Studies on the Mechanism of Sodium Excretion during Drug-induced Vasodilatation in the Dog

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ABSTRACT The administration of vasodilating agents such as bradykinin and acetylcholine cause an increase in urinary sodium excretion. Yet the mechanisms involved in this natriuretic effect are not clear. Recent studies with another renal vasodilator, secretin have shown this drug also causes a profound increase in renal blood flow but without major changes in sodium excretion. To attempt to delineate the basis of this difference in sodium excretion with these drugs, the renal functional effects of secretin and bradykinin were compared at an equivalent vasodilating dose. Bradykinin increased renal blood flow from 222 to 342 ml/min, urine volume from 0.2 to 1.2 ml/min, and urine sodium excretion from 28 to 115 μ eq/min. Urine osmolality fell from 1,230 to 401 mosmol/kg. Secretin caused a comparable increase in renal blood flow (216 to 325 ml/min) while changes in urine flow, sodium excretion, and urine osmolality were significantly less.

In further studies papillary plasma flow was estimated using the albumin accumulation technique. Control papillary plasma flow was 29 ml/min per 100 g. Bradykinin increased urinary sodium excretion 108 μ eq/min and decreased urinary osmolality from 1,254 to 516 mosmol/kg in association with a rise in papillary plasma flow to 62 ml/min per 100 g. Urine sodium excretion, urinary osmolality, and urine flow rate, as well as papillary plasma flow rate (32 ml/min per 100 g) were unchanged from control when secretin was administered. Studies with acetylcholine were qualitatively similar to those of bradykinin. Renal blood flow increased from 150 to 248 ml/min, urinary sodium excretion increased from 20 to 243 μ eq/min, urinary osmolality decreased from 1,237 to 411 mos-

mol/kg and papillary plasma flow increased from 39 to 52 ml/min per 100 g. It is suggested that the natriuretic effect of some vasodilators is due, at least in part, to alterations in medullary hemodynamics, as evidenced by the increase in papillary plasma flow seen with bradykinin and acetylcholine, but not secretin.

INTRODUCTION

It is well known that renal vasodilating agents such as acetylcholine, bradykinin, and prostaglandin E_2 increase urinary sodium excretion. Yet, the mechanisms involved in this natriuretic effect of drug induced vasodilatation are not clear. It has been suggested that the hemodynamic effect of these agents alters Starling forces in the peritubular capillary circulation leading to a fall in the proximal tubular reabsorption of sodium (1). Direct micropuncture studies have shown that neither bradykinin nor prostaglandin E_2 alters proximal tubular sodium reabsorption (2). Earley and Friedler (3) suggested that renal vasodilatation may cause a natriuresis as a consequence of the washout of the hypertonic medullary interstitium occurring in this setting. Furthermore, recent studies from this laboratory have suggested that medullary washout may preferentially depress sodium reabsorption in the more inner cortical nephrons (4).

Recently, Marchand and associates (5, 6) have observed that secretin, a gastrointestinal hormone, may cause a marked increase in renal blood flow with little rise in urinary sodium excretion. It thus seemed possible that the further utilization of this unique drug might lead to a better understanding of the basis of the natriuresis that occurs with other forms of renal vasodilatation. Studies were therefore designed to compare the effects of bradykinin and secretin, at a comparable vasodilating dose, on a number of parameters of renal function. Studies with acetylcholine were performed as well. The results of these studies indicate

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that bradykinin and acetylcholine have major effects on the inner medullary circulation, whereas secretin does not.

METHODS

Mongrel dogs, 13–28 kg, were deprived of food and water for 12 h before study. Anesthesia was induced with intravenous sodium pentobarbital, 30 mg/kg and a constant level of anesthesia was maintained by using additional 5-mg injections as needed. After endotracheal intubation, the animal was ventilated using a Harvard Respirator Pump (Harvard Apparatus Co., Cambridge, Mass.). The femoral vein was cannulated and after an 800-mg intravenous bolus of 4% inulin, a 2% inulin infusion was maintained at a constant rate of 0.7 cm³/min.

The femoral artery was cannulated for arterial pressure measurement as well as for collecting blood samples. Blood pressure was determined using a Hewlett-Packard Transducer and Recorder (Hewlett-Packard Co., Waltham, Mass.).

A Goodale-Lubin catheter was threaded through the right carotid artery into the left ventricle for the purpose of radioactive microscope injection. A lower abdominal midline incision was made and both ureters were cannulated using PE 160 tubing.

The left renal artery was exposed through a small flank incision and fitted with a 2.5–3.0-mm flow probe (Zepeda Instruments, Seattle, Wash.) for continuous monitoring of renal blood flow. Zero flow was determined using a snare placed distal to the probe. The flow probe was calibrated *in vivo*.

A curved 21-gauge scalp vein needle was inserted into the renal artery near its origin from the aorta and kept open with Ringer's solution at 0.3 cm³/min. At least 30 min after completion of surgery, three control urine collections were made. Blood was obtained at the midpoint of the first and third collections.

During the initial control period and during the infusion of each test agent, an injection of radioactive microspheres (3M Company, St. Paul, Minn.) was given for determining total renal blood flow and cortical blood flow distribution. The technique of injection and of counting the various nuclides has been described elsewhere (7). The nuclides used were Scandium 46, Cerium 141, and Strontium 85. A different nuclide was used in each period and the sequence of injection was altered from experiment to experiment.

The following studies were performed:

Group I—clearance studies with bradykinin and secretin (*n* = 11). After the control collections, either bradykinin, 0.125–0.25 µg/kg per min, or secretin, 60–120 mU/kg per min, was administered intrarenally at a rate of 0.38–0.76 cm³/min. 5 min after the drug infusion was initiated, three further 10-min collections were begun and the drug was then discontinued. 45–60 min were allowed to lapse after drug discontinuation for renal function to return to control levels. Following this, a second control period consisting of three timed urine collections was obtained. Then, the second test agent was given in a dose that resulted in approximately the same increase in blood flow (as measured by flow meter) as was noted with the first agent. The order in which the two drugs were given was alternated from study to study. Renal blood flow was continuously monitored using the Zepeda electromagnetic flow probe and meter and recorded on a Hewlett-Packard recorder.

In the group I studies, secretin from two sources was used. Five studies were performed with secretin from Warren-

Teed Pharmaceuticals, Inc. (Columbus, Ohio) and six with secretin with Kabi Diagnostica (Stockholm, Sweden). (Although the Warren-Teed form was associated with a greater increase in urinary sodium excretion, this difference was not significant when compared with the Kabi secretin.) All group II studies were performed with Kabi secretin.

Group II—papillary plasma flow studies with bradykinin, secretin, and acetylcholine. 36 mongrel dogs were deprived of food and water for 12 h. The general protocol was similar to the group I studies with the following additions to the method. The jugular vein was cannulated and a peripheral line established for infusion of Ringer solution at 1 cm³/min. Bilateral flank incisions were made and umbilical ties were loosely fitted around each renal hilum and exteriorized. Plastic tubing was placed over the ties and supported to avoid any tension on the hilum. The left renal artery was fitted with a flow probe, and a scalp vein needle was inserted at its origin as described previously. The animal was then placed in the prone position. After control urine collections, an infusion of either carrier solution, bradykinin, secretin, or acetylcholine was begun. 5–10 min later, a repeat urine collection period was obtained and papillary plasma flow (PPF)¹ was then determined.

PPF was determined using the modified Lilienfeld technique (8). An infusion of ¹²⁵I-albumin (Mallinckrodt, Inc., Maryland Heights, Mo.) and 7% FDC green dye 3 were begun via the jugular vein. To decrease dead space, the jugular vein catheter was primed with ¹²⁵I-albumin such that the meniscus of the dye solution interphase was at the level of the vein. Simultaneous with the albumin infusion, blood was collected from the femoral artery. The rates of infusion and withdrawal were assured to be identical as a two-syringe reciprocal action Harvard pump was used. After a perfusion collection period of either 20 or 30 s, the kidneys were simultaneously ligated and removed. The kidneys were frozen at –10°C to assure uniform cutting and sections of the inner papilla were weighed and counted along with 1-cm³ aliquots of plasma. PPF was calculated to be the ratio of papillary to arterial plasma counts per unit time, as follows:

PPF (ml/min per 100 g)

$$= \frac{\text{cpm/100 g papilla}}{\text{cpm/ml plasma}} \times \frac{60 \text{ s/min}}{\text{perfusion time (s)}}$$

Four groups of dogs were studied.

Control (*n* = 6). Control animals were prepared in the standard manner with infusion of Ringer solution at 0.76 cm³/min being given in the renal artery of one kidney.

Bradykinin (*n* = 9). After control collections, bradykinin 0.25 µg/kg per min was infused into one renal artery. After a 5–10-min equilibration period, a clearance collection was obtained. During the infusion of bradykinin, PPF was determined as outlined above and the experimental kidney was compared with the contralateral control kidney.

Secretin (*n* = 11). These studies were performed exactly as above except that secretin 120 mU/kg per min was given.

Acetylcholine (*n* = 11). These studies were performed as above except that acetylcholine was given intrarenally at 2.0 µg/kg per min.

Group III—PPF studies during water diuresis. These studies were performed in a manner similar to the group II studies with the exception that before measurements the dogs

¹ Abbreviation used in this paper: PPF, papillary plasma flow.

were given 2.5% dextrose in water at 2.5 cm³/min until the urine osmolality was 200 mosmol/kg H₂O.

Urine and plasma inulin concentrations were determined with a Technicon Autoanalyzer (Technicon Inc., Tarrytown, N. Y.). Plasma and urine osmolality was measured with an Advanced Osmometer (Advanced Products, Inc., Newton Highlands, Mass.) and sodium concentrations in plasma and urine were determined with an Instrumentation Laboratory Flame Photometer (Instrumentation Laboratory, Inc., Watertown, Mass.).

The results were analyzed with standard statistical methods.

RESULTS

Group I studies. Table I summarizes the results with secretin and bradykinin on urine flow, glomerular filtration rate, renal blood flow, sodium excretion, urine osmolality, and mean arterial pressure. Neither agent caused a significant change in mean arterial blood pressure or glomerular filtration rate, but both were associated with significant increases in renal blood flow. Secretin increased renal blood flow from 216 to 325 ml/min, whereas with bradykinin, renal blood flow increased from 222 to 312 ml/min. Fig. 1 compares the change in urine volume, sodium excretion, and urine osmolality that occurred after administration of the two vasodilating agents in these 11 experiments. Secretin caused small but significant changes in urine flow rate (+0.12 ml/min), urinary sodium excretion (+26 μ eq/min) and urine osmolality (-115 mosmol/kg H₂O). In contrast, these changes

FIGURE 1 Comparison of the changes in urine flow, sodium excretion, and urine osmolality during drug-induced vasodilatation with secretin or bradykinin in the group I studies.

with bradykinin, at a similar level of renal vasodilatation, were considerably larger. With bradykinin administration urine flow rate increased 1 ml/min, urinary sodium excretion increased 87 μ eq/min, and urinary osmolality decreased 829 mosmol/kg H₂O. Thus, the changes in each of these parameters was consistently and significantly greater ($P < 0.005$) with bradykinin than with secretin.

The distribution of cortical blood flow was determined in 9 of the 11 dogs studied. These results are summarized in Table II. Zone I represents the most outer cortical zone and zone IV the most inner cortical

TABLE I
Summary of Paired Clearance Data for Studies ($n = 11$) in Which Bradykinin and Secretin Were Given into the Dog Renal Artery

	V	GFR	RBF	MAP	U _{Na} V	FE _{Na}	U _{osm}
	cm ³ /min	cm ³ /min	cm ³ /min	mm Hg	μ eq/min	%	mosmol/kg
Control	0.27 ± 0.03	37 5	216 28	149 4	37.6 7.2	0.78 0.16	972 102
Secretin	0.39 ± 0.04	39 5	325 36	144 5	63.6 6.4	1.17 0.13	857 78
$P \leq$	0.005	NS	0.001	NS	0.001	0.005	0.05
Control	0.20 ± 0.02	40 5	222 24	146 4	27.6 4.3	0.51 0.08	1,230 100
Bradykinin	1.20 ± 0.17	37 5	342 33	141 4	115.1 16.9	2.30 0.26	401 20
$P \leq$	0.001	NS	0.001	NS	0.001	0.001	0.001
Secretin vs. bradykinin							
$P \leq$	0.001	NS	NS	NS	0.02	0.005	0.001

V, urine flow rate; GFR, glomerular filtration rate; RBF, renal blood flow (microsphere data); MAP, mean arterial pressure; U_{Na} V, urine sodium excretion; FE_{Na}, fractional sodium excretion; U_{osm}, urinary osmolality; NS, not significant.

TABLE II
Effect of Intrarenal Bradykinin and Secretin on the Redistribution of Cortical Blood Flow (%) as Measured with Radioactive Microspheres (n = 11)

Cortical zone	Control	Secretin	Bradykinin
I			
Mean	43	39	31
SEM	1.7	1.8	1.3
P	<div> <div>0.01</div> <div>0.001</div> <div>0.05</div> </div>		
II			
Mean	32	33	34
SEM	1.1	0.8	1.0
P	<div> <div>NS</div> <div>NS</div> <div>NS</div> </div>		
III			
Mean	18	19	22
SEM	0.9	0.9	0.8
P	<div> <div>NS</div> <div>0.001</div> <div>0.001</div> </div>		
IV			
Mean	7	10	13
SEM	0.8	1.1	1.2
P	<div> <div>0.05</div> <div>0.001</div> <div>0.05</div> </div>		

zone. The percentage of total blood flow to this region decreased from 43 to 39% with secretin. However, this decrease was not as marked as when bradykinin was infused (43–31%) even though the increase in total

renal blood flow was similar with both agents. There was no appreciable change in zone II distribution with either agent. Although secretin caused no consistent change in zone III, bradykinin led to a small but significant increase in this zone from 18 to 22%. Zone IV blood flow increased from 7 to 10% after secretin was infused. With bradykinin, there was a further increase in the fractional distribution of flow to zone IV to 13% which was a significant increase when compared with both control and with secretin administration. Thus, both agents caused a redistribution of blood flow to inner cortical nephrons, but the magnitude of the change was greater with bradykinin.

Group II studies. Table III summarizes the results of urine flow rate, sodium excretion, and urine osmolality in these studies. Again, bradykinin caused a marked increase in urine volume and sodium excretion and a fall in urine osmolality. These changes were significant when compared with the contralateral kidney as well as with the studies from control animals. In contrast, secretin did not significantly increase urine flow rate or sodium excretion, nor did it cause a fall in urine osmolality when compared with the contralateral control kidney.

The hemodynamic data are summarized in Fig. 2. Both secretin and bradykinin led to significant increases in total renal blood flow. This was the case whether the results were compared with the control kidney in the same animal or with values from control animals. Although both bradykinin and secretin led to significant increases in total renal blood flow, only bradykinin was associated with a significant increase in PPF (62 vs. 42 ml/min per 100 g, experimental vs.

TABLE III
Effect of Intrarenal Bradykinin, Secretin, and Acetylcholine on Urine Flow Rate, Sodium Excretion, and Urinary Osmolality

Group II	Control		Bradykinin		Secretin		Acetylcholine	
	n = 6		n = 9		n = 8		n = 11	
	C	E	C	E	C	E	C	E
V, ml/min								
Mean	0.10	0.12	0.13	1.07	0.19	0.24	0.14	1.76
SEM	0.01	0.03	0.01	0.14	0.06	0.08	0.02	0.28
P≤	NS		0.001		NS		0.001	
U_{Na} V, μeq/min								
Mean	17	20	33	141	40	42	20	243
SEM	5	5	6	20	15	15	4	40
P≤	NS		0.001		NS		0.001	
U_{osm}, mosmol/kg								
Mean	1,385	1,194	1,254	516	1,245	1,240	1,237	411
SEM	122	125	147	41	170	191	123	21
P≤	0.02		0.001		NS		0.001	

C, control kidney; E, experimental kidney; other abbreviations as in Table I.

FIGURE 2 Total renal blood flow and PPF in the group II studies. Adjacent bars represent values from the two kidneys in each animal. While bradykinin, secretin, and acetylcholine all increased total renal blood, only bradykinin and acetylcholine increased PPF.

control kidney, $P < 0.05$). In contrast, secretin did not increase PPF in the experimental kidney (31 vs. 33 ml/min per 100 g, experimental vs. control kidney, respectively). This was also the case whether the results of PPF of the secretin infused kidney were compared with the control kidney in the same animal or with values from control animals.

Fig. 2 and Table III also summarize the results of the acetylcholine studies and compare them with those of bradykinin and secretin. The experimental kidney demonstrated a marked increase in urine flow rate,

sodium excretion, and total renal blood flow when acetylcholine was given. In addition, there was a fall in urine osmolality. PPF was estimated during acetylcholine administration and was found to be significantly greater in the experimental kidney than in the control kidney (52 vs. 39 ml/min per 100 g).

Group III studies. The results of the group III studies are shown in Table IV. Urine flow rate was greater and urine osmolality was lower than values found in the group I and group II studies. In spite of this lower urine osmolality, the average value for PPF was 42

TABLE IV
Summary of Clearance Data and Measurements of PPF during Water Diuresis

V	GFR	RBF	MAP	$U_{Na}V$	FE_{Na}	U_{osm}	PPF
cm^3/min	cm^3/min	cm^3/min	mmHg	$\mu eq/min$	%	mosmol/kg	ml/min per 100 g
1.80	28	182	149	57	1.45	144	42
± 0.19	3	34	5	8	0.18	15	5

Abbreviations as in Table I. Results are mean $\pm$ SEM for nine kidneys from six dogs. RBF was measured in seven of the nine kidneys.

ml/min per 100 g. Thus, although the urine osmolality was lower in these group III studies, the level of PPF remained well below the values found during bradykinin or acetylcholine administration (group II).

DISCUSSION

This study compared the effects of three different vasodilators on renal function in the dog; bradykinin and acetylcholine that led to a sustained increase in both renal blood flow and sodium excretion and secretin that caused only trivial increases in sodium excretion. Since all agents increased renal blood flow, but only bradykinin and acetylcholine consistently increased sodium excretion, we systematically evaluated a number of other functional parameters to attempt to determine the basis for this difference.

The group I studies allowed the effect of both bradykinin and secretin to be studied in the same animal while in the group II studies, in which PPF was estimated, only one vasodilator was given to each animal. There were no consistent changes in systemic blood pressure or glomerular filtration rate in any of the groups of studies. In all groups of studies, however, there was comparable renal vasodilation with each drug.

Although the increase in total blood flow was similar with both secretin and bradykinin, in both the group I and group II studies (Tables I and III and Fig. 1), bradykinin caused a greater increase in sodium excretion when compared with secretin. In fact, an increase in sodium excretion was seen with secretin only in the group I studies. The absence of any change in sodium excretion in the group II studies may have been due to the fact that only the more purified form of secretin was used in these latter experiments.

Marchand and associates previously evaluated the effect of acetylcholine and secretin on various parameters of renal function. It was concluded that the increase in sodium excretion found with acetylcholine but not with secretin might be related to an increase in cortical interstitial pressure (found with an implanted capsule) noted with the former compound only and that this would lead to a decrease in proximal tubular sodium reabsorption (6). In contrast to acetylcholine, however, no change in proximal tubular sodium reabsorption occurs with bradykinin (2). Thus, the tubular site at which a decrease in sodium reabsorption occurs with bradykinin is beyond the proximal tubule of superficial nephrons.

In addition to the differences in sodium excretion found with bradykinin and acetylcholine and secretin in the present studies, there were also marked differences in the change in urine flow rate and urine osmolality. While there was a tendency for urine flow rate to increase and urine osmolality to fall with se-

cretin, these changes were markedly greater with bradykinin and acetylcholine.

Although both bradykinin and secretin increased blood flow distribution to the inner cortex, this inward redistribution was more marked with bradykinin than with secretin. The radioactive microsphere method is presumed to be an index of glomerular blood flow in various portions of the renal cortex. As can be noted from Table II, both bradykinin and secretin caused a redistribution of flow to inner cortical nephrons although the magnitude of the distributional changes was considerably greater with bradykinin. The flow parameter measured in zone IV (the most inner cortical zone) should be a reasonable index of the blood flow that enters juxtamedullary nephrons. It should be emphasized, however, that the blood leaving these nephrons may enter cortical peritubular capillaries, descend into the vascular bundles in the outer medulla, or lastly enter vasa recta and perfuse portions of the inner medulla. The radioactive microsphere method cannot differentiate between these possibilities. Since it has been suggested that the natriuretic and diuretic effect of vasodilators such as bradykinin and acetylcholine is due to an increase in blood flow in the inner medulla (3, 4), we measured this parameter with the albumin accumulation technique in bradykinin-, acetylcholine-, and secretin-treated animals. Although the changes in total kidney blood flow were similar in the bradykinin, acetylcholine, and secretin vasodilated animals, there were marked differences in PPF with the three agents. As can be noted in Fig. 2, bradykinin and acetylcholine caused significant increases in PPF while secretin did not. This increase in PPF would not appear to be dependent solely on the decrease in urine osmolality since in the group III studies the urine osmolality was lower than that found during acetylcholine or bradykinin administration, but PPF remained lower than it was during administration of these two renal vasodilators.

It is tempting to consider how this increase in papillary flow might be linked to the increase in sodium excretion and decreases in urine osmolality observed with bradykinin and acetylcholine. If papillary flow increased sufficiently, this might wash out the hypertonic medullary interstitium. Studies demonstrating a decrease in papillary solute concentration after bradykinin administration are compatible with this view (9). This decrease in papillary solute concentration would then decrease water abstraction out of the descending limb of Henle's loop. Earley and Friedler (3) previously suggested a model in which this sequence of events (reduction in papillary tonicity, decreased water abstraction from the descending limb, etc.) could cause an increase in sodium excretion. This model is dependent on the presence of a relatively

fixed minimal sodium concentration for fluid exiting from the thick ascending limb of Henle's loop. Thus, any increase in volume flow to the ascending limb would cause a linear increase in sodium delivery to the distal tubule and an eventual natriuresis. In addition, recent studies from this laboratory have defined a model in which washout of the medullary interstitium would cause a preferential inhibition of sodium transport in juxtamedullary nephrons (4). In any case, it seems possible that the differences in papillary flow and sodium excretion noted with bradykinin and acetylcholine on the one hand and secretin on the other, may be mechanistically related.

There are several possibilities for the fall in urinary osmolality observed after bradykinin and acetylcholine administration: (a) bradykinin and acetylcholine could have a direct pharmacologic action to inhibit collecting duct permeability, (b) an increase in prostaglandin E_2 synthesis, a secondary effect of bradykinin (10), and acetylcholine (unpublished observations), may have antagonized the effect of ADH on collecting duct permeability, or (c) bradykinin and acetylcholine may have increased medullary blood flow, washing out interstitial solute and thus decrease medullary tonicity. There are no data at present to support a direct effect of bradykinin or acetylcholine on collecting duct permeability. Previously work by Anderson et al. (11), would seem to lend credence to the second hypothesis. However, if a prostaglandin E-mediated decrease in collecting duct permeability were the only alteration to occur with bradykinin and acetylcholine, one would expect the interstitium to remain relatively hypertonic. To the contrary, studies have demonstrated that bradykinin (9) and acetylcholine (12) markedly decrease papillary tonicity. Thus, while a prostaglandin E-mediated decrease in collecting duct water permeability may have played a role, other factors may also be important. Recent studies from our laboratory have demonstrated that increased medullary blood flow can be associated with a decrease in urine osmolality (13). Since previous studies have noted that the medullary solute falls during bradykinin and acetylcholine administration, it may be that the decrease in medullary solute associated with the increase in papillary flow is the primary explanation for the decrease in urine osmolality observed during bradykinin administration.

In conclusion, three renal vasodilators, bradykinin, acetylcholine, and secretin, were compared. Although all three increased total renal blood flow to a comparable extent, the increase in urine flow and sodium excretion and fall in urine osmolality were markedly greater with bradykinin and acetylcholine. In addition, only bradykinin and acetylcholine increased PPF. It is suggested that these data are consistent with a model in which increased papillary flow leads to a

decrease in medullary solute concentration and that this hemodynamic alteration in turn limits sodium reabsorption.

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REFERENCES

1. Lewy, J. E., and E. E. Windhager. 1968. Peritubular control of proximal tubular fluid reabsorption in the rat kidney. *Am. J. Physiol.* **214**: 943-954.
2. Stein, J. H., R. C. Congbalay, D. L. Karsh, R. W. Osgood, and T. F. Ferris. 1972. The effect of bradykinin on proximal tubular sodium reabsorption in the dog. Evidence for functional nephron heterogeneity. *J. Clin. Invest.* **51**: 1709-1721.
3. Earley, L. E., and R. M. Friedler. 1965. Changes in renal blood flow and possibly intrarenal distribution of blood during the natriuresis accompanying saline loading in the dog. *J. Clin. Invest.* **44**: 929-941.
4. Osgood, R. W., H. J. Reineck, and J. H. Stein. 1978. Further studies on segmental sodium transport in the rat kidney during expansion of the extracellular fluid volume. *J. Clin. Invest.* **62**: 311-320.
5. Marchand, G. R., K. A. Hubel, and H. E. Williamson. 1972. Effects of secretin on renal hemodynamics and excretion. *Proc. Soc. Exp. Biol. Med.* **139**: 1356-1358.
6. Marchand, G. R., C. E. Ott, F. C. Lang, R. F. Gregor, and F. G. Knox. 1977. Effect of secretin on renal blood flow, interstitial pressure and sodium excretion. *Am. J. Physiol.* **232**: F147-F151.
7. Stein, J. H., S. Boonjarern, C. B. Wilson, and T. F. Ferris. 1973. Alternations in intrarenal blood flow distribution. *Circ. Res.* **32-33**(Suppl. 1): 161-72.
8. Lilienfield, L. S., H. C. Maganzani, and M. H. Bauer. 1961. Blood flow in the renal medulla. *Circ. Res.* **9**: 614-617.
9. Willis, L. R. 1977. Effect of bradykinin on the renal medullary osmotic gradient in water diuresis. *Eur. J. Pharmacol.* **45**: 173-183.
10. McGiff, J. C., N. A. Terragno, K. U. Malik, and A. J. Lonigro. 1973. Release of a prostaglandin E-like substance from canine kidney by bradykinin. *Circ. Res.* **33**: 479-488.
11. Anderson, R., K. M. McDonald, and R. W. Schrier. 1975. Evidence for in vivo antagonism between vasopressin and prostaglandin in the mammalian kidney. *J. Clin. Invest.* **56**: 720-726.
12. Martinez-Maldonado, M., N. Tsaparas, G. Eknoyan, and W. N. Suki. 1972. Renal actions of prostaglandins: comparison with acetylcholine and volume expansion. *Am. J. Physiol.* **222**: 1147-1152.
13. Chuang, E. L., H. J. Reineck, R. W. Osgood, R. T. Kuna, and J. H. Stein. 1978. Studies on the mechanism of reduced urinary osmolality after exposure of the renal papilla. *J. Clin. Invest.* **61**: 633-637.