TABLE 1

Differences in Blood Pressure, Age, Weight, Renin Substrate, and Serum Renin Activity in Normotensive Wistar and Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th></th>
<th>Group 1: matched by weight</th>
<th>Group 2: matched by age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive Wistar</td>
<td>Spontaneously hypertensive</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>117.5 ± 5.1 (14)</td>
<td>155.5 ± 7.5 (14)*</td>
</tr>
<tr>
<td>Age (weeks)</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>135.8 ± 2.3 (14)</td>
<td>143.7 ± 4.2 (14)</td>
</tr>
<tr>
<td>Renin Substrate (ng angiotensin I/ml)</td>
<td>1247 ± 66 (14)</td>
<td>1506 ± 89 (14)*</td>
</tr>
<tr>
<td>Serum renin activity (ng angiotensin I/ml hour⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unanesthetized</td>
<td>3.76 ± 0.80 (7)</td>
<td>3.01 ± 0.70 (7)</td>
</tr>
<tr>
<td>Anesthetized</td>
<td>6.16 ± 0.84 (7)</td>
<td>15.97 ± 2.18 (7)*</td>
</tr>
</tbody>
</table>

Each value represents the mean ± SE for the number of rats given in parentheses.

*P < 0.01 compared with normotensive Wistar rats in the same group.
†P < 0.05 compared with normotensive Wistar rats in the same group.

They killed by sodium thiopental anesthesia. Careful inspection of the methods of Bozovic and Efendic reveals that they administered blows to the heads of the unanesthetized rats to stimulate renin release before decapitation and were, in fact, studying the effects on renin release of increased sympathetic activity induced by this painful stress. When the levels of serum renin activity measured in our studies (Table 1) are compared with those of Sen et al., the data reveal that the serum renin activity in our unanesthetized rats killed by decapitation (1.82–3.76 ng angiotensin I/ml hour⁻¹) is about one tenth that of Sen et al. (13.0–48.6 ng angiotensin I/ml hour⁻¹), who employed anesthesia. Incidentally, the absolute values (Table 1) for serum renin activity in our anesthetized spontaneously hypertensive rats are similar in magnitude to those of Sen et al. even though different anesthetic agents were used.

In conclusion, the use of anesthesia in the rat has plagued the investigative area of renin, angiotensin, and aldosterone for many years, resulting in unique properties being attributed to the rat (Am J Physiol 216:1476–1480, 1969; Am J Physiol 208:1026–1030, 1965; Endocrinology 76:657–664, 1965). These misleading conclusions have been discovered only by the use of unanesthetized rats (Am J Physiol 221:1071–1074, 1971; Science 184:994–996, 1974). Similarly, an elevated serum renin activity in young spontaneously hypertensive rats appears to be an artifact of anesthesia or of equating weight and age when comparing spontaneously hypertensive and normotensive Wistar rats.

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REPLY TO THE ABOVE LETTER

There are several points to be considered in the comments of Dr. Campbell on renin in the spontaneously hypertensive rat. First, Dr. Campbell and Dr. Pettinger are reporting data from 3-week-old normal Wistar rats which weighed 135.8 ± 2.3 g and 5-week-old normal Wistar rats which weighed 173.4 ± 4.7 g. These weights are very surprising unless they have special rats or special conditions of feeding, etc. In my experience, normal rats 3 weeks of age weigh about 50 g. This weight agrees with the observations of other investigators (Circ Res 30:106, 1972, Table 1; Spontaneous Hypertension, 1972, p168, Fig. 2). Normal rats do not reach 135 g in weight until they are approximately 7 weeks of age (Circ Res 30:341–349, 1972), and the literature provided by suppliers of the normal Wistar rat (Carworth, Sprague-Dawley) show the same rates of growth. This point raises a serious question about the age of the normal Wistar rats used by Dr. Campbell and Dr. Pettinger. Second, the conclusion that it...
LETTERS TO THE EDITOR

TABLE 2
Serum Renin Activity Data from Pettinger et al.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (weeks)</th>
<th>Spontaneously hypertensive rats</th>
<th>Normal Wistar rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td></td>
<td>376.0</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>134.4 ± 4.2</td>
<td>129.0 ± 5.1</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>287 ± 60*</td>
<td>182 ± 40</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>140 ± 20</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>301 ± 70</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>124.2 ± 13.9</td>
<td>112.8 ± 16.8</td>
</tr>
</tbody>
</table>


*P < 0.025 compared with value in 3-week-old spontaneously hypertensive rats.

is not valid to equate age with weight in spontaneously hypertensive and Wistar rats does not agree with my experience that spontaneously hypertensive rats and American Wistar rats do not differ in weight during the first 7–8 weeks of life. Other investigators agree with my experience on this point (Circ Res 24:85–91, 1969). After 8 weeks of age, the growth rate of the spontaneously hypertensive rat slows compared with that of the normal American Wistar rat. However, compared with the Kyoto-Wistar rate, the growth rate of the spontaneously hypertensive rat remains the same. Thus, in the age range of 3 to 7 weeks, weight matching is valid.

Third, I am confused by the conclusion of Dr. Campbell and Dr. Pettinger that serum renin activity does not change with age in unanesthetized rats, for their published data coupled with the data presented in the preceding letter (Table 2) seem to show that serum renin activity changes with age in both spontaneously hypertensive and normal Wistar rats. The latter conclusion is not supported by the observations of my group or the observations of others and raises a question about the validity of the method used to determine the serum renin activity in these experiments.

Regarding the method for determination of serum renin activity, I would like to make two comments: (1) these authors incubated serum for 16–24 hours without adding exoge-}

uous substrate and did not demonstrate that substrate remained in excess during that entire period, and (2) they did not use angiotensinase inhibitors during incubation.

Incidentally, De Jong et al. (Proc Soc Exp Biol Med 139:1213–1216, 1972) have also shown an increased plasma renin activity in unanesthetized, decapitated spontaneously hypertensive rats. I have no comments on Dr. Campbell's speculation that spontaneously hypertensive rats are more prone to release renin under anesthesia than are normotensive rats, since I have no data on unanesthetized rats. However, before accepting this theory, further experimentation is required.

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Potassium Canrenoate and Digitalis Intoxication

Reply to the Above Letter
Subha Sen

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