Reduction of Experimental Renal Hypertension by Kidney Perfusion

By W. J. Kolff, M.D.

Normal kidneys were transplanted to the neck of 15 dogs with experimental renal hypertension. In 6 a reduction of blood pressure of 52 mm Hg (32-102) took place during the first 2 hours of perfusion. It is hypothesized that renin or angiotensin in minute amounts impairs, blunts or frustrates the normal blood pressure reducing function of the kidney.

As an introduction to a discussion of the blood pressure reducing function of the kidneys, I want to review what I believe to be the basic facts of renoprival hypertension. We have compared the average increase in blood pressure in groups of dogs treated in certain ways after bilateral nephrectomy. The overhydrated dogs developed renoprival hypertension more rapidly than the others, but all dogs finally got some increase in blood pressure. The removal of the kidneys is the basic underlying fact, and overhydration and diet, are at most accelerating factors. If we varied the sodium level of the dog's blood serum we could sometimes raise and lower the blood pressure with the serum sodium level, if the excursions were large enough. Occasionally we came across a dog which for some reason did not develop hypertension after bilateral nephrectomy. It was not immune to the vascular changes which occur in renoprival disease.

If dogs are nephrectomized and overhydrated they develop hypertension; however, under the same conditions if their ureters are transplanted into the vena cava, then hypertension does not develop. It is the presence of renal tissue that prevents the occurrence of hypertension even though its excretory function is frustrated by leading the urine back into the blood stream. These experiments confirm the earlier observations of Dr. Grollman. Chronic renal hypertension in dogs will persist after bilateral nephrectomy, which makes it unlikely that the hypertension is due to the constant secretion of a pressor substance by the kidney.

We have reported that hypertension has been reduced in 9 of 10 nephrectomized, overhydrated dogs by transplanting a pair of normal dog kidneys to the neck of the hypertensive animal. Transplantation by the same technic of a pair of hind legs did not lead to a significant fall in blood pressure. Transplantation of normal kidneys into normotensive dogs caused no fall in blood pressure. The blood pressure reduction in renoprival hypertensive dogs did not depend upon loss of extracellular fluid or sodium excreted by the transplanted kidneys. Kidney perfusions of renoprival hypertensive dogs which had not been overhydrated gave the same results. Perfusion for 2 hours of a spleen from a very large dog caused no reduction in blood pressure, but subsequent kidney perfusion by the same hypertensive dog caused a fall in blood pressure of 48 mm Hg in 11/2 hours. Direct connection of the carotid artery to the jugular vein for 1/2 hour, allowing an arteriovenous shunt many times greater than the flow through a pair of kidneys, did not cause a fall in blood pressure.

The purpose of the present study was to determine whether a reduction of hypertension would also occur during transplantation of a pair of normal kidneys to the neck vessels of renal hypertensive dogs. The protective mechanism of the kidney, as advocated by Grollman, in this case not only would have to compensate for the blood pressure-reducing factor that supposedly fails in the
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nephrectomized animal, but also would have to compete with the pressor system (renin, angiotonin, sustained pressor principle), if any, of the experimentally damaged kidney.

METHODS

Fifteen dogs were made hypertensive, according to Page's method,* by wrapping both kidneys in cellophane or by wrapping one kidney in cellophane while the other kidney was removed. Arterial pressures were taken at approximately weekly intervals, and also on the morning before the renal perfusion, by direct puncture of a femoral artery with a 20-gage needle connected to a mercury manometer.

Dogs that perfused kidneys or hind legs, as in previous reports, are termed "perfusors;" dogs that donated kidneys for the perfusion are termed "donors." The carotid and jugular vessels of the perfusor were connected with a Blakemore-Lord vitallium cannula,* allowing intima-to-intima anastomoses to the lower abdominal aorta and vena cava of the kidney donor. When the anastomoses were opened, the aorta and vena cava were closed under the diaphragm so that the kidneys were switched from the circulation of the donor to the circulation of the perfusor without interrupting the renal blood supply. This technie devised by Brull has been described previously. Brull's7 and Dumont's8 technies of hind leg perfusion were modified slightly.

The perfusor dogs were anesthetized with chloralose or Nembutal, the donor with Nembutal. The anesthesia was maintained with a slow, intravenous drip of chloralose, or by an automatic syringe delivering 120 mg. of Nembutal in 3 hours in the average dog of 10 Kg.† Urine formed by the transplanted kidneys was collected and an equivalent amount of a mixture of 5 per cent dextrose in water and normal saline solution was administered intravenously. At the end of the experiments antibiotics were administered. All perfusor animals survived except those having malignant hypertension.

RESULTS

Renal Transplantation. A typical experiment is shown in figure 1. The perfusor dog had malignant hypertension, a blood pressure of 220 mm. Hg, and blindness. One kidney was wrapped in cellophane 27 days before the experiment. Blood pressures rose as follows:

168, 215, 196, and 220 mm. Hg. First an arteriovenous anastomosis was made between the carotid artery and the jugular vein. No reduction of blood pressure resulted. During readjustment of the position of the dog on the table some irregularities occurred (arrow 2). Thereafter, a pair of normal kidneys was connected to the neck vessels. During kidney perfusion a gradual reduction in blood pressure occurred which was interrupted by a temporary rise (arrow 4) when 50 ml. of 25 per cent dextrose with 0.45 per cent saline was accidently given intravenously. During the first 2 hours of kidney perfusion, the pressure was reduced from 212 to 160 mm. Hg and after 3 hours to 140 mm. Hg. After the removal of the transplanted kidneys there was a tendency for the blood pressure to go back up. Total urine during the first 3 hours of perfusion was 125 ml. and total blood loss was 80 ml. To compensate for this a total of 250 ml. of a mixture of half 5 per cent dextrose and half normal saline was infused intravenously over the same period. The weight of the perfusor dog was 7.8 Kg.; the transplanted kidneys 72 Gm. The urine formed contained 73 mEq. of sodium and 29 mEq. of potassium per L. and the dextrose-saline mixture contained 85 mEq. of sodium per L.

Five days later the same dog was used for a second experiment. Under the same anesthesia the blood pressure proved to have returned to its previous level, 200 to 230 mm. Hg. During the second experiment the blood pressure fell 56 mm. Hg within the first 2 hours of kidney perfusion. At autopsy it was found that there were multiple hemorrhages in the gastrointestinal tract and in the pancreas, supporting the diagnosis of malignant hypertension.

Reduction of Blood Pressure. In 6 of 15 dogs the blood pressure was lowered an average of 52 mm. Hg (32 to 102) after 2 hours of kidney perfusion (fig. 2). In 5 others the blood pressure was lowered at some other time during the course of the experiment (fig. 3). The remaining 4 dogs showed no significant reduction of blood pressure at any time during the perfusion. In the following discussion, we shall take into account only the re-

*Austenal Laboratory, Inc., New York, N. Y.
†We are much indebted to Dr. D. B. Paul and Dr. H. Beckman of the Pharmacology Department, Marquette University School of Medicine, for sending us one of their automatic syringes for trial.
ductions in blood pressure that were present after 2 hours of kidney perfusion. A perfusion was started only after the blood pressure had been constant for at least 1½ hour.

Urine Volume and Reduction in Blood Pressure. A low urine volume produced by the transplanted kidneys did not exclude a fall in blood pressure. Of the 7 dogs in which urine volumes were less than 40 ml. in the first 2 hours, the blood pressure came down in 2, but of the 4 dogs in which urine volumes were larger than 100 ml., the blood pressure came down in 3 not withstanding the fact that the urine volume was replaced with an equivalent amount of a mixture of 5 per cent dextrose in water and normal saline solution intravenously (table 1).

Malignant Hypertension. In 4 experiments the perfusor dog had developed malignant hypertension, as judged from rapid increase of blood pressure, blindness due to retinal detachment, and extensive petechial hemorrhages seen mainly in the gastrointestinal tract at postmortem examination. In 3 dogs with malignant hypertension the blood pressure was reduced. In the fourth experiment it was reduced only for 1 hour, but later went back up.

Duration of Hypertension Prior to Kidney Perfusion. In 3 experiments the hypertension had existed for only 1 to 3 weeks prior to the kidney perfusion. In 2 of these experiments the hypertension was malignant; in the third dog with hypertension of short duration, no reduction of blood pressure took place. In the 12 other experiments the hypertension had existed for 2½ to 8 months. Reduction of blood pressure occurred in 5, 3 times after 4 months and 2 times after 8 months.

Kidney Weight and Reduction in Blood Pressure. With large donor kidneys there were greater falls in blood pressure (table 1). In 3 experiments in which the ratio of weight in grams of donor kidneys : body weight of perfusor in kilograms was 8.2 to 9.2, the average fall in blood pressure during the first 2 hours of perfusion was −62 mm. Hg (32 to 102). In these experiments the weight of the donor dog was greater than that of the perfusor dog. Of the 7 experiments in which kidney weight : body weight ratios were under 4 Gm. per Kg., only one significant fall in blood pressure (−82 mm. Hg) occurred; all others showed no fall or a fall less than 20 mm. Hg.

Influence of Hind Leg Perfusion and Arteriovenous Anastomosis on Blood Pressure. Two hind leg perfusions were performed and
in 2 cases arteriovenous anastomoses were made between the carotid artery and the jugular vein, thus allowing a vascular shunt much larger than the total blood flow through any pair of transplanted kidneys. Reduction of blood pressure attributable to these procedures was not observed.

**Discussion**

We observed a reduction of hypertension in 6 of 15 renal hypertensive dogs after 2 hours of kidney perfusion and in 11 of the 15 if the arbitrary 2 hour limit is disregarded. This proportion is in contrast to a reduction in 9 of 10 renoprival hypertensive overhydrated dogs previously described. In the experiments with renoprival hypertension we were reassured by the lack of effect on the blood pressure of hind leg perfusion, spleen perfusion, and of arteriovenous anastomosis, but such reassurance is more difficult to obtain in the present investigation. We have found no influence from hind leg perfusions or arteriovenous anastomoses in 4 dogs with renal hypertension, but in order to contrast with the 6 significant reductions during 15 kidney perfusions a much larger number of hind leg perfusions would be required.

During the course of the experiments it was observed that relatively small amounts of saline-dextrose (60 or 80 ml.) could cause considerable rises in blood pressure. This makes us suspect that the observed fall in blood pressure may not be specific and that the results, although suggestive, should not be accepted as proof.

The marked reduction in hypertension in all 3 of the renal hypertensive dogs that perfused large kidneys is consistent with the previous findings of Braun-Menendez. Katz, Friedman, Rodbard, and Weinstein many years ago expressed the view that hypertension is the result of a disproportion between normal and abnormal renal tissue. In our previous experiments in renoprival hypertensive dogs there was no abnormal renal tissue; therefore a blood pressure reduction after kidney perfusion was more frequent than in
TABLE 1.—Reduction of Experimental Renal Hypertension in Dogs by Kidney Perfusion

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Duration B.P. over 160 mm. Hg</th>
<th>Duration B.P. over 250 mm. Hg</th>
<th>Hypertension malignant: blindness, hemorrhages</th>
<th>B.P. in a.m. (mm. Hg)</th>
<th>Urine vol. in first hr. (ml.)</th>
<th>Dextrose and saline in first 2 hr. (ml.)</th>
<th>B.P. change after 2 hrs. (mm. Hg)</th>
<th>B.P., greatest change (mm. Hg)</th>
<th>Ratio of kidney wt., Gm.: dog weight, Kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>93</td>
<td>1 wk.</td>
<td></td>
<td>+</td>
<td>180</td>
<td>10</td>
<td>-14</td>
<td>1 hr.</td>
<td>-44</td>
<td>4.7</td>
</tr>
<tr>
<td>102</td>
<td>3 mo.</td>
<td>1 wk.</td>
<td></td>
<td>204</td>
<td>340</td>
<td>300</td>
<td>-26</td>
<td>6 hr.</td>
<td>-54</td>
</tr>
<tr>
<td>103</td>
<td>8 mo.</td>
<td>3 mo.</td>
<td>+</td>
<td>230</td>
<td>50</td>
<td>50</td>
<td>-102</td>
<td>2 hr.</td>
<td>8.9</td>
</tr>
<tr>
<td>104</td>
<td>8 mo.</td>
<td>3 mo.</td>
<td>+</td>
<td>157</td>
<td>25</td>
<td>30</td>
<td>-48</td>
<td>2 hr.</td>
<td>4.6</td>
</tr>
<tr>
<td>105</td>
<td>4 mo.</td>
<td>5 wk.</td>
<td></td>
<td>210</td>
<td>100</td>
<td>200</td>
<td>-52</td>
<td>3 hr.</td>
<td>9.2</td>
</tr>
<tr>
<td>106</td>
<td>3 wks.</td>
<td>1 wk.</td>
<td>+</td>
<td>200</td>
<td>30</td>
<td>60</td>
<td>-82</td>
<td>3 hr.</td>
<td>3.6</td>
</tr>
<tr>
<td>108</td>
<td>18 days</td>
<td></td>
<td></td>
<td>190</td>
<td>55</td>
<td>85</td>
<td>-10</td>
<td>3 hr.</td>
<td>3.3</td>
</tr>
<tr>
<td>122</td>
<td>4 mo.</td>
<td>2 mo.</td>
<td></td>
<td>214</td>
<td>140</td>
<td>80</td>
<td>-32</td>
<td>4 hr.</td>
<td>4.8</td>
</tr>
<tr>
<td>123</td>
<td>2½ mo.</td>
<td></td>
<td></td>
<td>170</td>
<td>65</td>
<td>65</td>
<td>-20</td>
<td>3 hr.</td>
<td>2.5</td>
</tr>
<tr>
<td>124</td>
<td>4 mo.</td>
<td>2 mo.</td>
<td></td>
<td>254</td>
<td>40</td>
<td>100</td>
<td>None</td>
<td>None</td>
<td>2.5</td>
</tr>
<tr>
<td>125</td>
<td>6 mo.</td>
<td></td>
<td></td>
<td>192</td>
<td>40</td>
<td>120</td>
<td>-2</td>
<td>2½ hr.</td>
<td>6.0</td>
</tr>
<tr>
<td>126</td>
<td>4½ mo.</td>
<td>4½ mo.</td>
<td></td>
<td>230</td>
<td>30</td>
<td>40</td>
<td>+6</td>
<td>½ hr.</td>
<td>3.0</td>
</tr>
<tr>
<td>127</td>
<td>3 mo.</td>
<td></td>
<td></td>
<td>188</td>
<td>35</td>
<td>100</td>
<td>-18</td>
<td>2½ hr.</td>
<td>3.4</td>
</tr>
<tr>
<td>128</td>
<td>2½ mo.</td>
<td></td>
<td></td>
<td>175</td>
<td>1½ hr.</td>
<td>1½ hr.</td>
<td>-14</td>
<td>1 hr.</td>
<td>4.0</td>
</tr>
<tr>
<td>129</td>
<td>4 mo.</td>
<td></td>
<td></td>
<td>194</td>
<td>55</td>
<td>125</td>
<td>-32</td>
<td>3½ hr.</td>
<td>8.2</td>
</tr>
</tbody>
</table>

The present experiments in which the hypertensive effect of the cellophane-wrapped kidneys also had to be overcome. Floyer\textsuperscript{12, 13} has suggested that something coming from the diseased kidney destroys the ability of an untouched kidney to maintain normal blood pressure. We suggest renin or angiotonin as the substance that impairs, destroys or blunts this beneficial function of the kidney.

The amount of renin or of angiotonin required to blunt this normotensive function of the kidney might be much smaller than the amount necessary to give a direct pressor response. This hypothesis will reconcile the convincing evidence presented by Dr. Wakerlin and Dr. Goldblatt that antirenin cures renal hypertension in dogs with the difficulties experienced in demonstrating the presence of angiotonin in circulating blood in amounts large enough to cause pressor responses. It will also explain why Dumont\textsuperscript{14} was unable to see a rise in blood pressure when he transplanted the kidneys of a renal hypertensive dog, renal artery constriction.
and all, to the neck of a sensitive perfusor, although application of a clamp to these kidneys then produced a pressor response.

**Summary**

The reduction of renoprival hypertension can be repeated as often as one wants by transplanting normal kidneys to the neck of renoprival hypertensive dogs. In these experiments the phenomenon occurred within 2 hours after transplantation of the kidneys. Muirhead, Stirman, Lesch and Jones with other technics have shown that the transplantation of a kidney to the neck of a renoprival hypertensive dog reduced its blood pressure, and that this reduction did not depend upon the loss of water and electrolytes. The evidence obtained for the blood pressure reducing function of the kidney in renal hypertensive animals, both in Floyer's rats with renal arteries clamped and in our dogs with kidney transplantation, is suggestive but cannot be accepted as proved. We have, however, obtained very valuable support from the experiences of Merrill, Murray, Harrison and Guild in Boston. After transplantation of a normal kidney, the blood pressure of their patient with malignant hypertension first came down, which may be interpreted as evidence of the blood pressure reducing function of the transplanted kidney. The pressure then started back up until the patient's own contracted kidneys were removed. This may show that the contracted kidneys impaired or frustrated the blood pressure reducing function of the normal transplanted kidney and that this function was restored after their removal. Two more kidney transplantsations in identical twins with a similar effect on the blood pressure were recently reported.  

**Acknowledgment**

Mr. Janis Egalis gave skillful assistance during the transplantation experiments.

**References**


17. **Guild, W. R.:** Personal communication.
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