking until recent years. Kolff in 1958 and Skinner and co-workers in 1963 found that a decrease in mean arterial blood pressure is accompanied by an increase in renin secretion (265, 401, 403). The later investigators demonstrated a rise in renin secretion in some experiments with only a 5 to 10 mmHg fall in mean blood pressure while the renal blood flow remained constant.

Tobian et al and Hartroft et al have, in general, found an inverse relationship between the arterial blood pressure and the juxtaglomerular granulation. The JGI has been elevated in kidneys with a clipped renal artery, in the unclipped kidney after removal of the clipped kidney,

in hemorrhagic hypotension, and pharmacologic hypotension, (see Table I). The JGI is decreased in the untouched kidney when the contralateral kidney's renal artery is clipped, in an isolated kidney subjected to a high perfusion pressure, in pharmacologic elevation of the blood pressure, in metacorticoid hypertension, and in adrenal regeneration hypertension (see Table II).

Many investigators have amply confirmed the above mentioned changes in JGI and the associated change in renal pressor substance; but a necessary inverse correlation of these parameters with the level of arterial blood pressure has not always been apparent. In some experiments the lack of correlation is partially obscured by the employment of more than one stimulus known to affect renin release (19, 23). It has been observed that the JGI, renal pressor substance, and renin output (197) in rats and dogs (37) with unilateral constriction of a renal artery (36, 55, 197, 368, 377, 431), perinephritis (37, 195), figure-of-eight ligature (124), or hydronephrosis (124) may change in the usual manner in both the homolateral and contralateral kidney in the absence of concomitant changes in blood pressure. Gross has summarized reports that there is little correlation between blood pressure and renal pressor substance in rats, mice, rabbits, and dogs given desoxycorticosterone and salt (189). However, the fact that kidneys of rats with renal artery lesions treated with salt and desoxycorticosterone have an incomplete diminution of renin content (189), and that rats treated with high salt and desoxycorticosterone still show a small rise in renal renin content when the renal artery is constricted (23) argues for some effect of renal blood pressure.

Elaut reported hypergranularity of the J-G cells in animals with neurogenic hypertension (300). Chernigorski reported a rise in renal renin content in rats with neurogenic hypertension (65). Smeby and associates have shown that some dogs with neurogenic hypertension have elevated angiotensin levels (406). However, Eliddal and co-workers found that renal renin content is normal in dogs with neurogenic hypertension (37). Sirotina observed a fall in extractable renin in neurogenic hypertensive rabbits (397). Carpenter and associates were not able to block secondary hyperaldosteronism in non-hypophysectomized dogs with chronic thoracic caval constriction by producing neurogenic hypertension (62). Bartter et al (16, 17) and Gann and Travis (137) produced hyperaldosteronism in normal dogs by bilateral carotid constriction, but Biglieri and Ganong showed that this could be blocked by hypophysectomy (21). Finally, Skinner et al were able to partially block the elevated renin secretion in dogs in which an oncometer had been applied to the surface of the kidney by bilateral carotid occlusion (403).

Vander and Miller have demonstrated a fall in renin secretion in dogs when aortic constriction above the renal arteries is accompanied by the infusion of various diuretic agents (445, 446). In addition, Paladini and Scornik found no change in angiotensin levels in dogs made hypotensive with trimethaphan camphor sulfonate (342). Brown et al and Barbour et al have shown that clamping the renal artery in dogs on a low salt diet does not augment renin or aldosterone secretion (12, 53).

It should be noted that the rat may be unique in its mechanism of renin release. It seems that both kidneys may be necessary for renin secretion (23, 189, 190, 197, 367-369). This question is unsettled in

the rabbit (371, 448), but the dog needs only one kidney (31, 37, 405). There is much evidence in favor of an increased renin secretion in dogs with constriction of the aorta above the renal arteries, a situation similar to constriction of one renal artery in a unilaterally nephrectomized dog (see Table I). Furthermore, recent evidence suggests that the renin-angiotensin system may not be important in the regulation of aldosterone secretion in the rat (59, 294, 353). The possible peculiarity of the renin-angiotensin-aldosterone system in the rat is mentioned because it is an extremely common experimental animal and many authors who have not observed an inverse relationship between blood pressure and renin release have employed the rat in their experiments.

To summarize, it seems that a diminution in mean blood pressure is a stimulus for renin release, but there are other as yet poorly defined factors that may modify the effect of mean blood pressure.

C. The Role of Renal Blood Flow. Reference has been made above to the experiments of Corcoran and Page and Hawthorne who were able to produce renal hypertension in dogs without changing the measured renal blood flow (74, 220). Kohlstaedt and Page and Skinner et al found increases in renin release without any detectable change in renal blood flow (263, 264, 403). Skinner and associates decreased the renal blood flow as much as 50% by constricting the renal vein, but found no change in renin secretion (403). A comparable reduction in renal blood flow by constricting the renal artery was accompanied by a significantly increased renin output. The failure of aldosterone secretion to increase in hypophysectomized dogs in which the renal venous pressure was raised and renal blood flow most certainly reduced in experiments done in this

laboratory are in agreement with the findings of Skinner and associates. Braun-Menendez et al observed that renal blood flow had to be diminished by 80 to 90% before a rise in renin secretion could be detected, but the extraction and assay techniques were relatively crude (45). Stimulation of the renal nerves in dogs reduces the renal blood flow (394) and glomerular filtration rate (394), but does not alter the aldosterone secretion in hypophysectomized dogs (279). Renin secretion is stimulated by hydralazine hypotension which is accompanied by an increase in renal blood flow (230, 295). Fasola and Helmer have found that renin secretion increases with exercise in normal and hypertensive humans (224). The mechanism involved is not clear, but exercise is normally associated with a rise in systemic blood pressure and a fall in renal blood flow and glomerular filtration rate.

It seems unlikely that renal blood flow per se could regulate renin release in physiological situations because of the well-known property of the kidney to maintain a fairly constant blood flow over a wide range of perfusion pressures. However, the kidney is not a perfect autoregulator of its blood flow, and the renal perfusion pressure has been lowered below the autoregulatory range in many of the experiments designed to measure renin secretion by constriction of the renal blood supply. It is possible that the severe arteriolar narrowing seen in malignant hypertension or chronic hydronephrosis with hypertension may restrict the blood flow sufficiently to stimulate renin release.

One must conclude that renal blood flow does not stimulate renin release under physiological situations. However, severe restriction of blood flow may be associated with renin secretion. In the latter situation, there is bound to be a concomitant fall in blood pressure at

the level of the J-G cells.

D. The Role of Renal Arteriolar Vasoconstriction.

1. Angiotensin. Katz has suggested that angiotensin stimulates renin release, since he found an increase in JGI after infusing angiotensin (256, 258). This octapeptide is a strong vasoconstrictor of renal arterioles and produces a fall in renal blood flow. Wathen et al have not observed any change in renin secretion after infusing angiotensin into the renal artery of dogs (454, 456), and Ganong and Van Brunt have pointed out that the renin-angiotensin-aldosterone mechanism would tend to perpetuate itself in an uncontrolled fashion if Katz' hypothesis is correct (146). Vander and Geelhoed have recently observed that angiotensin II blocks the normal rise in renin produced by suprarenal aortic constriction in dogs (444). It appears that angiotensin and/or the vasoconstriction accompanying it does not result in renin secretion. It is conceivable that the findings of Katz might be explained on the basis of salt depletion secondary to angiotensin natriuresis in an animal in which angiotensin II does not stimulate aldosterone secretion (59, 294, 353).

2. Epinephrine and Norepinephrine. Wathen et al found that infusion of epinephrine or norepinephrine into the renal artery was followed by a decrease in renal blood flow, glomerular filtration rate (GFR), and a rise in renal vein renin levels. (454-456). If these catecholamines were given intravenously, there was no change in renin secretion until the renal blood flow and GFR had decreased. They concluded that the renal arterial bed must be vasoconstricted in order for catecholamines to increase renin secretion, and that the absence of renin release upon intravenous administration before renal arteriolar

vasoconstriction argued against a direct effect of these catecholamines on the J-G cells. Scornik and Paladini found only a small rise in angiotensin levels after giving dogs epinephrine or norepinephrine intravenously (382). Vander has reported that epinephrine and norepinephrine given intravenously stimulate renin secretion in dogs in which the renal artery blood pressure was kept constant by means of a renal aortic clamp (443). This result is difficult to interpret because constriction of the aorta above the kidneys is a strong stimulus for renin secretion by itself.

Katz found no change in the JGI in animals given these catecholamines (257), and Laragh noted a fall in aldosterone secretion in some salt depleted humans given epinephrine or norepinephrine (272). Dunihue likewise observed a fall in the JGI of salt depleted rats given norepinephrine or reserpine (110).

The evidence to date indicates that pharmacologic amounts of epinephrine and norepinephrine produce intense renal arteriolar vasoconstriction with an acute augmentation of renin secretion. Chronic experiments do not support this action of these catecholamines. Why vasoconstriction with catecholamines, and not with angiotensin, stimulates renin secretion is not known. It may be that they act on different parts of the vasculature or that angiotensin II has a direct inhibitory effect on J-G cell renin release as reported by Vander and Geelhoed. Brody has shown angiographically that catecholamines produce dilation of the larger arteries with vasoconstriction of smaller vessels (47), but the effect of angiotensin was not evaluated.

3. Renal Nerves. There is some evidence that sympathetic nerves to the renal arterioles may influence renin secretion. Introzzi

et al, Fasciolo and Taquini, and Taquini et al have reported a decrease in renal pressor substance in rats and dogs after chronic renal denervation (120, 247, 418). Tobian and associates have recently noted a 40% decrease in the JGI of rats three weeks after renal denervation (428). They interpret their results as indicating afferent arteriolar vasodilation with denervation so that the J-G cells respond to a higher than normal perfusion pressure by degranulating.

Grimson was able to abolish neurogenic hypertension in dogs by cutting the renal nerves (184), and Chernigorski found an increase renal renin content in dogs with neurogenic hypertension, which was blocked by renal denervation (165). As previously discussed, there is reason to doubt that neurogenic hypertension stimulates renin secretion in the first place. Blalock reviewed many early experiments showing that section of the splanchnic nerves does not inhibit hypertension produced by constriction of the renal arteries(34). Carpenter and co-workers demonstrated that the hyperaldosteronism response to chronic thoracic caval constriction in dogs is not blocked by renal denervation of an intact kidney or by transplanting the kidney into the neck (62, 63).

An increase in renal arteriolar vasoconstriction and an increased frequency of action potentials in the renal nerves has been reported in response to hemorrhage, carotid clamping, and anoxia (146, 160, 235, 267). Huidibro and Braun-Menendez found that renal denervation did not block the increase in renin secretion in response to hemorrhage (244), but Holzbauer and Vogt observed a block in aldosterone secretion in hemorrhaged normal dogs with denervated kidneys (240). The results in the latter experiment may be explained by a marked drop in adrenal blood flow with section of the splanchnic nerves. Huidobro and Braun-Menendez

and Skinner et al did not find an increased renin secretion in dogs subjected to anoxia (244, 403). Dunihue and Goldfarb and Tobian could demonstrate no change in the JGI of anoxic rats (109, 162, 163). Lastly, constriction of the carotid arteries does not appear to stimulate renin release (21, 403).

Wakerlin and Chobot could find no change in renal renin content after stimulating the splanchnic nerve (451). In spite of a diminution in GFR, renal blood flow and increased vascular resistance, Lee and Ganong have recently demonstrated that stimulation of the renal nerve in hypophysectomized dogs does not alter aldosterone output (279). Vander has, however, observed a rise in renin secretion after stimulating the renal nerves in the dog (443).

One may conclude that renal arteriolar vasoconstriction per se is probably not involved in the acute release of renin. The renal nerves may function in renin secretion, but they do not play an obligatory role and do not appear to stimulate enough renin release to increase aldosterone secretion in acute experiments.

E. The Role of Intravascular Volume and Venous Receptors. In 1948, Peters hypothesized that a "volumeter" functions in the maintenance of sodium balance (352), and more recently Epstein suggested the arterial tree as a likely site of these receptors (114, 115). Several experimental situations in animals and clinical conditions in man in which volume changes have been reported may be associated with changes in renin and/or aldosterone secretion. Experimental thoracic caval constriction, experimental low output congestive heart failure with edema, humans with congestive heart failure and edema, experimental and clinical nephrotic syndrome with ascites, cirrhosis with ascites and a low salt diet in animals and man have been

associated with an increase in renin secretion (see Table I). The renin secretion in cirrhosis without ascites (473) and the JGI in rats with aminonucleoside nephrosis without ascites (433) have been shown to be normal. However, pregnancy in humans and experimental high output cardiac failure in dogs, both circumstances in which the blood volume is expected to be higher than normal, is also associated with an increase in renin secretion (see Table I). It may be that a disparity between intravascular volume capacity and circulating blood volume makes these latter two conditions analagous to those in which there is a diminution in intravascular volume. Since volume is directly related to blood flow, which in turn is directly related to blood pressure, it is quite difficult to isolate and study the effect of blood volume per se. The evidence in favor of a diminution in mean arterial blood pressure stimulating renin secretion without detectable changes in other parameters has been reviewed. Also, since renal blood flow does not appear to influence renin release, a renal volume receptor seems unlikely.

Bartter and associates observed an inverse relationship between fluid volume and aldosterone excretion in man (14). They also demonstrated a fall in aldosterone excretion in a hypoproteinemic patient after the administration of albumin. Bartter and Gann showed that hyperaldosteronism produced by acute constriction of the thoracic vena cava in two normal dogs could be reversed by infusing blood above the constriction (17). In a similar experiment Davis and co-workers were unable to alter the hyperaldosteronism by increasing the plasma volume to normal levels with dextran (88). The serum sodium concentration remained constant. Fine et al increased the intravascular volume in

humans with hyperaldosteronism induced by phlebotomy and noted no change in aldosterone excretion (123).

Hirashima and Takaku found a decrease in the JGI of hypertransfused rats (238), and Ziegler and Gross observed a decrease in the release of a renin-like pressor substance after hypertransfusing rats for 24 hours (474). The latter authors did not, however, find any change in renal pressor substance in the same experiments. Hartroft and Hathaway found no significant change in the JGI of rats given pitressin on a low salt diet in comparison to rats on a low salt diet alone (213). However, Marks et al observed an increase in the JGI in rats given vasopressin (295), and Cade and Perinich found that large doses of vasopressin increased aldosterone secretion in the rat (59).

Gauer and associates have shown that atrial pressure is directly related to arterial blood pressure and suggest that the distensible venous system is a likely site for a volume receptor controlling aldosterone secretion (148). Anderson et al observed that stretching of the right atrium in normal dogs produced a fall in aldosterone secretion (3). Baisset et al made the same observation in normal and hypophysectomized dogs (7). There is considerable evidence against a role of right atrial receptors in aldosterone secretion. Bartter and Gann showed that the hyperaldosteronism secondary to acute constriction of the inferior vena cava in dogs could not be blocked by vagotomy but that the normal fall in aldosterone secretion after release of the caval ligature was inhibited by vagotomy (17). Carpenter and co-workers have also shown that vagotomy has no influence on the hyperaldosteronism in chronic thoracic caval constriction in dogs (60). It thus appears

that a reduction in right atrial pressure does not stimulate aldosterone via the vagus nerve. The fact that Davis et al were able to demonstrate hyperaldosteronism in dogs with heart failure produced by pulmonary stenosis, in which the right atrial pressure is elevated, is against a high right atrial pressure inhibiting aldosterone secretion (78, 86, 90).

Orloff and co-workers have recently hypothesized that there are hepatic receptors which respond to elevated pressure and in turn release a humoral substance that stimulates renin secretion. They showed that both acute and chronic constriction of the hepatic vein in normal dogs resulted in an increase in aldosterone secretion (337). The hyperaldosteronism was blocked by nephrectomy but not by a portocaval shunt (335). In addition, the blood of a nephrectomized donor dog, in which the hepatic vein was constricted, resulted in an augmentation in aldosterone secretion when crosscirculated into a normal donor animal (336). The dogs were not hypophysectomized, but the cortisol and corticosterone secretion rates indicate that ACTH was probably not responsible for the increase in aldosterone secretion. Blood volumes were said to remain relatively constant and, although blood pressure was measured, values were not reported. Since the donor animals were nephrectomized, the effect of the hypotension on the renin producing J-G cells was not operative. The metabolic clearance rate of aldosterone is diminished in this type of experiment (89), but this alone could not explain the very high elevation in aldosterone secretion. The fact that chronic constriction of the thoracic inferior vena cava in normal dogs results in an increase in aldosterone secretion has been amply confirmed by several investigators (see Table I). Preliminary

reports have indicated that the hyperaldosteronism in response to acute thoracic caval constriction is blocked by hypophysectomy (84, 94, 137, but see: 30).

If these reports and those of Orloff and associates are confirmed, this raises the question of a hypothalamic or hypophyseal factor other than coricotropin releasing factor or ACTH affecting aldosterone secretion in response to increased hepatic pressure. Davis and co-workers have shown that decapitation or hepatectomy does not block the aldosterone secretion in response to hemorrhage or chronic thoracic caval constriction (79), but this does not rule out a role for hepatic or cerebral factors. It is, however, indirect evidence that these factors do not operate via the renin-angiotensin system. If hypothalamic-hypophyseal factors other than CRF and ACTH are involved in aldosterone secretion, Ganong and associates have shown that they are probably localized to the median eminence region in the dog (141).

Evidence against an infrahepatic venous system volume receptor will be reviewed in a later section. There is no convincing evidence to date indicating that a venous or hepatic receptor operates in aldosterone secretion via the renin-angiotensin system; however, the findings of Orloff et al deserve further investigation. Since changes in volume are readily sensed by changes in arterial pressure, there is no need to invoke a receptor for volume changes alone. Such a receptor may operate but evidence for it is lacking at the present.

F. The Role of Sodium Balance. Sodium depletion by a low salt diet or diuretic therapy and adrenal insufficiency have been associated with a rise in renin production (see Table I). Similarly, salt loading

and administration of mineralocorticoids are accompanied by a decrease in renin release (see Table II). Since there is a tendency for the intravascular volume to contract and the blood pressure to drop with sodium depletion (326), the increase in renin secretion may be due to a small decrease in mean arterial blood pressure. Though Pitcock and Hartroft reported a closer correlation of the JGI with the plasma sodium concentration than with the blood pressure in humans during their last week of life (358), it seems that plasma sodium concentration has no direct effect on renin release. Hartroft has observed that when sodium is restricted, there is evidence for increased renin secretion before there is any noticeable change in plasma sodium concentration (212). Tobian perfused isolated rat kidneys with high concentrations of sodium at a constant pressure for three hours without observing any significant change in granulation of the juxtaglomerular cells (436). However, Gross has noted that it takes about 12 to 16 hours to detect a change in renal pressor substance in salt loaded rats (189).

Failing to find a close relation between blood pressure and renin secretion, several authors have suggested a subtle change in sodium balance as the essential stimulus, and have inferred that it may be a shift in the intracellular to extracellular sodium ratio. Dunihue et al suggested that a movement of sodium into the extracellular fluid might be responsible for their observation that the JGI decreased in sodium depleted rats given reserpine or norepinephrine (110). The hypothesis that a small change in intracellular sodium or osmolarity, perhaps in the J-G cells, could alter renin release is a fascinating one, but there is no direct evidence to support it at present. Gross and Schmidt detected no change in sodium concentration in the aorta or

any other tissues in rats treated with salt and desoxycorticosterone (198).

G. The Role of Increased Renal Interstitial Pressure. Winton introduced the concept of intrarenal pressure as the amount of ureteral pressure which results in a reduction of urine flow (466, 468). He found this value to be about 10mmHg in the dog. Bush et al devised a method of estimating the interstitial pressure by plunging a fine bore needle into the renal parenchyma (58). Various observers have noted the "needle pressure" in the dog kidney to be between 15 and 25 mmHg (307, 310, 311, 378, 412, 420). The needle undoubtedly ruptures tubules, peritubular capillaries and the interstitial tissue. So, the pressure measured is a combination from these three sources. Gottschalk found that the intratubular and peritubular capillary pressures are almost identical when measured by micropuncture; unless arterioles are ruptured, a combined pressure should not be a source of error in measurement. Micropuncture is a much more delicate, and undoubtedly a much more accurate method of measuring the interstitial pressure, but needle pressure has been shown to vary as the micropuncture pressure in most instances. It was used in these experiments because of ease of measurement and the information desired was the relative change in interstitial pressure.

There is some controversy concerning whether or not the interstitial pressure parallels changes in the intravascular hydrostatic pressure. Swann et al, Hinshaw et al and Miles and De Wardener have observed a direct relation between the arterial pressure and the "needle pressure" (232, 234, 236, 307, 412, 413, 416). Gottschalk et al, Thureau, Leysacc,

and others using micropuncture techniques, and Winton have shown that the interstitial pressure remains constant over a wide range of arterial pressures (172, 173, 177, 282, 422). The discrepancies appear to relate to the method of measurement. Gottschalk has reported, however, that the intratubular pressure as measured by micropuncture in the rat does fall off with severe hemorrhage (177). The result has a direct relation to the "stretch" theory of renin release. For, if the extravascular pressure changes as the hydrostatic pressure, there will be no change in the pressure differential across the J-G cell with constriction of the renal artery. A constant interstitial pressure would, however, provide for variation in the stretch across the renin secreting cells.

1. The Effect of Increasing the Ureteral Pressure. Interstitial pressure has been shown to increase with ureteral pressure by many investigators. The interstitial pressure begins to increase as the ureteral pressure approaches the control IRP; then the IRP rises to a maximum of about 40 mmHg, regardless of the level of the ureteral pressure.

Braun-Menendez reviewed earlier experiments showing that chronic ureteral obstruction infrequently produces hypertension (45). Hartroft et al and Fisher have found an increase in the JGI and renal pressor substance in rats with hydronephrosis (124, 211). The effect of ureteral pressure is not clear in this situation because of the concomitant development of vascular lesions in the chronic preparation.

An increase in blood pressure in acute experiments in which the ureteral pressure is raised is uncommon and was not found in the experiments in this laboratory (158, 168, 218, 329). Malvin et al did observe a rise in blood pressure with an increase in ureteral pressure

and suggested that this effect might be due to renin (292). Accordingly, Vander and Miller observed that elevation of the ureteral pressure in dogs is accompanied by an increase in renin secretion (444-446). Renin levels decreased with release of ureteral pressure, or with intravenous administration of angiotensin (449). Tu has measured an increase in renin secretion in humans during the oliguric phase of acute tubular necrosis, which decreases during the diuretic phase (438). The reason for discrepancy with results reported here is not apparent. The experimental procedure was somewhat different in that the dogs reported here were uninephrectomized, hypophysectomized, and aldosterone was used as an index of renin secretion. The dog does not need both kidneys to secrete renin, and there is abundant evidence that hypophysectomized dogs can secrete renin. Mulrow and Ganong have shown that as little as 0.008 of a dog kidney in which renin has been extracted by the method of Haas and Goldblatt will produce a large increase in aldosterone secretion when administered intravenously to a hypophysectomized, nephrectomized dog (322). Experiments in which angiotensin has been infused intravenously or into the adrenal artery have shown that small, sub-pressor amounts of angiotensin II do not increase aldosterone secretion (32, 63, 317, 322). In fact, it appears that the threshold for a rise in blood pressure and for an increase in aldosterone secretion in response to angiotensin II are about equal (32, 63, 322). Thus, in the experiments reported in this laboratory one cannot rule out the possibility that there was a rise in renin secretion which did not produce a significant increase in aldosterone secretion.

The hemodynamic changes that result from raising the ureteral pressure are not settled. Several workers have observed a small decrease in renal blood flow with high ureteral pressures in acute experiments (232, 261, 281, 387, 392). However, many recent reports indicate that there is no change

or even an increase in renal blood flow with high ureteral pressures (293, 325, 329, 376, 385, 457). It has been suggested that these discrepancies may be explained by a low renal blood flow in in situ experiments and a normal or high renal blood flow in in vivo experiments (420). The experiments of Thureau, Waugh, and Gilmore also infer that renal arteriolar vasodilation occurs with an increase in ureteral pressure (158, 159, 419, 457). The significance of these hemodynamic changes in relation to renin release with respect to the experiments reported above is not clear.

2. The Effect of Increasing the Renal Venous Pressure. Occlusion of the renal vein and increased renal vein pressure has been shown conclusively to raise the intrarenal pressure (172, 232, 307, 390, 414, 468). As with the ureteral pressure, there is no rise in IRP until it is exceeded by the venous pressure. The IRP then increases linearly with the venous pressure without reaching a maximum value. There is evidence that partial occlusion of the renal vein is followed by a slow rise in blood pressure over a period of weeks. Pederson found this to be true in rabbits and Braun-Menendez found a rise in blood pressure in 50% of dogs, which could be blocked by renal denervation (45). More recently Anderson et al and Derrick et al were able to produce hypertension in some dogs with chronic renal vein obstruction (4, 97). Necrotic changes in the outer renal cortex have been noted as early as two days and may be related to the rising blood pressure (393). Selkurt noted necrotic tubular changes and cortical petechiae after short periods of renal vein obstruction (386). Sandrolini et al found protein droplets in tubular cells and glomerular basement membrane thickening after five to nine days of renal vein obstruction (373). It is possible that with chronic renal vein obstruction a nephrotic syndrome with hypertension and secondary hyperaldosteronism may be obtained. Selkurt et al and Blake et al found no change in arterial blood pressure when the renal vein of dogs was

partially occluded (33, 388).

Although Davis et al first thought that the increased venous pressure of chronic thoracic caval constriction was involved in the resultant hyperaldosteronism (88), further experiments by these workers have made this possibility an unlikely one. Ball and Davis did not observe hyperaldosteronism in dogs with constriction of the abdominal inferior vena cava above the adrenal veins (8). Higgins and co-workers did not note any increase in thoracic duct renin after constricting the abdominal inferior vena cava (230), and Carpenter et al showed that chronic thoracic caval constriction increases aldosterone secretion even when the kidney and adrenal have been transplanted to the neck (64). Blair-West and associates have, however, observed an increase in aldosterone secretion in normal sheep upon constriction of the portal vein or subhepatic inferior vena cava (31). ACTH release cannot be ruled out as the source of this aldosterone response. As mentioned above, Skinner et al obstructed the renal vein enough to produce a severe diminution in blood flow (and undoubtedly a large rise in intrarenal pressure), but noticed no change in renin secretion in seven of ten dogs (403). These results are consistent with those reported in the experiments in this laboratory.

As the renal vein is obstructed and the interstitial pressure exceeded, there is a dimunition in renal blood flow reported by most investigators (33, 176, 205-207, 233, 235, 237, 246, 330, 386, 388). However, Thureau has observed a transient fall in renal blood flow and then reestablishment of normal blood flow with tissue pressures of 50 mmHg (419). Even when the renal blood flow is decreased, the total renal resistance is decreased unless constant flow is maintained. And, high venous pressure has been found to inhibit autoregulation so that

the possibility of arteriolar vasodilation exists. These changes are similar to those found with elevation of ureteral pressure except that in the case of a significant elevation in renal venous pressure, there is almost surely a diminution in renal blood flow.

3. The Effect of Diuresis. Diuresis with a large number of agents has been shown to increase tubular diameter and increase the renal interstitial pressure (172, 173, 307, 413, 416, 467, 468). Although there is good evidence that chronic diuretic therapy is associated with an increase in renin secretion (see Table I), Vander and Miller have observed no change in renin secretion in acute experiments with dogs (445, 446). However, Brown and co-workers found an increase in renin and aldosterone secretion within two hours of mercuhydrin administration to dogs (52). Vander and Miller have also observed that a variety of diuretics, but especially osmotic diuretics, block renin secretion in dogs in response to suprarenal aortic constriction, renal nerve stimulation, and intravenous administration of catecholamines (443, 446). These authors suggest that these findings are more consistent with control of renin release by the macula densa than by renal baroreceptors. Since diuretics increase the renal interstitial pressure and thus lower the transmural pressure across the J-G cells, one would expect an augmented renin secretion in these experiments, according to the "stretch" hypothesis of renin secretion. It is of interest that there is an increase in renin secretion with chronic administration of diuretic agents with salt depletion, in spite of an associated diuresis.

Hemodynamic effects of diuretics have not been completely elucidated, but none of those thus far proposed seem to explain a diminution in renin secretion with administration of diuretics. Mannitol has been shown to increase renal blood flow in animals with hemorrhagic hypotension and with renal artery stenosis (40, 41, 218, 324, 329, 351, 384, 410). Because it abolishes autoregulation and increases renal blood flow in the above mentioned circumstances, mannitol and other hyperosmotic solutions are thought to have a vasodilating effect on renal arterioles (40, 41, 158, 419). It has also been suggested that mannitol increases medullary blood flow (410, 410b). Since vasoconstriction and/or a decrease in renal blood flow probably do not stimulate renin release, it is likely that vasodilation and an increase in renal blood flow do not block renin release.

It is tentatively concluded that the unphysiological precedure of reducing the transmural pressure by elevating the renal interstitial pressure does not stimulate renin secretion. The "stretch" theory of renin release in its most rigorous interpretation is therefore not supported. The juxtaglomerular cells do seem to function as barostats, however, and it may be that they respond to variation in the intramural hydrostatic pressure alone.

H. The Role of Endocrine Factors. Since renin secretion cannot always be explained by changes in blood pressure, several investigators have hypothesized that a humoral substance is involved. Regoli et al have suggested that in the rat there may be an exchange of some humoral substance between the kidneys which influences renal renin content (369). To date, there is no direct evidence for a renal hormone which regulates renin release. Hartroft has observed degranulation of the J-G cells after giving renin (212), but this may be secondary to changes attending

an augmented aldosterone secretion.

Evidence against angiotensin II stimulating renin secretion was presented in an earlier section, as were experiments concerning the role of catecholamines in renin release. The finding of Vander and Geelhoed that, within thirty minutes, angiotensin II blocks renin secretion in response to suprarenal aortic constriction is an interesting observation. If their findings are confirmed, angiotensin must be an extremely potent inhibitor of renin release. The fact that other investigators have found that renin and aldosterone secretion in response to suprerenal aortic constriction persists as long as the stimulus is applied in acute experiments of up to at least two to three hours suggests that the circulating angiotensin II was not blocking renin release (see Table I).

Dunihue and associates have shown repeatedly in the past that the JGI in several species is inversely proportional to the mineralocorticoid level (107-111). A negative feedback mechanism between aldosterone and renin, therefore, is a possibility. Other workers have concluded that the effect of mineralocorticoids is an indirect one, as a result of changes in sodium balance, blood volume, and blood pressure. Bernardis and Kamura and Gross et al have found that mineralocorticoids produce no change in JGI or renal pressor substance in salt depleted animals (19, 187). A high salt diet alone can suppress renin release (see Table II). Gross and co-workers have found that pharmacologic amounts of aldosterone must be used to inhibit renin secretion in rats (187, 197). Blair-West et al gave aldosterone to sodium-depleted sheep and found no diminution of endogenous aldosterone secretion (31).

There are conflicting reports concerning the role of ACTH and

glucocorticoids in renin secretion. Dougherty observed hypertrophy of the J-G cells in mice after injecting "adrenotropic hormone" (102). Garber et al, and Marks et al observed an increase in the JGI in rats given ACTH (147, 295). While the latter authors showed that the adrenal was not necessary for this repsonse, Haynes and co-workers observed an increase in renin release after administering corticosterone (222). Das Gupta and Giroud found that corticosterone increased aldosterone secretion in normal rats (76). However, Gross, Sokabe et al, Bernardis and Kamura, and Masson et al found that the renal renin content and JGI in rats was unaffected by administration of glucocorticoids (19, 189, 299, 409). Sokabe et al and Dunihue et al observed that ACTH had no effect on renal pressor substance or on the JGI in rats (111, 409). Yoshinga and co-workers did not find an elevation in renin secretion in patients with Cushing's Syndrome (473), and Howard measured normal levels of angiotensin in patients with Cushing's Syndrome (243). The Hartrofts did not observe any change in the JGI of hypophysectomized rats (212, 214), and Williams et al did not detect any change in renal pressor substance in similar experiments (461). Recently, Bruinvels and associates found that hypophysectomy in rats enhanced the renal pressor substance by 50% over a six week period (54). The tendency of hypophysectomized animals to become hypotensive should be considered in these experiments.

It must be concluded that present evidence does not permit a definite statement concerning the role of glucocorticoids, ACTH, or the pituitary in renin release. Since the renin-angiotensin-aldosterone system functions in hypophysectomized animals, ACTH or other hypophyseal

factors do not play an obligatory role in renin release. Most of the above experiments were done on the rat, and the role of these endocrine factors deserves further investigative effort.

I. The Role of the Macula Densa. In 1933, Zimmerman named the darkly staining cells which mark the start of the distal convoluted tubule the macula densa. The function of the macula densa cells is not known, but the close proximity to the J-G cells has tempted many investigators to speculate that these cells are in some way connected with the synthesis, storage, or release of renin. Goormaghtigh observed degenerative changes in the intercalated segment of the distal tubule after constriction of the renal artery and suggested that urine content or flow might influence the secretion of the J-G cells via the macula densa (168). McManus observed that changes in the J-G cells were usually accompanied by changes in the macula densa, as if the entire J-G apparatus was involved in any change in function (300). More recently, Reeves et al have noted concomitant swelling of the macula densa and an increase in the JGI in patients with hyponatremia (366). McManus also noted that the golgi apparatus in the macula densa is located basally, as opposed to its supranuclear position in the surrounding distal tubule (301). This brought up the possibility that substances might be transported basally through the basement membrane to the J-G cells. There have been reports of intercellular bridges between the macula densa and J-G cells, but some electron micrographs have shown that there are no openings in the basement membrane of the macula densa, so that convincing proof of anatomical connection between the macula densa and J-G cells in lacking (215, 217, 276, 334). Latta and Maunsbach have observed a decreased number of infolded basal membranes and mitochondria in the macula densa as well as a thick luminal plasma

membrane which they think indicates a decreased resorption of fluid (276). Barajas and Latta have noted the presence of extracellular compartments, which suggest to them that the macula densa is involved with fluid transport in a special way (9). The Hartrofts have observed that under certain abnormal situations, the J-G cells closest to the macula densa become most prominent in the arteriolar wall, suggesting some mutual interaction (217).

There is some evidence in support of the macula densa being the site of renin production. Bing and Kazimierczak found a high renin content in glomeruli with juxtaglomerular tissue attached, and found only very small amounts of renin in the afferent and efferent arterioles (25, 26, 27). They concluded from bioassay of the different areas that most of the pressor activity is in the macula densa and a much lesser amount is in the arterioles. These workers also found renin in the subcapsular zone of the newborn pig kidneys (28). This area is said to contain the "premacular" cells and is devoid of afferent or efferent arterioles. Hess and Regoli have tentatively confirmed this finding in rat fetuses (228). Hartroft et al have demonstrated J-G cells in the outer cortex of the pig metanephros by Bowie and fluorescent antibody techniques, but they have not yet been able to find these cells in the mesonephros (216). However, Edelman and Hartroft found no localization of antirenin in the macula densa (112). Friedberg calculated that in rats the extractable pressor substance correlates well with the JGI but not with the distribution of the macula densa (132). Demopoulus et al constricted the arterial supply to the kidney such that they observed complete atrophy of all cortical and medullary tubules. In the absence of any microscopic evidence of any macula densa tissue, the JGI and the

extractable pressor substance increased (96).

Histochemical estimation of enzyme activity in the macula densa and J-G cells has been utilized by several investigators. The pentose shunt enzymes, glucose-6-phosphate dehydrogenase and 6-phosphogluconic dehydrogenase, are located in the macula densa and have been shown to change in activity in parallel with renin content and JGI in response to constriction of one renal artery, adrenalectomy, salt loading, figure-of-eight ligature around one kidney, and unilateral hydronephrosis (see Table I and II). α-glycerol phosphate is located in the J-G cells and has been shown to vary in activity as the amount of extractable renin in response to clamping of the renal artery, adrenalectomy, and administration of mineralocorticoids plus high salt (see Tables I and II). The significance of these enzyme changes is not clear. A biochemical link between the macula densa and J-G cells has been suggested, with the possibility that the different enzymes are interdependent. The pentose shunt enzymes are involved in RNA synthesis and it may be that their activity indicates participation in protein synthesis.

If the macula densa is involved in some phase of renin secretion, the stimulus that acts on the macula densa is not clear. Various authors have speculated that the activating mechanism may involve the urine flow, intrabular pressure, or the osmolarity or sodium concentration of the tubular fluid as sensed by the macula densa. There is no direct proof for any of these theories, and very little indirect evidence.

The rate of urine flow can be seen to be proportional to renin secretion in many situations, as with hemorrhage, constriction of the aorta or renal artery, constriction of the thoracic inferior vena cava,

salt depletion and perhaps exercise and diuresis. However, the glomerular filtration rate is proportional to the renal blood flow, and there is good evidence that large changes in renal blood flow do not affect renin secretion. In physiological situations the GFR is constant over a wide range of arterial pressures, and a small decrease in mean pressure is followed by an increase in renin output. Large increases of the venous pressure are probably accompanied by a fall in GFR, and this has not been shown to increase renin release.

Leyssac has postulated that the macula densa signals renin release in response to an initial drop in intratubular pressure with renal artery constriction (282). Renin and angiotensin then constrict the efferent arteriole so that the GFR and tubular flow increase to restore the intratubular pressure to normal. There is no direct evidence for this hypothesis. The fact that raising the intratubular pressure by diuresis or venous occlusion does not seem to be associated with renin release is consistent with a possible role for the intratubular pressure. However, the report of an increased renin secretion with increased ureteral pressure is not explained by this hypothesis. The observation that the intratubular pressure measured by micropuncture remains constant with a drop in arterial pressure appears to rule out a significant effect of intratubular pressure on renin release via the macula densa. Since intratubular pressure is directly related to urine flow, arguments against the flow per se would apply to changes in pressure.

The osmolality or sodium concentration at the level of the macula densa has not been measured. The fluid in the first 10% of the distal tubule in the rat cannot, in general, be sampled by micropuncture techniques. In the dog, the distal tubules are apparently not close

enough to the surface to be sampled by micropuncture techniques (67). The fluid entering the distal tubule is hypotonic under a variety of situations, including hydropenia, osmotic diuresis, and diabetes insipidus (174, 175). Glucose and mannitol diuresis produce a less hypotonic urine in the early distal tubule than with sodium diuresis or antidiuresis in rats (174, 175, 441). However, urea diuresis in rats does not appear to raise the osmolality of early distal tubular fluid of the rat compared to antidiuretic animals (441). In addition, mannitol and urea produce a marked fall in the early distal tubular sodium concentration in rats in relation to antidiuretic animals (175, 441). Vander and Miller did not find that glucose, mannitol, sodium chloride, or urea increased renin release (445, 446). The fact that all decreased renin secretion when given after suprarenal constriction of the aorta argues against a rise in osmolality of sodium concentration being the inhibitory stimulus. If this were so, glucose and mannitol, which increase the osmolality, would inhibit renin release and sodium chloride and urea would not. And, if an increase in sodium concentration at the macula densa blocks renin secretion, mannitol and urea would be expected to be relatively ineffective in comparison with non-osmotic diuretics.

Another approach in investigating this hypothesis is suggested from the finding of Clapp and associates that the electronegativity of the distal tubule is increased by the infusion of polyanionic, non-reabsorbable anions (66). Substances such as bisodium sulfate would tend to prevent sodium reabsorption and might decrease renin release. Vander and Miller observed that bisodium sulfate acted on renin secretion

in the same manner as other diuretics used in their experiments (445, 446).

There is no good evidence that the sodium concentration or osmolality at the macula densa varies under physiological circumstances. Giebisch and associates produced diuresis in rats with .9% and 4% sodium chloride loading and found that there was no difference in the tubular fluid to plasma sodium concentration in the first 30% of the distal tubule, even when overall sodium excretion increased (157). Lassiter and co-workers observed that the tubular fluid to plasma osmolality in the early distal tubule remained fairly constant in both non-diuretic rats and those loaded with 5% sodium chloride (274, 275). Giebisch and Windhager observed that sodium reabsorption in the ascending limb of Henle's loop seems to increase compensatorily with an increase in sodium load, such that the sodium concentration presented to the distal tubule is constant (156). Likewise, Gottschalk has concluded that sodium transport in the thick ascending limb is not flow limited, since there is no good evidence for a transfer maximum (176).

In summary, the role of the macula densa is still far from being established. Although the theories suggested are intriguing, they lack experimental support. Hartroft et al have suggested an interesting method of possibly separating the macula densa function from that of the J-G cells. They have noted the proclivity of antirenin for the J-G cells, and have mentioned the possibility of linking antirenin with a substance toxic to the J-G cells (216). This preparation would then be analagous to β-cell destruction by alloxan in the pancreas, and the role of the macula densa might be more clearly elucidated.

SUMMARY AND CONCLUSIONS

The "stretch" hypothesis of renin secretion has been tested by measuring aldosterone secretion in hypophysectomized dogs in which the intrarenal pressure had been increased by partial obstruction of the renal vein or by raising the ureteral pressure. Although there was an apparent lowering of the transmural pressure gradient across the juxtaglomerular cells, there was no significant rise in aldosterone secretion. Since decreasing the transmural pressure by raising the intrarenal pressure does not seem to stimulate renin release, doubt is cast upon the validity of the "stretch" hypothesis in its strictest interpretation. It is suggested that renin may be secreted in response to a decrease in afferent arteriolar hydrostatic pressure and that the accompanying reduction in transmural pressure is not the necessary stimulus for renin release. However, it is not at all clear that a decrease in afferent arteriolar hydrostatic pressure explains the increase in renin secretion under all circumstances, and there may well be more than one mechanism whereby renin is released.

Evidence that the juxtaglomerular cells are the site of renin production is reviewed and several factors which have been claimed to influence renin secretion have been discussed. Although some of the findings are contradictory, it appears that renal blood flow, renal arterial pulse pressure, and renal arteriolar vasoconstriction do not stimulate renin secretion. There is no direct evidence at present that intravascular volume receptors, venous receptors, or endocrine factors influence renin release under physiological conditions.

The possibility that subtle changes in sodium balance and/or the

macula densa may be involved in the release of renin under certain circumstances is attractive. Even though there is no convincing evidence that either of these two factors influence renin release, it is difficult to evaluate the role of each because of limitations imposed by present investigational techniques.

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