THE RENAL AND CARDIODYNAMIC EFFECTS OF PROSTAGLANDINS (PGE_1, PGA_1) IN RENAL ISCHEMIA

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THE VASODEPRESSOR ACTIVITY of the prostaglandins has been recently reviewed by Bergström [1]. Two prostaglandins, PGE_1 and PGA_1, are powerful vasodilators and have been described by Weeks to increase cardiac output and decrease peripheral resistance [8]. Renal circulatory effects of these prostaglandins have been further described by Johnson [5], and by Lee, and Ferguson [6]. Generally, a fall in PAH extraction and an increase in urine flow and sodium excretion have been described [5, 6]. Others have noted little change in renal flow, and, moreover, have attributed the hypotensive action of these agents to vasodilatation of the mesenteric vascular bed [3, 7]. The present experiments were performed to characterize the consistent renal and cardiodynamic effects of two of the prostagladins (PGE_1, PGA_1) and to determine if these effects are different in hypertensive animals with renal ischemia.

MATERIALS AND METHODS

Thirty-four healthy-conditioned adult male and female dogs were used. Animals had the trigone chronically explanted to allow repeated collections of urine from each kidney with silastic ureteral catheters. Repeated studies were carried out on normotensive animals. Split-function studies on hypertensive animals were not performed. However, repeated studies in dogs with ischemic kidneys were done. Separate studies on ischemic and nonischemic kidneys in dogs with hypertension were not selected for study. The basic preparation herein described was used to compare the systemic effects of prostaglandins in hypertensive animals and nonhypertensive animals. Under general anethesia, calibrated electromagnetic blood flow transducers of appropriate size (Biotronex Laboratory, Inc., Silver Spring, Maryland) were placed on the base of the aorta, superior mesenteric artery, and left renal artery. Animals with more than one renal artery were not used. Periodic calibration of the transducers and associated flow meters showed that the flow-measuring systems were stable. Several days later, the dogs were anesthetized with i.v. pentobarbitol (30 mg./kg.), and mechanically ventilated with room air. Adequate hydration was provided (lactated Ringer's solution). During a steady-state infusion of PAH, creatinine, and inulin, baseline measurements were obtained of cardiac output (ml./min./

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kg. body weight), heart rate, stroke volume, mean femoral arterial pressure, total peripheral resistance, urine flow rate, sodium excretion, and clearance of inulin, creatinine, and PAH. After this 1 μg./kg. of freshly prepared PGA_1 (Upjohn Company Lot No. 9594-FHL-69), or PGE_1 (Upjohn Company Lot No. 8800-JMK-147C), were given intravenously over a 3-minute period and then all measurements were repeated during three to four subsequent 20-minute clearance periods.

In other experiments, similar observations were performed on dogs with chronically induced right renal artery stenosis (7- to 10-day duration) with renal ischemia and hypertension (mean arterial pressure increase > 50 mm. Hg).

Additional experiments were performed on animals with and without renal ischemia. Simultaneous renal venous and arterial samples were obtained for determination of extraction ratios of PAH, creatinine, and inulin before and after intravenous administration of PGA_1 or PGE_1.

$$\left(E = \frac{\text{arterial concentration}}{\text{arterial concentration}} \frac{- \text{venous concentration}}{\text{arterial concentration}}\right)$$

RESULTS

Cardiodynamic Alterations

Tables 1 and 2 summarize the cardiodynamic alterations noted in normotensive or hypertensive dogs after infusion of PGE_1 or PGA_1.

After PGE_1 infusion, normotensive and hypertensive dogs had a transient fall in cardiac output, blood pressure, and total peripheral resistance, with little change in measured heart rate, stroke volume, or superior mesenteric arterial flow. Normotensive dogs treated with PGE_1 had a transient fall in renal arterial flow. In contrast, hypertensive dogs after PGE_1 infusion had a sustained rise in renal arterial flow which was 264%, 157%, and 179% above control values during the three postinfusion periods ($p < .001$).

PGA_1 infusions in normotensive and hypertensive dogs resulted in a different pattern of cardiodynamic response (Table 2). Normotensive and hypertensive animals had a fall in aortic blood pressure, renal arterial flow, and superior mesenteric arterial flow. Total peripheral resistance, heart rate, and stroke volume values exhibited little change. Hypertensive animals had a transient rise in cardiac output ($p < .05$) immediately after PGA_1 infusion.

Renal Functional Changes

Tables 3 and 4 summarize the renal functional results obtained concurrently in the normotensive or hypertensive animals after PGA_1 or PGE_1 infusion. Since the results on repeated studies were similar in hypertensive and normotensive animals, they will not be separately enumerated.

After PGE_1 infusions, clearances of inulin, creatinine, and PAH were slightly decreased (< 20% maximal) in normotensive animals. In contrast, during the first postinfusion period hypertensive PGE_1-treated animals had > 60% measured decreases in inulin, creatinine, and PAH clearances. Normotensive and hypertensive animals had decreases in urine flow rate and immediate or delayed decreases in urinary sodium concentrations.

PGA_1-treated normotensive animals also had measured (< 30%) decreases in urine flow rate, inulin, creatinine, and PAH clearances. These decreases were sustained for shorter periods (Table 4) and were generally of lesser magnitude than those noted in normotensive PGE_1-treated animals. Urine sodium concentrations were not increased in PGA_1-treated normotensive animals. In contrast to all other groups, hypertensive dogs after PGA_1 treatment had marked elevations in inulin, creatinine, and PAH clearance. Urine flow rates, but not urine sodium concentrations, were increased throughout the observation periods.

Renal Extraction Ratios

The renal extraction ratios for creatinine, inulin, and PAH that were obtained in normotensive or hypertensive dogs given PGE_1 or PGA_1, are shown in Tables 5 and 6. PGE_1-treated animals, normotensive or hypertensive,

Table 1. Cardiodynamic Responses to PGE_1 Infusion in Normotensive and Hypertensive Dogs[a]

Period	Cardiac Output (ml./minute/kg. body weights)		Stroke Volume (ml./beat)		Mean Aortic BP (mm. Hg)		Heart Rate (beats/minute)	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	324.9 ± 28	234.4 ± 18	24.1 ± 5.0	18.6 ± 2.6	110 ± 3.7	150 ± 2.0	168 ± 3.5	160 ± 0.5
First period (post-injection 20 minutes)	328.5 ± 41	107.6 ± 17.1	38.6 ± 6.7	20.4 ± 1.5	96.0 ± 2.0	106.5 ± 5.2	175 ± 2.9	158 ± 1.4
Second period (20 minutes)	229.4 ± 24	209.78 ± 21	18.8 ± 1.5	20.4 ± 3.5	114.8 ± 4.3	112.6 ± 9.9	165 ± 2.5	151 ± 4.8
Third period (20 minutes)	344 ± 30	240.1 ± 22	27.0 ± 0.3	25.0 ± 3.6	129 ± 1.22	101.1 ± 3.8	172 ± 3	146 ± 4.8

	Renal Artery (ml./minute)		Superior Mesenteric Artery (ml./minute)		Total Peripheral Resistance (dyne cm.$^{-5}$)	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	191 ± 10.9	128.4 ± 12.5	163 ± 44	240.5 ± 16.5	1455 ± 64.5	3220 ± 558
First period (post-injection 20 minutes)	178 ± 2.3	334 ± 53.6	177 ± 6.9	247 ± 4.1	1120 ± 52	3050 ± 40
Second period (20 minutes)	190 ± 7.2	198 ± 34.1	165 ± 7.2	246 ± 2.5	1450 ± 92	2900 ± 54
Third period (20 minutes)	222 ± 4.1	189 ± 53.1	201 ± 4.1	221 ± 14.8	1100 ± 10.1	2850 ± 46.9

[a]Three hypertensive animals (15.6 kg. average body weight); three normotensive animals (17.45 kg. average body weight). All values are mean ± 1 standard error.

Table 2. Cardiodynamic Responses to PGA_1 in Normotensive and Hypertensive Dogs[a]

Period	Cardiac Output (ml./minute/kg. body weight)		Stroke Volume (ml./beat)		Mean Aortic BP (mm. Hg)		Heart Rate (beats/minute)	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	118.0 ± 2.4	181.09 ± 9.1	14.7 ± 2.3	13.9 ± 3.1	112.4 ± 6.3	160.8 ± 5.7	181.8 ± 8.2	185.0 ± 6.0
First period post-injection (20 minutes)	104.0 ± 5.2	231.8 ± 13.4	17.5 ± 2.6	22.7 ± 6.3	81.8 ± 3.2	118.2 ± 4.5	168.5 ± 3.4	189 ± 5.6
Second period (20 minutes)	99.6 ± 9.3	186.4 ± 6.8	13.2 ± 0.9	13.8 ± 0.6	95.9 ± 5.4	144.7 ± 8.4	158.9 ± 4.2	182.9 ± 4.6
Third period (20 minutes)	106.3 ± 8.2	182.3 ± 9.3	16.6 ± 0.9	13.5 ± 0.07	86.7 ± 5.9	168.5 ± 1.0	145.3 ± 4.0	192.5 ± 10

	Renal Artery (ml./minute)		Superior Mesenteric Artery (ml./minute)		Total Peripheral Resistance	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	150.4 ± 14.3	89 ± 4.3	204 ± 56	150 ± 15	3522 ± 593	4200 ± 600
First period post-injection (20 minutes)	118 ± 4.2	36 ± 7.3	215 ± 6.0	127 ± 6.5	3500 ± 70.8	3920 ± 51.7
Second period (20 minutes)	138 ± 5.5	66.5 ± 5.4	164 ± 9.3	120 ± 0.95	4200 ± 124	4820 ± 673
Third period (20 minutes)	133 ± 12.6	84 ± 5.6	159 ± 7.2	117 ± 1.3	4060 ± 62.5	5040 ± 100

[a]Six normotensive animals (12.5 kg. average body weight); three hypertensive animals (11.4 kg. average body weight). All values are mean ± 1 standard error.

Table 3. Renal Functional Responses to PGE_1 Infusion in Normotensive and Hypertensive Dogs[a]

Period	Inulin Clearance (ml./minute)		Creatinine Clearance (ml./minute)		PAH Clearance (ml./minute)	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	32.63 ± 3.2	18.6 ± 6.3	27.8 ± 1.4	14.2 ± 1.05	238.7 ± 28	49.4 ± 13.2
First period (20 minutes) (% control)	99.3% ± 10.2	15.5% ± 5.4	83.6% ± 2.3	18.3% ± 3.9	93.0% ± 6.6	38.0% ± 5.2
Second period (40 minutes) (% control)	93.0% ± 6.7	68.6% ± 20.5	83.4% ± 4.2	56.7% ± 13.7	79.6% ± 13.0	88.7% ± 15.6
Third period (60 minutes) (% control)	97.4% ± 8.2	51.5% ± 28.7	91.7% ± 5.3	53.9% ± 17.5	85.6% ± 5.2	59.5% ± 2.4

[a]After control period all values are expressed as percentage of control (100%) values. Values are mean ± 1 standard error.

	Urine Flow (ml./minute)		Urine Sodium Excretion (μEq./minute)	
	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	0.51 ± .11	0.26 ± .08	38.3 ± 1.4	33.3 ± 10.2
First period (20 minutes) (% control)	37.0% ± 0.2	16.0% ± 0.10	62.0% ± 15.2	26.1% ± 2.6
Second period (40 minutes) (% control)	31.0% ± .12	34.0% ± 0.08	43.8% ± 13.4	58.3% ± 4.7
Third period (60 minutes) (% control)	33.0% ± 3.0	68.0% ± .27	47.5% ± 12.2	62.2% ± 3.1

all had consistent decreases in the renal extraction ratios of creatinine, inulin, or PAH. Hypertensive animals with experimentally induced renal ischemia, initially had lower extraction ratios than other animals. The measured rise in renal arterial flow noted in PGE_1-treated hypertensive animals (Table 1) was not associated with increased flow through extractable areas of the kidney, e.g., renal cortex, as shown by the uniform decreases in renal extractions of PAH, creatinine, and inulin (Table 5). Similarly, the decreased urinary sodium concentration associated with the decreased renal extraction of PAH may also imply a drug-induced direct tubular impairment. All these intrarenal functional events, are likely to be also in part influenced by the decreased renal resistance and variable increase in renal flow as a result of renal vasodilatation.

PGA_1-treated normotensive dogs had lesser decreases in renal extractions of PAH, creatinine, and inulin. In fact, no sustained statistically significant decrease was noted in all the postinfusion periods. On the other hand, hypertensive PGA_1-treated dogs had moderate increases in the renal extraction ratios of creatinine, PAH, and inulin (Table 6). This was associated, in contrast to all other groups, with an increase in the clearance of inulin, creatinine, and PAH, and in urine flow rate (Table 4). These alterations were not associated with an increase in renal arterial flow (Table 2).

Table 4. Renal Functional Responses to PGA_1 Infusion in Normotensive and Hypertensive Dogs[a]

Period	Inulin Clearance (ml./minute)		Creatinine Clearance (ml./minute)		PAH Clearance (ml./minute)	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	28.1 ± 6.2	9.2 ± 3.2	32.2 ± 4.2	10.1 ± 3.6	89.5 ± 4.2	32.3 ± 15.5
First period (20 minutes) (% control)	63.8% ± 13.0	188.8% ± 31.9	62.9% ± 5.1	137.6% ± 13.0	68.6% ± 17.6	192.2% ± 14.16
Second period (20 minutes) (% control)	100.33% ± 19.4	247.9% ± 33.6	95.4% ± 13.3	177.8% ± 13.4	108.2% ± 9.1	209.0% ± 22.1
Third period (20 minutes) (% control)	78.5% ± 14.8	202.6% ± 29.7	76.1% ± 12.4	152.0% ± 12.1	81.5% ± 8.7	159.5% ± 9.8

	Urine Flow (ml./minute)		Urine Sodium Excretion (μEq./minute)	
	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	0.83 ± 0.22	0.31 ± 0.16	25.1 ± 7.2	15.1 ± 5.2
First period (20 minutes) (% control)	89.2% ± 2.3	202.9% ± 19.2	52.9% ± 10.5	38.0% ± 10.0
Second period (20 minutes) (% control)	97.8% ± 5.5	255.9% ± 50.4	75.1% ± 20.8	26.0% ± 4.5
Third period (20 minutes) (% control)	117.6% ± 13.0	235.0% ± 51.9	73.4% ± 20.5	43.0% ± 8.9

[a]After control period all values are expressed as percentage of control (100%) value. Values are mean ± 1 standard error.

Table 5. Renal Extraction in PGE_1-Treated Normotensive and Hypertensive Dogs[a]

Period	Inulin		Creatinine		PAH	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	0.37 ± 0.04	0.10 ± 0.04	0.28 ± .04	0.09 ± 0.07	0.75 ± 0.02	0.27 ± 0.08
First period (20 minutes postinjection)	0.28 ± 0.05	0.08 ± 0.05	0.24 ± 0.05	0.05 ± 0.02	0.67 ± .06	0.15 ± .10
Second period (40 minutes postinjection)	0.13 ± 0.03	0.03 ± 0.01	0.09 ± .04	0.06 ± 0.01	0.34 ± 0.01	0.05 ± 0.08

[a]All values are mean ± 1 standard error. Five animals in each group. Extraction ratio E = (arterial concentration − venous concentration)/(arterial concentration).

The renal alterations in hypertensive PGA_1-treated dogs must thus be attributed to localized intrarenal improvement in flow, e.g., decrease in afferent arteriolar resistance. This would account for the evident improvement in renal cortical perfusion in PGA_1-treated hypertensive dogs. Since urine flow rates were also increased in these dogs (Table 4), there may be some direct tubular effect as well. Extraction ratios in three dogs not treated with PGA_1 or PGE_1 did not vary ± 5% during similar observation periods. Two animals were normotensive; one was hypertensive with left renal artery stenosis.

DISCUSSION

The present studies conducted in dogs, normotensive or with experimentally induced renal ischemia and hypertension, have demonstrated that two prostaglandins (PGE_1, PGA_1) differ in their renal and cardiodynamic effects. In normotensive animals, PGE_1 produced reproducible and consistent vasodilatory effects on the splanchnic and the renal vascular beds (Table 1). The measured changes in flow were not a result of a marked increase in cardiac output or change in stroke volume. The effects were, however, different in hypertensive dogs. The hypertensive animals had an increase in renal arterial flow (Fig. 1). These renal circulatory changes are not associated with increased perfusion through the renal cortex, but more likely represent an intrarenal redirection of flow. The associated decreases in urine flow and variations in sodium excretion also suggest direct tubular effects. It is unknown to what extent PGE_1 may play a role in the regulation of intrarenal circulation and salt and water excretion. Edwards, Strong, and Hunt [4] have recently detected PGE_1-like

Table 6. Renal Extraction Ratios in PGA_1-Treated Normotensive and Hypertensive Dogs[a]

Period	Inulin		Creatinine		PAH	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
Control	0.24 ± 0.05	0.10 ± 0.01	0.29 ± 0.03	0.05 ± 0.02	0.66 ± .12	0.24 ± .08
First period (20 minutes postinjection)	0.21 ± 0.03	0.14 ± 0.02	0.14 ± 0.02	0.09 ± 0.03	0.54 ± 0.03	0.27 ± 0.09
Second period (40 minutes postinjection)	.22 ± .04	.12 ± .04	0.09 ± 0.04	0.06 ± .01	0.56 ± .10	0.33 ± .08

[a]All values are mean ± 1 standard error; three animals in each group. Extraction ratio, E = (arterial concentration − venous concentration)/(arterial concentration).

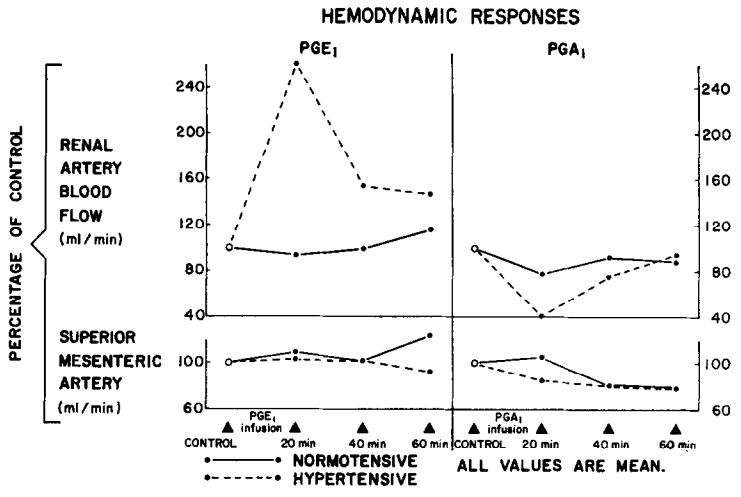

Fig. 1. The renal artery blood flow rate is markedly increased in hypertensive dogs by PGE_1 treatment.

substances in the renal venous blood of hypertensive (human) patients. It is, however, clear that the vascular effects of exogenous PGE_1 in the dog are different in the presence of renal ischemic hypertension.

PGA_1 has not been isolated from the kidney but it is possible that in some species PGA_1 may normally alter sodium excretion as it is not metabolized by the lung [6]. In the present experiments, the effects of PGA_1 differed in normotensive and hypertensive dogs (Tables 2 and 4). PGA_1 does not increase renal arterial flow (Fig. 1). However, in hypertensive animals there is improvement in renal function characterized by increased renal clearances, i.e., elevation in creatinine, inulin, and PAH clearance (Fig. 2). Renal extraction ratios (Table 6), unlike those noted in response to PGE_1, are improved in hypertensive dogs treated with PGA_1. Carr has recently noted improved renal function in hypertensive humans given PGA_1 infusions [2]. These two prostaglandins, PGE_1 and PGA_1, thus appear to have significant and reproducible renal effects in the presence of hypertension and renal ischemia that are not evident in the normotensive state. Either substance may play a role in the intrarenal regulation of flow and salt and water homeostasis. To what degree and by what mode these activities are altered in hypertension is not known [4, 6]. The fact that hemodynamic and renal functional responses to PGA_1 and PGE_1 in experimental hypertension differ, may prove to be of prac-

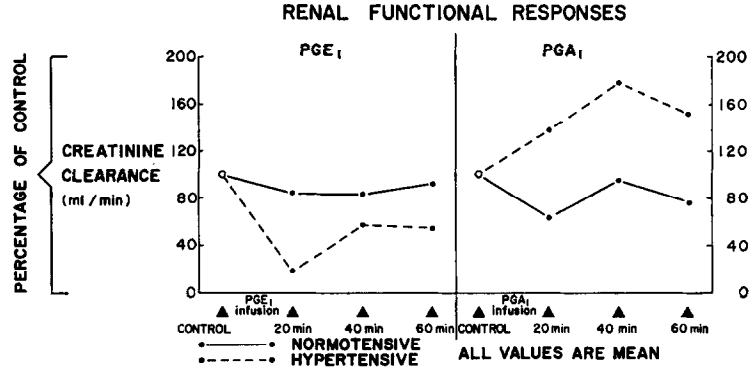

Fig. 2. PGA_1 treatment of hypertensive dogs results in significantly improved renal function. The creatinine clearance, for example, is significantly increased.

tical therapeutic or diagnostic aid. Further purification and characterization of these substances will undoubtedly occur [1]. The renal effects in ischemic hypertension may then be further clarified and enchanced.

The present studies have clarified the differences in response of the ischemic kidney in the hypertensive dog from those noted in the non-ischemic kidney of normotensive animals. These responses were indeed different to the two agents employed—PGE_1, PGA_1. There may be added differences of potential clinical value in comparing the non-ischemic and ischemic kidneys in hypertensive dogs. The changes of extraction ratio and urinary sodium concentration would be the most likely specific alterations. The simultaneous measurement of extraction ratios from both renal veins and arteries, however, presents a formidable, if not technically impossible task, even under experimental conditions.

SUMMARY AND CONCLUSION

Dogs with chronically implanted electromagnetic aortic, superior mesenteric, and renal arterial transducers were studied for renal and cardiodynamic responses to two prostaglandins, PGA_1 and PGE_1. Animals were normotensive or hypertensive as a result of recent stenosis of the right renal artery. Extraction ratios of PAH, creatinine, and inulin were also determined before and after drug infusion in hypertensive or normotensive dogs. The response to PGE_1 and to PGA_1 differ in dogs with renal ischemia and hypertension. PGE_1-treated hypertensive animals had a marked rise in renal arterial flow associated with decreased renal extraction and intrarenal shunting of blood from noncortical tissue. PGA_1-treated hypertensive dogs had improved renal extraction ratios, increased urine flow rates, and elevated clearances of PAH, inulin, and creatinine without elevation of renal arterial flow. The improved cortical perfusion was evidently a result of decreased afferent glomerular arteriolar resistance.

REFERENCES

1. Bergström, S., Carlson, L. A., and Weeks, J. R. The prostaglandins: A family of biologically active lipids. *Pharmacol.* Rev. 20: 1, 1969.
2. Carr, A. A. Hemodynamic and renal effects of a prostaglandin, PGA_1 in subjects with essential hypertension. *Amer. J. Med. Sci.* 259:21, 1970.
3. Covino, B. G., Lee, J. B., and McMorrow, J. Circulatory effects of renal prostaglandins. *Circulation* (Suppl. VI to Vols. 37 and 38): 60, 1968.
4. Edwards, W. G., Strong, C. G., and Hunt, J. C. A vasodepressor lysis resembling prostaglandin E_2 (PGE_2) in the renal venous blood of hypertensive patients. *J. Lab. Clin. Med.* 74: 389, 1968.
5. Johnston, H. H., Herzog, J. P., and Lauler, D. P. Effect of prostaglandin E on renal hemodynamics sodium and water excretion. *Amer. J. Physiol.* 213:939, 1967.
6. Lee, J. B., and Ferguson, J. F. Prostaglandins and natriuresis. The effect of renal prostaglandins on PAH uptake by kidney cortex. *Nature London* 222: 1185, 1969.
7. Nakano, J., and Cole, B. Effects of prostaglandins E_1 and F_2 on systemic, pulmonary and splanchnic circulations in dogs. *Amer. J. Physiol.* 217:222, 1969.
8. Weeks, J. R. The prostaglandins: Biologically active lipids with implications in circulatory physiology. Circ. Res. (Suppl. I to Vols. 24, 25): 125, 1969.