Circulatory and Humoral Changes In the Reversal of Renovascular Hypertension in Sheep by Unclipping the Renal Artery


ABSTRACT
The renal arterial clip was removed from 11 sheep with chronic experimental renovascular hypertension (previous unilateral nephrectomy, unilateral renal arterial constriction for 3 to 8 weeks, blood pressure elevated and stable). In five animals cardiac output, blood volume, plasma $[Na^+]$, and plasma renin concentration were measured the day before, 1 day after, and 4 days after unclipping. In the other six animals, plasma $[Na^+]$, plasma renin concentration, and blood angiotensin concentration were determined before and after unclipping. After unclipping, blood pressure returned to normal levels in 24 to 96 hours; cardiac output and blood volume were essentially unaltered during the period of observation. No natriuresis was seen, nor any change in plasma $[Na^+]$, plasma renin concentration, or blood angiotensin concentration, which remained within the appropriate normal ranges throughout. Nephrectomy of five similarly hypertensive animals, and six previously unilaterally nephrectomized normotensive sheep, was performed as a control. Variables similar to those measured before and after unclipping were determined at similar time intervals. The second nephrectomy of hypertensive animals was followed by maintained hypertension; and of normotensive animals by maintained normotension. The role of the kidney in the maintenance and reversal of chronic experimental renovascular hypertension is evaluated in the light of these results.

ADDITIONAL KEY WORDS unclipping nephrectomy renin blood pressure cardiac output angiotensin blood volume sodium peripheral resistance renal vasodepressor

[In uninephrectomized rats with a clip on the remaining renal artery, removal of the clip (hereafter called unclipping) is followed by restoration of the blood pressure to normal levels within 12 hours of operation (1, 2). The acute circulatory changes over the 6-hour period after unclipping were subsequently reported in similarly hypertensive rats maintained under pentobarbital anesthesia (3). Peripheral resistance, already elevated in the chronic hypertensive state, rises sharply upon unclipping, and has returned to its initial, elevated level at the end of 6 hours. Cardiac output falls even more sharply upon unclipping, remaining well below baseline levels throughout the period of study. Blood pressure gradually decreases into the normotensive range over 6 hours.

Previous work from this laboratory (4) on uninephrectomized sheep with a clip on the remaining renal artery showed that chronic renovascular hypertension is not associated with elevated plasma levels of renin and]
demonstrated that the maintenance of chronic renovascular hypertension is not dependent upon the presence of adrenal steroids.

Accordingly, the rationale of the series of unclipping experiments reported in this paper is twofold. First, a more extended study of the hemodynamic changes attendant upon unclipping was made by measuring cardiac output and blood volume over a 96-hour period after unclipping in conscious, unanesthetized animals. Similar observations on uninephrectomized hypertensive and normotensive animals subjected to a second nephrectomy were made as a control. Second, to delineate more precisely the roles of Na\(^+\), renin, and angiotensin in the maintenance of chronic renovascular hypertension, measurements of plasma renin concentration, blood angiotensin concentration, plasma Na\(^+\), and urinary Na\(^+\) output were made over the period of fall in blood pressure after unclipping.

Materials and Methods

SURGICAL PROCEDURES

Twenty-two mature sheep (20 wethers and 2 ewes) were used in the study. All animals were given 0.4 kg food but denied water for 24 hours before operation; such a regime obviates operative regurgitation. After thiopentone induction and endotracheal intubation, anesthesia was maintained with halothane and oxygen; all operations were performed with full aseptic technique. All animals underwent an initial operation of unilateral nephrectomy and the formation of a Van Leersum cutaneous carotid artery loop; 16 animals subsequently had a screw-type Goldblatt clip applied to the remaining renal artery at least 3 weeks after the first operation and after basal blood pressure recordings. A satisfactory degree of renal artery constriction, the artery was unclipped in 11 of the hypertensive sheep, the other 5 hypertensive sheep and the 6 normotensive uninephrectomized sheep were subjected to a second nephrectomy to serve as controls. The two ewes in the study were in the group of hypertensive undergoing nephrectomy and findings in them were undistinguishable from those in the wethers.

The operation of unclipping is both tedious and hazardous; the arterial wall, previously supported by the clip, is friable and occasionally balloons out after removal of the constriction. In sheep 11, a longitudinal split was made in the vessel at operation, and through this 150 ml of blood was lost before hemostasis was obtained with 5-0 Dexon chromic suture. In sheep 10, a degree of retroperitoneal and perirenal fibrosis, previously unencountered made visualization of the kidney impossible and the unclipping procedure doubly difficult.

ROUTINE MAINTENANCE AND OBSERVATIONS

Each animal was housed in a separate metabolism cage; each day 0.8 kg oat-alfalfa chaff and tap water ad libitum was offered, and the amount of food ingested was recorded. Daily urine output was measured, and a sample taken for [Na\(^+\)] and [K\(^+\)] determination with a Technicon Autoanalyzer. Feces were collected twice weekly and discarded. Systolic and diastolic blood pressure was measured by carotid loop sphygmomanometry and auscultation with the animal standing with head erect. Records were made at least once, and usually twice, a day; each record was the mean of several consecutive readings.

EXPERIMENTAL PROCEDURES

The 11 animals subjected to unclipping were maintained postoperatively on a regime of intake and observation identical to that detailed under routine maintenance. The 11 control animals were allowed neither food nor water after their second nephrectomy, to minimize the possibility of interference by volume changes in the anephric state.

Blood volume and cardiac output were determined in these 11 animals and five of those undergoing unclipping the day before surgery, the day after, and again 4 days after. Cardiac output was determined by method of Lilienfeld and Kovach (6). A known dose of \(^{131}\)I-labeled sheep globulin was given as a single injection into the jugular vein through a standardized polyethylene cannula; serial 3-second samples of blood were taken through an intracarotid indwelling polyethylene cannula. Blood volume was determined concurrently with cardiac output by carotid artery sampling 5, 10, and 15 minutes after the injection of \(^{131}\)I-globulin.

Blood angiotensin concentration was determined in the remaining six animals subjected to unclipping the day before unclipping, and 1, 4, 8, and 10 days after, by the method of Catt et al. (7). In all animals undergoing unclipping, plasma renin concentration was measured by a modified Skinner assay (8) the day before, the day after, and again 4 days after operation; renal...
## Table 1

Findings before and after Undipping at Time Zero in Study A

<table>
<thead>
<tr>
<th>Sheep No.</th>
<th>Day in relation to unclipping</th>
<th>SBP</th>
<th>DBP</th>
<th>CR</th>
<th>ur Na+</th>
<th>BV</th>
<th>CO</th>
<th>PR</th>
<th>[Na+]</th>
<th>PRC</th>
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<td>140</td>
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<td>9</td>
<td>1.8</td>
<td>4.8</td>
<td>3</td>
<td>1.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>156</td>
<td>143</td>
<td>60</td>
<td>9</td>
<td>1.8</td>
<td>4.8</td>
<td>3</td>
<td>1.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>158</td>
<td>145</td>
<td>60</td>
<td>9</td>
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<td>1.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>160</td>
<td>147</td>
<td>60</td>
<td>9</td>
<td>1.8</td>
<td>4.8</td>
<td>3</td>
<td>1.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>162</td>
<td>149</td>
<td>60</td>
<td>9</td>
<td>1.8</td>
<td>4.8</td>
<td>3</td>
<td>1.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>164</td>
<td>151</td>
<td>60</td>
<td>9</td>
<td>1.8</td>
<td>4.8</td>
<td>3</td>
<td>1.8</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Abbreviations used: SBP = systolic blood pressure (mm Hg); DBP = diastolic blood pressure (mm Hg); CR = cardiac rate (beats/min); ur Na+ = urinary Na+ excretion (mEq); BV = blood volume (liters); CO = cardiac output (liters/min); PR = peripheral resistance (arbitrary units); [Na+] = [Na+] (mEq/liter); PRC = plasma renin concentration (ng/hour/ml); SL = sample lost. Number in parentheses below number of animal is duration of hypertension in weeks.

## Figure 1

Average values for mean blood pressure (BP, mm Hg), cardiac rate (CR, beats/min), peripheral resistance (PR, arbitrary units), cardiac output (CO, liters/min) and blood volume (BV, liters) before and after the operation period in hypertensive sheep undergoing nephrectomy (open triangles), hypertensive sheep undergoing unclipping (solid circles) and normotensive sheep undergoing nephrectomy (open squares). Operation at time zero.

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Results

The data on unclipping reported in this paper are from two separate, sequential series of experiments. In the first series (study A, sheep 1 to 5), measurements of blood volume and cardiac output were made over the unclipping period, in the second series (study B, sheep 6 to 11), measurements of blood angiotensin concentration were made. Although in both series of experiments, blood pressure, cardiac rate, plasma $[\text{Na}^+]$, plasma renin concentration and urinary $\text{Na}^+$ excretion were measured, the course of measurement of these variables (with the exception of plasma renin concentration) was extended to cover a period of 16 days after unclipping in the second series. For ease of reference, therefore, the results of the two series of unclipping experiments are reported separately.

Unclipping of Hypertensive Animals—Study A.—The effects of unclipping are shown for sheep 1 to 5 in Table 1; average values over the period of observation are shown in Figure 1 (solid circles).

Unclipping of animals with chronic renovascular hypertension was followed by a rapid fall in blood pressure to normal levels. This reduction in blood pressure was not a result of acute diminution of circulatory volume, as measured blood volume remained unchanged over the course of the unclipping. The fall in blood pressure 24 hours after unclipping appears to be largely due to a diminished cardiac output and, to a lesser extent, a fall in peripheral resistance; by the fourth postoperative day, when blood pressure had returned to normal for 48 to 72 hours, the peripheral resistance had fallen, and the cardiac output returned to normal levels. The difference between peripheral resistance after unclipping and that before single nephrectomy (Fig. 1, open squares) is a function of the fortuitously smaller average size of the animals subjected to unclipping—a difference that is similarly reflected in blood volume values.

Cardiac rate rose sharply upon unclipping, thereafter returning gradually toward preoperative levels over the period of observation. No natriuresis was seen; plasma $[\text{Na}^+]$ and...
### Table 2

Findings before and after Unclipping in Study B

<table>
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<tr>
<th>Sheep no.</th>
<th>SBP</th>
<th>DBP</th>
<th>CR</th>
<th>[Na⁺]</th>
<th>BAC</th>
<th>PRC</th>
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<td>142</td>
<td>142</td>
<td>134</td>
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<td>114</td>
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<td>96</td>
<td>84</td>
</tr>
<tr>
<td>8 (6)</td>
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<td>154</td>
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<td>120</td>
<td>102</td>
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<td>106</td>
<td>96</td>
</tr>
<tr>
<td>10 (10)</td>
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<td>168</td>
<td>168</td>
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<td>11 (5)</td>
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<td>156</td>
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<td>SBP</td>
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<td>DBP</td>
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<td>95</td>
</tr>
<tr>
<td>[Na⁺]</td>
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<td>95</td>
<td>95</td>
<td>95</td>
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<tr>
<td>BAC</td>
<td>74</td>
<td>74</td>
<td>74</td>
<td>74</td>
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<tr>
<td>PRC</td>
<td>84</td>
<td>84</td>
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<td>84</td>
</tr>
</tbody>
</table>

### Abbreviations same as for Table 1. BAC = blood angiotensin concentration (ng/100 ml).

### Number in parenthesis below number of animal represents duration of hypertension in weeks.

* Died

Unclipping of Hypertensive Animals—Study B.—The effects of unclipping are shown for sheep 6 to 11 in Table 2; urinary Na⁺ excretion for the 24 hours before operation and each of the subsequent 16 days is shown for each animal in Table 3. Grouped data (study A and B) are shown in Figure 2.
(kidney wrap) type of hypertension, inadvertently produced at the first operation, is impossible to say. Sheep 11 died 48 hours postoperatively with malignant hypertension.

Cardiac rate followed the same pattern as in study A, an initial acute increase gradually falling to levels before unclipping. Plasma [Na\(^+\)] and plasma renin concentration (normal range 0.9±0.4 ng/hour/ml, mean ± 1 so, n = 119) remained unaltered after unclipping, with the exception of the plasma renin estimation immediately before death of sheep 11. Blood angiotensin concentration similarly remained in the normal range for Na\(^+\)-replete sheep (2.2±1.0 ng/100 ml, mean ± 1 so, n = 9) with the exception of the preoperative sample from sheep 10. The finding of an angiotensin level of 8.0 ng/100 ml, and a plasma renin of 0.2 (at the lower limit of normal) remains unexplained; similarly unexplained is the normal angiotensin level consistent with a plasma renin concentration of 150 ng/hour/ml in the sample immediately before death from sheep 11. Because of the disparity between renin and angiotensin measurements in this instance, an assay of circulating renin substrate was made, and the level was well within the normal range. As in study A, no natriuresis was seen after unclipping; again, as in study A, interpretation of urinary Na\(^+\) excretion in any individual animal is difficult because of wide variation in output over any particular 24-hour period.

Nephrectomy of Hypertensive and Normotensive Controls.—The effects of nephrectomy are shown in Table 4 (hypertensive) and Table 5 (normotensive); average values are shown in Figure 1 (open symbols).

### Table 3

<table>
<thead>
<tr>
<th>Sheep no.</th>
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<th>3</th>
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<th>6</th>
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<td>50</td>
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</tbody>
</table>

### Table 4

Findings in Chronic Renoureteral Hypertensive Sheep during the Paraneprhectomy Period

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<th>Sheep no.</th>
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<th>3</th>
<th>4</th>
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<td>5</td>
<td>2</td>
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</tbody>
</table>

### Table 5

Daily Urinary Na\(^+\) Excretion over the Period of Unclipping in Study B

<table>
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<th>Sheep no.</th>
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<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>Mean</td>
<td>72</td>
<td>53</td>
<td>53</td>
<td>58</td>
<td>61</td>
<td>99</td>
<td>104</td>
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<td>53</td>
<td>49</td>
<td>54</td>
<td>50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Abbreviations

- SBP: Systolic blood pressure
- DBP: Diastolic blood pressure
- CR: Cardiac rate
- CO: Cardiac output
- BV: Blood volume
- PR: Peripheral resistance

Abbreviations same as for Table 1. Number in parentheses below the number of animal is duration of hypertension in weeks.

*Cardiac rate was not recorded for sheep.
REVERSAL OF RENOVASCULAR HYPERTENSION

TABLE 5

Findings in Previously Uninephrectomized Normotensive Sheep before and after Second Nephrectomy

<table>
<thead>
<tr>
<th>Sheep</th>
<th>SBP</th>
<th>DBP</th>
<th>CO</th>
<th>BV</th>
<th>CR</th>
<th>PR</th>
<th>Day in return to unclipping</th>
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<tr>
<td>22</td>
<td>100</td>
<td>108</td>
<td>110</td>
<td>110</td>
<td>120</td>
<td>130</td>
<td>130 130 130 130 130 130 130 130 130 130 130 130 130 130 130 130 130 130 130</td>
</tr>
</tbody>
</table>

Days in relation to unclipping.

The second nephrectomy of animals with chronic renovascular hypertension was followed by essentially unchanged blood pressure and peripheral resistance, which at no stage approached the levels either before or after the second nephrectomy in hypertensive animals.

Values for renal renin concentration in hypertensive control animals were 3, 4, 5, 8, and 9 units/g cortex; those for normotensive animals 2, 4, 5, 10, 15, and 26 units/g cortex. The normal range for Na⁺-replete sheep in this laboratory is 8 ± 5.7 units/g (mean ± 1 so, n = 25).

Discussion

The purpose of this series of experiments was twofold: (1) to examine changes in conscious, trained sheep in hemodynamic variables when chronic experimental renovascular hypertension is reversed by unclipping and (2) to study the Na⁺-renin-angiotensin system over the period of fall in blood pressure.

In the series of experiments reported in this paper, blood pressure fell, although less rapidly than it does in rats (1, 2) with similar hypertension subjected to unclipping. The course of the fall in blood pressure appears to follow no obligatory relationship with the duration or severity of the hypertension, nor, within individual animals, with any of the measured variables. Although blood pressure in the rat may have returned to normotensive levels 6 to 12 hours after unclipping, there is strong evidence that return of other cardiovascular variables to normal follows a time course similar to that seen in the sheep (2, 3). For instance Ledingham and Cohen (3) found that 8 hours after unclipping, with normotensive blood pressure levels, cardiac output is markedly reduced below basal and peripheral resistance is at hypertensive levels before unclipping.

Changes in cardiac output and calculated peripheral resistance over the course of unclipping are difficult to interpret. Marked variation between animals in pattern of response was noticeable. Twenty-four hours after unclipping, cardiac output was substan-
Initially reduced in sheep 2 to 4, and their peripheral resistance was at the levels measured before unclipping (cf. ref. 3). In sheep 1, cardiac output remained unaltered over the first 24 hours and fell thereafter, in sheep 5, cardiac output rose progressively over the period of observation. On the average, cardiac output was lowered 24 hours after unclipping, and at this time constituted the major component of the fall in blood pressure; on the average, it had returned to the levels before unclipping after 96 hours; at this stage, the peripheral resistance had fallen in all animals and constituted the major component in the fall of blood pressure to normotensive levels.

Blood volume changes were small and fell into no pattern. In four of the five animals, circulating volume was slightly reduced at the 24-hour point and had returned to close to the preoperative level by the fourth day. Within the group, no relationship appears to have existed between the small changes in blood volume and either the changes in cardiac output or the rapidity of blood pressure fall.

If changes in cardiac rate are an index, even an incomplete one, of sympathetic activity, the identity of the blood pressure and cardiac rate curves after unclipping (Fig. 2) is consistent with a relationship between sympathetic tone and the fall in blood pressure. Evidence for a lowered sympathetic tone in the onset phase of experimental renovascular hypertension is the reduced sensitivity at this stage in the hypertension to ganglion blockade (9). Similarly, in the hypertension of acute glomerulonephritis, bilateral procaine block of the carotid sinus nerves in the acute stage of the hypertension is followed by a much greater rise in cardiac rate than in the chronic phase (10). In both dogs (11) and rats (12) cardiac rate is lowered during the period of ascending blood pressure after clipping. That the baroreceptors adjust and buffer blood pressure about the elevated level in chronic hypertension—clinical and experimental renovascular—has been demonstrated by a variety of techniques (13-15).

The acute tachycardia upon unclipping in our experiments—demonstrably not merely a postoperative phenomenon (see nephrectomy data)—would seem consistent with an acute elevation of sympathetic discharge in an attempt to maintain the blood pressure about the elevated hypertensive level. The gradual decline of the acutely elevated cardiac rate similarly would appear consistent with a second adjustment, this time downward, of the baroreceptors (a "re-reset"?) concomitant with the lowering of blood pressure and a consequent decline in the level of sympathetic discharge. Ancillary evidence supporting a gradual readjustment in the extrarenal mechanisms of renovascular hypertension is found in the experiments of Floyer (2) in which a second nephrectomy was performed at various times after unclipping. If 28 days elapsed between unclipping and nephrectomy, the time of onset of "renoprival" hypertension was identical to that in animals with previously unmanipulated kidneys. A slightly more rapid onset was seen in a series nephrectomized 8 to 14 days after unclipping, and an even quicker onset in the series with 3 days between operations. All animals responded to unclipping by a prompt decline in blood pressure to normal levels and were normotensive at nephrectomy (2).

Over the period of unclipping, levels of plasma [Na+]+, urinary Na+ output, plasma renin concentration, and blood angiotensin concentration remained unaltered in the appropriate normal ranges. Accordingly, it seems probable that the fall in blood pressure is not a consequence of gross changes in the Na+ -renin-angiotensin system. That changes in plasma [Na+] may not truly mirror changes in effector site [Na+] is undeniable; that circulating levels of renin or angiotensin may not have an unvarying relationship to tissue or bound levels is also an open question. Even were effector-site activities of Na+-angiotensin in fact unchanged, what this would mean cannot be delineated precisely in the light of their known interactions with vascular wall polyanions (16) and catecholamine metabolism (17).

The maintained elevated blood pressure after nephrectomy of a hypertensive animal—
a hypertension quantitatively and qualitatively different to that which sometimes gradually develops in the anephric animal—is evidence that the renin-angiotensin-Na⁺ system is not essential to the maintenance of the elevated blood pressure of chronic renovascular experimental hypertension, and that, in this state, an extrarenal mechanism is capable of maintaining the elevated blood pressure. Demonstration of unchanged levels of these variables after unclipping—with the caveat in terms of tissue binding and interaction outlined above—would seem to deny a primary role for renin-angiotensin-Na⁺ in the reversal of experimental renovascular hypertension. This is not to deny a possible primary role for a renin-angiotensin-Na⁺ interaction in the onset of experimental renovascular hypertension, although the normal development of hypertension in animals with high circulating levels of antiangiotensin antibodies may be evidence against such a role (18, 19).

If changes in the renin-angiotensin-Na⁺ system do not have a primary role in the reversal of the hypertension, and there is evidence for active, though increasingly accommodating, opposition to the fall in blood pressure on the part of the sympathetic nervous system, the question of the prime mover in the observed normotensive response remains unanswered. The isolation of renal vasodepressor material—both acidic prostaglandins and neutral lipids—has been the subject of several studies (20, 21); the antihypertensive activity of the normal kidney grafted into hypertensive animals has been found dependent upon the perfusion pressure (22).

There have been several recent reports of release of prostaglandin-like material into renal venous blood, from the experimental or contralateral kidneys or both, after a variety of manipulations of one kidney (23, 24). Precise definition of the roles of such compounds in the specific situation of unclipping—and perhaps, by extrapolation, in the more general area of cardiovascular homeostasis—must await development of adequate methods of measurement.

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