Observations on the Pathogenesis of Spontaneous Inherited Hypertension and Constricted Renal-Artery Hypertension in Rats

By Richard Laverty, Ph.D., and F. Horace Smirk, K.B.E., M.D., F.R.C.P., F.R.A.C.P.

A study has been made of the circulatory changes in rats (B rats) from a colony bred to develop hypertension spontaneously (Smirk and Hall1). The B rats were compared with rats made hypertensive by application of a silver clip to the renal artery of the sole remaining kidney, usually one to seven days before (AR rats); also with chronic renal hypertensive rats (CR rats) in which the renal artery to the sole remaining kidney had been clipped for four or more weeks.

The bloods of B, AR, and CR rats and controls (C rats) were examined for the presence of vasoactive substances by the method of Field, De Graaf, Wallis,2 and Field and Laverty,3 whereby blood from either of two donor rats could be pumped at a constant rate of 1 ml./min. through the hind-limb blood vessels of a recipient rat, the venous blood being returned to the donor by a second pump.

A study has also been made of the degrees to which the peripheral resistances of the hind-limb blood vessels of B, CR, and C rats are neurogenically maintained.4

The statement that a type of hypertension or of increased vascular resistance is neurogenically maintained implies only that blockade of the vasomotor nerves will remove the blood-pressure elevation or the increased vascular resistance. It does not, for example, make the tacit assumption that neurogenically maintained blood-pressure elevation or vasoconstriction is due to an increased discharge down sympathetic nerves; vasoconstriction might be due to this, but, alternatively, it might be due to enhanced catecholamine release at sympathetic endings, to enhanced reactivity of smooth muscle to nervous stimulation, or to some combination of these.

The B rats are of interest in that hypertension and cardiac enlargement are present in the sixth postnatal week. At ages under three months, the kidneys of B and C rats are indistinguishable by light microscopy.

We confirm the observation of others5,6 that a circulating pressor substance is present for a few days after renal-artery constriction. This finding serves to authenticate the method as we have applied it to the study of our rats with spontaneously developed hypertension.

An admirable review by Hoobler7 of the proceedings of a University of Michigan conference on the basic mechanisms of hypertension indicates that the extent to which circulating pressor agents affect blood pressure after chronic renal-artery constriction remains a matter of dispute. It seems difficult to escape the conclusion that the clip on the renal artery determines the persistence of blood-pressure elevation, for when it is removed, the blood pressure falls.8-10 On the other hand, there is evidence that the nervous system plays some part in maintaining the blood-pressure elevation. Ogden11 found that in rats the falls of blood pressure from sodium pentobarbital, yohimbine, and 883F were larger in chronic than in acute renal hypertension. The rise of blood pressure in chronic renal hypertension of rats can be prevented by reserpine (Hodge12). In man, considerable blood-pressure falls may be induced by hexamethonium in the presence of chronic renal hypertension.
We are unaware of previous work on the pathogenesis of spontaneous hypertension in rats.

Methods

Male albino Wistar rats, six months old, and usually weighing between 275 and 375 Gm., were used throughout. Renal hypertension was induced by the method of Wilson and Byron, in which unilateral nephrectomy is performed and a silver clip applied to the remaining renal artery one week later. A clip 0.0095 inch in diameter was used. Pre-experimental blood pressures were measured by a tail-cuff technique.

The cross-transfusion experiment was set up using the techniques of Field and Laverty. Two donor rats were prepared simultaneously under chloralose anesthesia (50 mg./Kg.), with their carotid arteries connected to a Y-piece (fig. 1, A). By clamping either at (B) or (C), blood was taken from either of the donor animals. A venous pump returned blood to the donor. A third rat, marked “recipient” in figure 1, was used for preparation under ether anesthesia of a de-nervated, vascularly isolated hind limb. After the pumps and tubing had been washed free from saline with 6 to 10 ml. of blood taken from normal donors, one of the donor rats, which usually depending on their relative degree of hemostasis, was given 1,250 units of heparin. The femoral artery and vein of the recipient hind limb were then cannulated, the pumps were started, and the perfusion pressure recorded. In all experiments, there were three successive periods of perfusion, lasting 30, 60, and 30 minutes. The mean of the perfusion pressures in periods one and three, using one donor, was compared with the perfusion pressure in period two, using the other donor. In all three experiments, one donor was a C rat; the second was either another C rat, an AR rat, a CR rat, or a B rat. The recipient was always a C rat.

Two types of experiment were performed concerning the nervous control of blood vessels. First, a C rat was used as blood donor, its blood being pumped at 1 ml./min. into the femoral artery of a recipient rat and returned from the femoral vein through a venous pump to the donor. Connections between the recipient rat and its perfused hind limb were cut except for the femoral and sciatic nerves and the bone. The innervated but vascularly isolated perfused hind limb might be that of a B, CR, or C rat.

In the second type of experiment, only one rat was used, blood from one femoral artery being pumped at 1 ml./min. into the opposite femoral artery by a constant output pump, without vascular isolation of the limb. Otherwise, the technique was similar to that described previously. This class of experiment also employed B, CR, and C rats. The perfusion pressure was recorded by small-capacity mercury manometers.

The experiments on B rats of series 1 were made about 12 months before those of series 2. During this time, selective breeding had increased the blood pressures of the B rat colony.

Results

Effect on Rat Blood Vessels of Rat Blood from Controls and Hypertensives

Comparison of Bloods from Pairs of Control Rats

When donor blood is perfused at constant rate through the vascularly isolated hind limb of a recipient rat, the perfusion pressure is a measure of the peripheral resistance. Using two normotensive C rats as donors, there is no appreciable difference (8 experiments) between the perfusion pressures recorded with the blood of one C donor and with that of another C donor rat (fig. 2, table 1). Only pairs of results obtained by perfusion of blood from two sources through one rat hind limb are comparable. As perfusion rate is constant, perfusion pressure will be higher if a smaller rat is used for the recipient limb preparation than if a larger rat is used.

Cannulation of the carotid arteries of donor rats in these and subsequent experiments caused a rise of blood pressure in some rats to above the level before cannulation. Hence, some controls exhibited over-average blood pressures. This is probably a carotid-sinus effect. There was no evidence that it altered the vasoconstrictor content of the blood. Mean blood pressure for controls was 127.95 mm. Hg; mean perfusion pressure with blood of the 35 controls with higher blood pressures was
Table 1
Comparison of Effects on Perfusion Pressure of Blood from Control Donor Rats with Effects of Blood from Donor Rats with Acute Renal Ischemia (AR) and Chronic Renal Ischemia (CR) and from Rats Bred to Develop Hypertension Spontaneously (B)

<table>
<thead>
<tr>
<th>Type of rat compared with control</th>
<th>Number of experiments</th>
<th>Mean blood pressure mm. Hg*</th>
<th>Blood compared with control</th>
<th>Difference mm. Hg* (y — x)</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Another control</td>
<td>8</td>
<td>120.6 ± 4.5</td>
<td>130.0 ± 8.5</td>
<td>41.6</td>
<td>40.8</td>
</tr>
<tr>
<td>AR group 1†</td>
<td>11</td>
<td>128.2 ± 3.5</td>
<td>161.8 ± 5.7</td>
<td>42.3</td>
<td>55.5</td>
</tr>
<tr>
<td>AR group 2†</td>
<td>13</td>
<td>127.7 ± 5.0</td>
<td>116.2 ± 5.0</td>
<td>43.4</td>
<td>47.8</td>
</tr>
<tr>
<td>CR</td>
<td>13</td>
<td>122.8 ± 4.8</td>
<td>195.8 ± 8.3</td>
<td>37.4</td>
<td>37.7</td>
</tr>
<tr>
<td>B</td>
<td>13</td>
<td>156.4 ± 4.4</td>
<td>160.4 ± 4.9</td>
<td>48.9</td>
<td>46.8</td>
</tr>
</tbody>
</table>

*± Standard error of mean in each case.
†AR group 1 rats had a rise of blood pressure above 140 mm. Hg at the time of experiment; rats of AR group 2 did not.

42.8 mm. Hg, and mean perfusion pressure of the 31 controls with blood pressures below the mean was 41.9 mm. Hg.

Comparison of Blood from Rats with Unilateral Nephrectomy and Acute Unilateral Renal-Artery Constriction with Blood from Control Rats

When blood from an AR rat is perfused through the hind limb of another rat, there is usually a rise in perfusion pressure above the level obtained when blood from a C rat is perfused through the same preparation.

This rise occurred more frequently (9 of 10 instances) when the blood pressures of the AR donor rats had risen than when no rise had occurred (6 of 14 instances) table 1, AR groups 1 and 2). As others have found, the blood pressure in AR rats does not always rise above the preoperative level in the first postoperative week and, indeed, may fall.

The increase in perfusion pressure of the whole AR group is statistically significant (t = 3.07, d.f. = 23, P < 0.01), and remains significant even if the four greatest increases are disregarded.

Comparison of Blood from Rats with Unilateral Nephrectomy and Chronic Unilateral Renal Hypertension with Blood from Control Rats

In contrast with AR rats, a high proportion of CR rats (12 of 13) developed hypertension. Their mean blood pressure measured directly during the experiment was 195.8 mm. Hg, and that of the control rats used in the same experiment was 122.8 mm. Hg.

When these CR rats were used as donors 4 to 10 weeks after renal-artery constriction, the mean perfusion pressure was 37.7 mm. Hg, approximately the same as the mean of 37.4 mm. Hg obtained when C rats were used as donors. The difference between perfusion pressures using blood from CR hypertensive and blood from control rats is set out in figure 2 and table 1.

Even when the denervated, vascularly isolated hind limb of the recipient rat is perfused with blood from rats with a blood pressure of over 200 mm. Hg, there is no increase in perfusion pressure above the level observed when the same hind limb is perfused with blood from the control rat.

Comparison of Blood from Rats Bred to Develop Hypertension Spontaneously with Blood from Control Rats

When B rats are used as donors, the perfusion pressures do not differ from those obtained with blood from control animals (fig. 2, table 1). The average perfusion pressures were 46.8 mm. Hg with blood from B rats and 48.0 mm. Hg with C rat blood. Hence in rats bred to develop hypertension spontaneously, as in rats with hypertension from chronic
renal ischemia, there is no evidence to suggest presence of a circulating pressor substance in amounts detectable by the present method. It should be noted that height of the perfusion pressure depends on size of the rat hind limb. Probably, smaller recipient rats were used in this than in the preceding experiments.

**Effect of Hexamethonium on Peripheral Resistance of Hind-Limb Blood Vessels in Control and Hypertensive Rats**

**Relationship Between Preoperative Blood Pressures and Blood Pressures During Experiments Involving Surgery**

In our early attempts to distinguish between the neurogenically maintained part of peripheral vascular resistance and the part not so maintained, we used the preparation in which all connections between the perfused hind limb and the rest of the body were severed except nerves and bone. Unfortunately, the surgical procedures decreased the blood pressure from an average of 136.9 to 105.4 mm. Hg, thus precluding use of the preparation to study blood-pressure elevation. An alternative preparation was devised in which blood from one femoral artery is pumped at a constant rate into the distal end of the other femoral artery, the perfusion pressure providing an index of the hind-limb peripheral resistance.

With this milder surgical procedure under chloralose anesthesia, blood pressure of C and CR rats during experimentation was often slightly higher than pre-experimental blood pressure measured by a tail-cuff method. However, the results of our first series of experiments on B rats, though undesired, proved eventually to be of considerable interest, as they provided evidence concerning the cause of these differences in blood-pressure levels. The undesired feature was that only 9 of 25 series 1 B rats maintained blood pressures of 140 mm. Hg or more during experimentation. In later experiments (series 2, B rats) blood pressures exceeding 140 mm. Hg were obtained in 15 out of 16 instances by using only rats with consistently high pre-experimental blood pressures. The B rats in series 2 were all compared with matched C rats of equal body weight. When the nine B rats of series 1, that had experimental blood pressures of 140 mm. Hg or more, are compared with the B rats of series 2, the results correspond closely (table 2).

**Effect of Hexamethonium on Blood Pressures of Inherited Hypertensive, Chronic Renal Hypertensive, and Control Rats**

Before hexamethonium administration, the mean blood pressure of B rats (series 2) was 149.44 mm. Hg and that of C rats (series 2) was 128.56 mm. Hg. After hexamethonium, the corresponding pressures were 76.88 and 79.31 mm. Hg. Since the difference between the blood pressures of B and C rats is abolished by hexamethonium, it would appear that the rise of pressure in B rats is neurogenically maintained.

In CR rats, mean blood pressure after hexamethonium was 86.54 mm. Hg, compared with 61.77 mm. Hg for matched controls. Our impression is that in CR rats there may be some mechanism which prevents the blood pressure from falling in proportion to the decrease of perfusion pressure in the hind limb. As the blood pressures after hexamethonium were lower in the controls for CR rats than in the controls for B rats, no conclusion will be drawn pending reinvestigation.

**Relationship Between Body Weight and Perfusion Pressure**

As rats varied in weight, a constant perfusion rate of 1 ml./min. led to higher mean perfusion pressures in smaller rats.
HYPERTENSION IN RATS

The expression $C_1 - C_2$ represents the difference in hind-limb perfusion pressures when two control rats are used alternately as the sources of blood for perfusion; AR-C when acute renal hypertensives, CR-C when chronic renal hypertensives, and B-C when inherited hypertensive rats are compared with controls.

Figure 2

The expression $C_1 - C_2$ represents the difference in hind-limb perfusion pressures when two control rats are used alternately as the sources of blood for perfusion; AR-C when acute renal hypertensives, CR-C when chronic renal hypertensives, and B-C when inherited hypertensive rats are compared with controls.

In the case of CR rats the regressions were not significant, but it is logical to suppose that the perfusion pressure would be increased when the limbs of small rats are used. For this reason, the same correction was applied as for B rats.

Comparison of Innervated Hind-Limb Perfusion Pressures in Rats Bred to Develop Spontaneous Hypertension and in Chronic Renal Hypertensive and Control Normotensive Rats

It will be seen in figure 3 that in all three groups of rats (B, CR, and C) there is a close relationship between the blood pressure during experimentation and the corresponding hind-limb perfusion pressure. Experimentation reduced the blood pressure of many B rats in series 1 and of a few CR rats to nor-
Table 2

Relationship Between Pre-experimental and Experimental Blood Pressures and Hind-Limb Perfusion Pressures

<table>
<thead>
<tr>
<th>Number</th>
<th>Average blood pressure mm. Hg</th>
<th>Average hind-limb perfusion pressures (weight-corrected) mm. Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-experimental</td>
<td>Experimental</td>
</tr>
<tr>
<td>All C rats of series 1</td>
<td>51</td>
<td>111.49</td>
</tr>
<tr>
<td>All B rats of series 1</td>
<td>25</td>
<td>144.00</td>
</tr>
<tr>
<td>B rats of series 1 with experimental blood pressures of 140 mm. Hg or more</td>
<td>9</td>
<td>148.33</td>
</tr>
<tr>
<td>All B rats of series 2</td>
<td>16</td>
<td>148.19</td>
</tr>
</tbody>
</table>

Only one of 16 B rats of series 2 fell into the normotensive range. Nine of 51 C rats of series 1 and two of 16 C rats of series 2 had rises of blood pressure during experimentation which brought them into the hypertensive range (140 mm. Hg or higher). When blood pressures during experimentation of B, CR, and C rats were similar, so, on the average, were their hind-limb perfusion pressures (fig. 3).

All values for perfusion pressures in figure 3 are adjusted to a theoretical rat weight of 320 Gm., but the relationships would be similar without the corrections.

The need for correction may be avoided by pairing B and C rats of equal body weight. It will be seen in table 3 that when rats of series 2 are matched approximately for body weight, mean hind-limb perfusion pressures are greater in B rats than C rats, indicating that increase in peripheral vascular resistance must be responsible, at least in part, for the higher blood pressures encountered in B rats.

C rats matched for body weight were used as controls for the CR rats, but the experiments were not necessarily performed on the same day (table 3).

Effect of Hexamethonium Administered to a Donor Rat upon Perfusion Pressure of an Innervated but Vascularly Separated Rat Hind Limb, Constant Flow Being Maintained by a Pump

As hexamethonium was to be used to abolish nervous vasomotor tone in the perfused hind limb, it was important to know that it had no direct effect on blood vessels in our experiments.

A rat hind limb was prepared by severing all structures other than bone, femoral artery, femoral vein, and nerves (femoral and sciatic). Blood from a donor rat was pumped at constant rate (1 ml./min.) and returned from the femoral vein to the donor rat. Hence, the only effective connection between the recipient rat and its perfused hind limb was by means of the nervous system. Administration of hexamethonium bromide (5 mg.) into the top half of the recipient animal promptly decreases the perfusion pressure of its vascularly separated hind limb; no further fall is induced by nerve section. If hexamethonium bromide (5 mg.) is given intravenously to the donor rat, or even injected close to the arterial cannula of the perfused limb, there is no alteration in perfusion pressure. In 22 such experiments on 15 rats, the mean change in hind-limb perfusion pressure was +0.3 mm. Hg, which was not significant. It may be concluded that effects of hexamethonium upon the perfusion pressure are exercised entirely through the nervous connections with the upper part of the animal.

Effect of Hexamethonium on Perfusion Pressures of Inherited Hypertensive, Chronic Renal Hypertensive, and Control Rats

When large doses of hexamethonium bromide (8 mg.) are administered intravenously in the anesthetized rat, there is a considerable fall in blood pressure and hind-limb perfusion pressure. As the perfusion rate is constant, the fall in perfusion pressure reflects the degree of relaxation of blood vessels in the hind limb, and represents removal of the neurogen-
Summary of Perfusion Results

<table>
<thead>
<tr>
<th>Experiment series</th>
<th>Mean rat weight Gm.</th>
<th>No. of rats used</th>
<th>Perfusion pressure uncorrected</th>
<th>Perfusion pressure fall with Cs (uncorrected) (uncorrected)</th>
<th>Perfusion pressure after Cs (corrected to rat weight of 320 Gm.)</th>
<th>Perfusion pressure fall with Cs (corrected to rat weight of 320 Gm.)</th>
<th>Perfusion pressure after Cs (corrected to rat weight of 320 Gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (series 1)</td>
<td>349.61</td>
<td>51</td>
<td>—</td>
<td>—</td>
<td>138.87</td>
<td>82.94</td>
<td>55.08</td>
</tr>
<tr>
<td>Controls (series 2), matched for weight with B hypertensives (series 2)</td>
<td>301.00</td>
<td>16</td>
<td>144.31</td>
<td>55.50</td>
<td>139.75</td>
<td>82.01</td>
<td>57.09</td>
</tr>
<tr>
<td>Controls for CR rats (from series 1)</td>
<td>346.73</td>
<td>26</td>
<td>127.35</td>
<td>75.46</td>
<td>133.98</td>
<td>80.62</td>
<td>54.42</td>
</tr>
<tr>
<td>All controls (series 1 and 2)</td>
<td>338.21</td>
<td>67</td>
<td>—</td>
<td>—</td>
<td>137.55</td>
<td>82.72</td>
<td>55.56</td>
</tr>
<tr>
<td>B hypertensives (series 1)</td>
<td>292.28</td>
<td>25</td>
<td>—</td>
<td>—</td>
<td>140.03</td>
<td>87.10</td>
<td>53.57</td>
</tr>
<tr>
<td>B hypertensives (series 1) with blood pressures 140 mm. Hg or more</td>
<td>295.00</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>151.52</td>
<td>101.18</td>
<td>50.86</td>
</tr>
<tr>
<td>B hypertensives (series 2), matched for weight with controls (series 2)</td>
<td>265.75</td>
<td>16</td>
<td>157.75</td>
<td>99.31</td>
<td>151.42</td>
<td>95.40</td>
<td>56.42</td>
</tr>
<tr>
<td>All B hypertensives (series 1 and 2)</td>
<td>294.80</td>
<td>41</td>
<td>—</td>
<td>—</td>
<td>144.48</td>
<td>90.34</td>
<td>54.68</td>
</tr>
<tr>
<td>CR hypertensive</td>
<td>346.04</td>
<td>26</td>
<td>152.50</td>
<td>97.08</td>
<td>160.29</td>
<td>101.83</td>
<td>57.87</td>
</tr>
</tbody>
</table>

ically maintained part of the vascular tone. The residual level of perfusion pressure after hexamethonium represents the part which is not maintained by nerve impulses. Figure 4 shows a close relationship between height of the perfusion pressure and extent of the perfusion-pressure fall after hexamethonium. The relationship is the same whether we are dealing with B, CR, or C rats. In B rats, decrease of blood pressure to low levels during experimentation is usually associated with low perfusion pressures and a small fall in perfusion pressure after hexamethonium. When B rats maintain high levels of blood pressure, their hind-limb perfusion pressures are high and the falls of perfusion pressure after hexamethonium are large. CR rats usually maintain high blood pressures, and high perfusion pressures and have large falls in perfusion pressure after hexamethonium.

Figure 4 suggests that the regression lines relating perfusion pressure to perfusion-pressure fall after hexamethonium, and those relating perfusion pressure to perfusion-pressure level after hexamethonium, may be similar for C, B, and CR rats. In statistical analyses, it will be seen that the regression lines for C, B, and CR rats do not differ significantly.

The difference between the perfusion-pressure falls in pairs consisting of a B rat and a weight-matched C rat was 13.81 mm. Hg; in pairs consisting of a CR rat and a weight-matched C rat, 21.62 mm. Hg. In the case of B rats, a t-test showed the significance of the difference to be \( P < 0.05 \); in the case of CR rats, \( P < 0.001 \).

Relationship of Residual Perfusion Pressure After Hexamethonium to Perfusion Pressure Before Hexamethonium

It can be seen in figure 4 that there is a slight positive relationship between perfusion pressure before hexamethonium administration and perfusion pressure after hexamethonium. There is, however, no significant relationship between perfusion-pressure fall and perfusion pressure after hexamethonium (see next section). The higher levels of the neuro-
genically maintained component of perfusion pressure found in CR and B rats neither increase nor diminish the expectation that the component not neurogenically maintained will be high; they are substantially independent variables. There is no inconsistency between these results in the sense that while (a) the neurogenically maintained and (b) the not-neurogenically maintained parts of the perfusion pressure appear to be almost independent variables, total perfusion pressure \((a + b)\) is likely to show a relationship to both parts as seen in figure 4. In this case, \(a\) is usually larger and more variable than \(b\).

**Statistical Analysis**

Statistical analysis of all results (C rats of series 1 and 2, B rats, and CR rats) indicates that there is a highly significant regression of perfusion-pressure fall on perfusion pressure in C, B, and CR rats, holding rat weight constant; in each case, \(P < 0.001\). The three regression lines did not differ significantly from each other. It would appear, therefore, that the relationship between perfusion pressure and perfusion-pressure fall with hexamethonium is the same for C, B, and CR rats.

There is a significant regression, holding rat weight constant, of the perfusion pressure after hexamethonium on the perfusion pressure in C rats \((P < 0.001)\), B rats \((0.001 < P < 0.01)\) and CR rats \((0.00 < P < 0.01)\). Again, the regression lines did not differ significantly. These regression lines slope less steeply than those relating perfusion-pressure fall to perfusion pressure.

There is no significant regression of the perfusion pressure after hexamethonium on the perfusion-pressure fall in C, B, or CR rats, when rat weight is held constant. The partial correlation coefficients are not significant.

**Discussion**

When, after one to seven days of renal-artery constriction, the blood of AR rats is perfused by a constant-output pump through the hind limb of another rat, a vasoconstrictor substance can be detected in the circulating blood. This demonstration of the presence of a vasoconstrictor agent in blood of AR rats adds significance to the observation that hind-limb perfusion pressure is not increased by using blood from either a B or a CR rat instead of from a C rat. Hence, these experiments support the view that circulating vasoconstrictors do not contribute significantly to elevation of peripheral resistance either in the B or in the CR rat.

Our observations also concern the extent to which hexamethonium reduces blood pressure and peripheral resistance of an innervated hind limb in B, CR, and C rats. For these experiments, we used a constant-output pump to perfuse a rat hind limb through its femoral artery with blood taken from the opposite femoral artery. The preparation takes advantage of our previous observation that
perfusion pressure of a vascularly isolated hind limb was unaffected by having a CR or B rat as donor instead of a C rat. Hence, we were led to believe that any differences in perfusion pressures in this preparation could not be attributed to differences between the bloods of B, CR, or C rats considered as perfusion media. An additional justification for perfusing the hind limb with the rat’s own blood comes from our demonstration that perfusion pressure is not altered by addition of hexamethonium to donor blood which is perfused through the innervated but vascularly isolated hind limb of a recipient rat. The preparation has the advantage that blood pressures of CR and C rats do not fall below their pre-experimental levels during experimentation, and that many B rats also maintain high blood pressures during experimentation.

The fall in perfusion pressure after administration of hexamethonium is a measure of the neurogenically maintained component of the hind-limb peripheral vascular resistance. Increased peripheral resistance of neurogenic origin was observed in both B and CR rats, but the results obtained do not warrant the conclusion that elevation of blood pressure in B and CR rats is of similar pathogenesis, or that it results from increase in the amount of nervous stimulation of blood vessels. The same amount of nervous stimulation may be associated with a larger release of noradrenaline at sympathetic endings, or the smooth muscle of blood vessels may be more reactive to nervous stimulation, or there may be some alteration in the structure of blood vessels so that equal contractions of smooth muscle lead to larger changes in peripheral resistance in B and CR rats than in C rats. In B and CR rats increased peripheral resistance is neurogenically maintained because, after hexamethonium, the peripheral vascular resistances fall to approximately the same average level in B, CR, and C rats. Hexamethonium in the dose used (8 mg.) induces complete chemical denervation, as no further fall in peripheral resistance occurs when the femoral and sciatic nerves, previously isolated, are cut.

Summary
A preparation is described in which blood is taken alternately from a pair of donor rats and perfused at constant rate through the same vascularly isolated, denervated recipient rat hind limb. The preparation, though sensitive to the vasoconstrictor agent released in acute renal hypertension, fails to detect any vasoconstrictor substance either in the blood of rats bred to develop hypertension spontaneously or in the blood of rats with chronic renal hypertension.

To study nervous tone in limb blood vessels, an innervated rat hind limb was perfused through a femoral artery with blood taken from the opposite femoral artery. After administration of hexamethonium, weight-corrected hind-limb perfusion pressures of spontaneous hypertensive (B), chronic renal hypertensive (CR), and control (C) rats (all series included) fall to the same average level. Hence, the component of the hind-limb peripheral resistance which is not neurogenically maintained must be of the same order of magnitude in all three groups. In B, CR, and C rats, the perfusion pressure falls after hexamethonium; all have the same relationship to the height of the blood pressure at the time the perfusion pressure is measured, high blood pressures being associated with high perfusion pressures and low blood pressures with low perfusion pressures. Therefore, since the differences between the hind-limb peripheral resistances of B, CR, and C rats, as measured by the perfusion pressure, are removed by administration of hexamethonium, it follows that they depend upon differences in the neurogenically maintained component of the peripheral resistance. After hexamethonium the blood pressures of B and C rats fall to the same average level.

Acknowledgment
The authors are indebted to Dr. A. M. O. Veale and Mr. G. F. Spears for statistical advice. The work was carried out with the assistance of the Life Insurance Research Fund of Australia and New Zealand.
References

Observations on the Pathogenesis of Spontaneous Inherited Hypertension and Constricted Renal-Artery Hypertension in Rats
RICHARD LAVERTY and F. HORACE SMIRK

doi: 10.1161/01.RES.9.2.455
*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1961 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/9/2/455

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation Research* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation Research* is online at:
http://circres.ahajournals.org/subscriptions/