Studies on Renin

II. CONTINUOUS INFUSION OF HOMOLOGOUS RENIN AT VERY LOW RATES IN INTACT OR NEPHRECTOMIZED, CONSCIOUS OR ANESTHETIZED DOGS

By Harry Goldblatt, Erwin Haas, and Robert Haas

ABSTRACT

We have devised a method of evaluation, in terms of Goldblatt units (GU), of the data obtained in various laboratories for the excretion of renin from canine and human kidneys. An average value of $1.3 \times 10^{-4}$ GU/min g$^{-1}$ normal renal tissue resulted for both dog and man. A blood pressure increase of 18–45 mm Hg was induced in normal or nephrectomized, conscious or anesthetized dogs by the continuous infusion of homologous renin at even lower rates ($0.25–0.50 \times 10^{-4}$ GU/min g$^{-1}$ renal tissue), i.e., at 20–40% of the rate excreted by the kidney. This suggests that renin, even at its normal rate of excretion from the kidney, participates in the maintenance of normal blood pressure. The increase of blood pressure and of concentration of renin in the dog’s blood was measured at infusion rates ($C$) of 0.0042, 0.0083, 0.0167, 0.0333, and 0.0667 GU/min. At each rate, after a fixed period of infusion ($t = 60$ minutes), a constant fraction (54% of the infused renin) was retained in the circulation. From this and the results of infusion experiments carried out for 30, 60, and 120 minutes, the total amount of exogenous renin, $R$, present in the circulation at time $t$ can be expressed as

$$R = \frac{C}{K} (1 - e^{-Kt}),$$

where $K = 0.0232$ minutes$^{-1}$ and represents the fraction of exogenous and, presumably, also endogenous renin that is being eliminated from the circulation of the normal dog per minute. Thus, the time required for removal of 50% of the renin from the blood is $t_{50} = \log_{e} 2/K = 30$ minutes.

KEY WORDS: excretion of renin, canine and human kidneys, evaluation in Goldblatt units, maintenance of normal blood pressure, efficiency of infused renin, retention of renin.

Renin is released continuously at low rates into the blood stream from the kidneys of normal dogs (1–4) and in greater amounts from the ischemic kidneys of dogs with experimental renal hypertension (3, 4). Renin is no longer detected in the dog’s plasma 1–2 days after bilateral nephrectomy (5, 6).

There have been many studies on the effect of single injections or of infusion of renin on the blood pressure, on the level of plasma renin, and on the rate of disappearance of renin from the blood. In most of these studies, heterologous (hog) renin (7–9) or homologous dog renin of low purity (10, 11) has been employed.

Some of these previous studies were carried out in nephrectomized, anesthetized and heparinized dogs (10, 12). It is known, however, that the blood pressure response of dogs to renin is enhanced after bilateral nephrectomy (13) and that there is a delay in the disappearance of injected renin (7), indicating that the kidney plays a part in the elimination of renin from the body. It is known, also, that dogs anesthetized with pentobarbital have a higher concentration of renin in their plasma (2, 14), but the blood...
INFUSION OF HOMOLOGOUS RENIN

pressure response of anesthetized dogs to the injection of single doses of renin is about a third of the normal response (8). Sealey et al. (15) have observed, furthermore, that heparin, in concentrations commonly used in the collection of plasma samples, reduced significantly the enzymatic activity of renin. In some of the previous studies (10, 12), unphysiologically large amounts (3-28 GU) of dog renin were infused rapidly; this procedure does not reflect the continuous slow release of renin by the kidney (1, 3).

A direct relationship between changes in blood pressure and plasma renin concentration has been established by Bianchi et al. (11) by intravenous infusion of exogenous homologous renin in conscious dogs. More recently (4), these authors showed that the linear regression between the increase of blood pressure and plasma renin concentration during the infusion of exogenous renin in conscious dogs was not statistically different from that during the secretion of endogenous renin observed within 2 hours after the production of renal ischemia.

Our previous studies have dealt with the pressor effect of continuous intravenous infusion of renin (9) or of the injection of single relatively large doses of renin. The amount which produced an increase of 30 mm Hg of the mean direct systemic arterial blood pressure in 2 minutes in the intact unanesthetized dog was arbitrarily designated a “dog unit” (16). This is being referred to now, generally (17), as a “Goldblatt unit” (GU) of renin. Expressed as an absolute quantity, 1 GU represents only approximately 1 µg of the purest renin presently available (18), yet based on its enzymatic activity this represents a relatively large dose.

The smallest amount of renin used in the present study was designed to simulate the presumably continuous release of endogenous renin in small quantities, 0.010-0.011 GU/min (1, 3), into the renal veins by the two kidneys of a normal dog.

The increase of the blood pressure in normal unanesthetized dogs that were not given heparin was measured, and the concentration of renin in the serum was determined prior to and after the continuous intravenous infusion of dog renin at various low rates.
(0.004–0.067 GU/min) and for various periods (30–120 minutes). The effect of anesthesia, heparinization, and nephrectomy on the blood pressure of the dog and on its response to small quantities of infused renin was likewise investigated.

The results of this study, which reveal an extraordinary efficiency of the continuous infusion of renin in minute amounts, are amenable to a mathematical analysis.

Methods

The methods for the preparation of dog renin (specific activity = 1.3 GU/mg protein) and for the assay of renin in the dog's blood have been described (19).

The plasma volume of the dogs was determined by using radioiodinated (131I) human serum albumin. This tracer (5 μc) was injected intravenously (saphenous), blood was withdrawn from the femoral artery after 10 minutes, and the radioactivity in the plasma was measured. In seven normal dogs, the average plasma volume was 44 ml/kg body weight.

### Table 1

<table>
<thead>
<tr>
<th>Dog</th>
<th>Rate of Infusion (GU/min)</th>
<th>Increase of Blood Pressure (mm Hg)</th>
<th>Concentration of Renin in Serum (GU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Individual Average</td>
<td>Calculated Found</td>
</tr>
<tr>
<td>1</td>
<td>0.0042</td>
<td>18</td>
<td>3.0 x 10^-4</td>
</tr>
<tr>
<td>2</td>
<td>0.0042</td>
<td>13 15</td>
<td>3.4 x 10^-4</td>
</tr>
<tr>
<td>3</td>
<td>0.0042</td>
<td>15</td>
<td>3.9 x 10^-4</td>
</tr>
<tr>
<td>4</td>
<td>0.0083</td>
<td>20</td>
<td>8.2 x 10^-4</td>
</tr>
<tr>
<td>5</td>
<td>0.0083</td>
<td>15 19</td>
<td>8.4 x 10^-4</td>
</tr>
<tr>
<td>6</td>
<td>0.0033</td>
<td>23</td>
<td>8.4 x 10^-4</td>
</tr>
<tr>
<td>7</td>
<td>0.0167</td>
<td>30</td>
<td>16 x 10^-4</td>
</tr>
<tr>
<td>8</td>
<td>0.0167</td>
<td>25 28</td>
<td>12 x 10^-4</td>
</tr>
<tr>
<td>9</td>
<td>0.0167</td>
<td>30</td>
<td>18 x 10^-4</td>
</tr>
<tr>
<td>10</td>
<td>0.0333</td>
<td>40</td>
<td>32 x 10^-4</td>
</tr>
<tr>
<td>11</td>
<td>0.0333</td>
<td>33 34</td>
<td>24 x 10^-4</td>
</tr>
<tr>
<td>12</td>
<td>0.0333</td>
<td>30</td>
<td>32 x 10^-4</td>
</tr>
<tr>
<td>13</td>
<td>0.0667</td>
<td>35</td>
<td>48 x 10^-4</td>
</tr>
<tr>
<td>14</td>
<td>0.0667</td>
<td>45 39</td>
<td>53 x 10^-4</td>
</tr>
<tr>
<td>15</td>
<td>0.0667</td>
<td>38</td>
<td>63 x 10^-4</td>
</tr>
</tbody>
</table>

Average retention of infused renin in 15 experiments was 54%.

CONTROL SALINE INFUSION EXPERIMENTS

NaCl solution (0.9% w/v, 0.67 ml/min for 60 minutes, iv) infused into an intact conscious dog (Table 1, Fig. 1) had no significant effect on blood pressure or serum renin concentration. Blood pressure of an anesthetized, heparinized intact dog or of an anesthetized, heparinized bilaterally nephrectomized dog was similarly unaffected (Fig. 2).

RENIN INFUSION EXPERIMENTS

Femoral arterial blood samples (15 ml) for the assay of serum renin were taken immediately before and at the end of the infusion of the renin (Tables 1 and 2). The renin was diluted in 0.9% NaCl solution to concentrations ranging between 0.0031 GU/ml and 0.100 GU/ml and infused intravenously (saphenous) at a uniform rate of 0.67 ml/min. This corresponds to infusion rates between 0.0021 units renin/min and 0.0667 units renin/min (Figs. 1, 2 and Tables 1, 2, 3).

Results

CHANGES IN BLOOD PRESSURE AND SERUM RENIN

Control mean systemic arterial blood pressure averaged 114 mm Hg (range 90 mm Hg...
to 132 mm Hg) in 31 experiments in conscious intact dogs. It was unchanged in the intact dog (Table 3, expts. 1, 2) or in the bilaterally nephrectomized dog (Table 3, expts. 5, 6) as the result of anesthesia with sodium pentobarbital (17-26 mg/kg) and heparinization (sodium heparin 34 USP units/min). The infusion of renin, even at the slow rates shown in Figures 1 and 2 and Tables 1, 2, and 3, raised the blood pressure in every dog.

Figure 1 shows that the blood pressure was increased significantly, even at a very low rate of infusion of renin (0.0042 GU/min). Furthermore, a plateau was reached after 30-40 minutes of continuous infusion at each of the five rates investigated.

The concentration of renin in serum, as measured by the bioassay procedure of the preceding study (19) was low (0.2 x 10^-1 to 0.5 x 10^-4 GU/ml) in the control period before the renin infusion, and it increased in each animal during the infusion of renin (Table 1).

The calculated concentration of renin (3 x 10^-4 to 63 x 10^-4 GU/ml) shown in Table 1 was determined by adding the endogenous renin (approximately 0.03 GU) to the amount of renin (0.25-4.0 GU) which had been infused into the individual dog and dividing the total by the previously determined plasma volume of the dog.

In this calculation we have not taken into account the possibility that the endogenous renin (0.2-0.5 x 10^-4 GU/ml) may be suppressed by the infusion of the exogenous renin (3.0-63.0 x 10^-4 GU/ml). However, because of the low concentration of endogenous renin, such a possible error would be negligible, especially at the higher rates of infusion.

After an infusion period of 60 minutes (Table 1), a remarkably constant fraction of the renin, 54% on the average, was retained in the circulation, even though in the 15 experiments shown: (1) the rate of infusion had been varied 16-fold (from 0.0042 GU/min to 0.0667 GU/min) and (2) the actual serum level of renin had been increased from approximately 4-fold in dog 4 (0.5-> 1.9 x 10^-4 GU/ml) to 175-fold in dog 3 (0.2-> 35 x 10^-4 GU/ml). A similar retention (49%) was obtained also with highly purified hog renin (specific activity = 123 GU/mg) after infusion for 60 minutes at a rate of 0.0167 GU/min.

This suggests that for any given period and a wide range of renin concentrations the fraction of the total amount of renin that is removed is a constant (K), independent of the concentration of renin.

### TABLE 2

<table>
<thead>
<tr>
<th>Infusion of renin</th>
<th>t (min)</th>
<th>C (GU/min)</th>
<th>C x t (GU)</th>
<th>Endogenous renin (GU)</th>
<th>Residual renin found (GU)</th>
<th>Retention of renin Found (%)</th>
<th>Retention of renin Calculated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60</td>
<td>0.0042</td>
<td>0.25</td>
<td>0.03</td>
<td>0.14</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.0083</td>
<td>0.50</td>
<td>0.03</td>
<td>0.30</td>
<td>56</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.0167</td>
<td>1.00</td>
<td>0.03</td>
<td>0.51</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.0333</td>
<td>2.00</td>
<td>0.03</td>
<td>1.10</td>
<td>54</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.0667</td>
<td>4.00</td>
<td>0.03</td>
<td>2.48</td>
<td>61</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>0.0167</td>
<td>0.50</td>
<td>0.03</td>
<td>0.36</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.0167</td>
<td>1.00</td>
<td>0.03</td>
<td>0.51</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>0.0167</td>
<td>2.00</td>
<td>0.03</td>
<td>0.65</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>0.0167</td>
<td>4.00</td>
<td>0.03</td>
<td>1.88</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>480</td>
<td>0.0167</td>
<td>8.00</td>
<td>0.03</td>
<td>3.72</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

**t = duration of renin infusion, C = rate of renin infusion, C x t = amount of renin infused.**

The experimental retention of renin is the residual renin divided by total renin. The calculated retention of renin is R divided by total renin, where R = C/K (1 - e^-Kt) units for K = 0.0232 minutes^-1.
By subjecting the results in Tables 1 and 2 to a mathematical analysis (see Appendix) we obtained a uniform value of $K = 0.0232$ minutes$^{-1}$ for the serum of conscious intact dogs under various experimental conditions. These include the continuous infusion of homologous renin at rates varying between 0.0667 GU/min and 0.0042 GU/min (Table 1) for periods of 30-120 minutes (Table 2) and also the rapid (15-second) injection of a single relatively large dose (1 GU) of dog renin. From this value of $K$ (0.0232 minutes$^{-1}$), we have calculated that 30 minutes was required uniformly for the removal of 50% of the renin: there is a considerable capacity to retain renin in the circulation.

$$t_{50} = \frac{0.693}{K} = \frac{0.693}{0.0232} = 30 \text{ minutes.}$$

After the injection of a very large dose (250 GU) of hog renin (8), however, we observed that the renin had disappeared more rapidly from the circulation (50% within 10 minutes), and that after 1 hour by our method less than 3% remained in the blood. With such a large dose of renin, the capacity for its retention in the circulation apparently had been exceeded, but less than 2% was excreted in the urine collected by catheterization during the 1- and 4-hour periods after the injection (8).

An improved method for the estimation of renin in human urine has shown (20) that this enzyme is excreted into the urine in very small amounts, a mean of 1200 Skinner units (0.008 GU) in 24 hours.\(^1\)

### EFFECT OF ANESTHESIA AND HEPARINIZATION ON THE PRESSOR RESPONSE TO RENIN

The continuous infusion of dog renin at a rate of 0.0042 units/min induced identical pressor effects (18 mm Hg in 40 minutes) in a dog, whether conscious or anesthetized and heparinized (Table 3, expts. 1, 2).

In contrast, the rapid injection of a single relatively large dose (1 GU) of renin under anesthesia gives only a third of the pressor response induced in the conscious dog (8).

### EFFECT OF BILATERAL NEPHRECTOMY ON THE BLOOD PRESSURE RESPONSE TO RENIN

After bilateral nephrectomy (48-72 hours) (Fig. 2 and Table 3), the infusion of renin at a very low rate, 0.0021 GU/min $(0.26 \times 10^{-4}$ GU/min g$^{-1}$ kidney), induced a significant elevation of the blood pressure—28 mm Hg in the conscious dog (Table 3, exp. 5) or 28-33 mm Hg under anesthesia (Table 3, expts. 6, 7). Therefore, nephrectomy enhanced the responsiveness of the dog to renin more than threefold. This rate of infusion of exogenous renin represents only 20% of the rate at which endogenous renin is being released $(1.3 \times 10^{-4}$ GU/min g$^{-1}$ kidney) by the normal kidneys (Table 4, refs. 1, 3).

### ENDOGENOUS SECRETION OF RENIN

The rate of release of renin by the kidney, i.e., the net rate at which renin is added to the

\[^1\]Dr. S. L. Skinner, University of Adelaide, South Australia has established that 1 GU = $1.54 \times 10^5$ Skinner units (personal communication).

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### TABLE 3

**Effect of Anesthesia and Bilateral Nephrectomy on the Pressor Response to Infused Dog Renin**

<table>
<thead>
<tr>
<th>Expt.</th>
<th>Dog</th>
<th>Bilateral nephrectomy (hours)</th>
<th>Pentobarbital</th>
<th>Heparin</th>
<th>Blood pressure (mm Hg)</th>
<th>Infusion of dog renin (units/min)</th>
<th>Increase of blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>0.0042</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>0.0042</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>48</td>
<td>+</td>
<td>+</td>
<td>90</td>
<td>0.0021</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>48</td>
<td>+</td>
<td>+</td>
<td>90</td>
<td>0.0042</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>48</td>
<td></td>
<td></td>
<td>120</td>
<td>0.0021</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>51</td>
<td>+</td>
<td>+</td>
<td>133</td>
<td>0.0021</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>72</td>
<td>+</td>
<td>+</td>
<td>128</td>
<td>0.0021</td>
<td>33</td>
</tr>
</tbody>
</table>

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Blood pressure response to continuous infusion of minute amounts of dog renin 72 hours after bilateral nephrectomy. Anesthesia: sodium pentobarbital, single dose of 17 mg/kg. Anticoagulant: sodium heparin, continuously infused at 34 USP units/min. (o) = infusion of saline; (•) = infusion of saline + 0.0021 units dog renin/min.

FIGURE 2

Blood pressure during its circulation through a kidney, has been determined by various investigators. These values are shown in Table 4 for anesthetized dogs, normotensive subjects, patients with benign uncomplicated essential hypertension (vascular grade 0), and patients with accelerated hypertension (vascular lesions in the kidney grade IV).

The various techniques used measured either the “concentration” of renin (Hosie et al. [3]) or the “activity” of renin (1, 21-23). The incubation times varied from 0.5-24 hours, and there were other technical differences such as pH, ionic strength, protein concentration during incubation, and differences in source and amount of substrate.

The values for the rate of renin secretion by one kidney or per gram of perfused kidney, as reported by various investigators, are shown in Table 4. Clearly, because of the differences in the assay procedures, these values are not suitable for a direct comparison of the results from the various laboratories, and they cannot be compared with the results of the infusion of exogenous renin in the present study.

To effect such a comparison, we have recalculated these values in terms of a common international standard unit of renin, the Goldblatt unit (Table 4). In the preceding investigation (19), we have tested the validity of our method of recalculation. To recalculate the results obtained by Hosie et al. (3) the

<table>
<thead>
<tr>
<th>Reference</th>
<th>Species</th>
<th>Blood pressure</th>
<th>Assay of plasma renin (hour)</th>
<th>Rate of renin secretion, mean value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosie et al. (3)</td>
<td>Dog</td>
<td>Normal</td>
<td>24</td>
<td>0.62 units/min × kidney * 1.4 × 10^-4</td>
</tr>
<tr>
<td>Vander and Miller (1)</td>
<td>Dog</td>
<td>Normal</td>
<td>0.5</td>
<td>96 ng/min × kidney † 1.2 × 10^-4</td>
</tr>
<tr>
<td>Kaneko et al. (21)</td>
<td>Human</td>
<td>Normal</td>
<td>24</td>
<td>1640 ng/min × kidney</td>
</tr>
<tr>
<td>Kaneko et al. (22)</td>
<td>Human</td>
<td>Benign essential hypertension</td>
<td>24</td>
<td>1220 ng/min × kidney</td>
</tr>
<tr>
<td>Hollenberg et al. (23)</td>
<td>Human</td>
<td>Benign essential hypertension</td>
<td>3</td>
<td>1.1 ng/min × g kidney † 0.7 × 10^-4</td>
</tr>
<tr>
<td>Hollenberg et al. (23)</td>
<td>Human</td>
<td>Malignant hypertension</td>
<td>3</td>
<td>13.5 ng/min × g kidney</td>
</tr>
</tbody>
</table>

*Reported as renin concentration in terms of Glasgow units.
†Reported as renin activity in terms of nanograms of angiotensin.

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exact equivalence of 1 Goldblatt unit = 112 Glasgow units was used (19). The following method of recalculation was employed for a dog kidney weighing 40 g: rate of renin secretion (Table 4, Hosie et al. [3]) = 0.62/(112 X 40) = 1.4 X 10^-4 GU/min g^-1 kidney.

We have previously reviewed 17 of the published methods for the assay of renin in blood (24), and in the procedures employed by Vander and Miller (1), Kaneko et al. (21, 22), and Hollenberg et al. (23) (Table 4) the rate of angiotensin formation was 4.0, 0.27, and 0.50 ng/ml serum hour^-1, respectively.

The following is an example of the method of recalculation as applied to the results of Vander and Miller (1) for a dog kidney weighing 40 g: rate of renin secretion = 96 X 10^-7 (0.5 X 4.0 X 40) = 1.2 X 10^-4 GU/min g^-1 kidney.

In summary (Table 4) the net renin secretion rate was approximately 1.3 X 10^-4 GU/min g^-1 (perfused kidney) in normal dogs, normotensive human subjects, and patients with benign uncomplicated essential hypertension. The rate of renin secretion was significantly elevated (9.0 X 10^-4 GU/min g^-1 kidney) in patients with accelerated or malignant hypertension.

Discussion
In the present study, the lowest rate of infusion of exogenous dog renin in normal intact unanesthetized dogs was 0.0042 GU/min, i.e., 0.0042 X 1/80 = 0.5 X 10^-4 GU/min g^-1 dog kidney. This corresponds to approximately 40% of the secretion rate of normal dog kidneys, yet it resulted in an appreciable elevation of the mean arterial blood pressure (Tables 1, 3 and Fig. 1).

In bilaterally nephrectomized dogs (Table 3 and Fig. 2) the infusion of renin at an even lower rate, 0.0021 GU/min (0.26 X 10^-4 GU/min g^-1 kidney), i.e., a fifth of the rate at which endogenous renin is normally excreted by the kidney, was sufficient to induce a significant elevation of blood pressure.

The rate of renin secretion was remarkably similar for normal human and dog kidneys, 1.3 X 10^-4 GU/min g^-1 (Table 4). This rate of secretion apparently is not a function of the total concentration of renin in normal kidney tissue. Human renal tissue contains 0.12 GU renin/g compared to 1.8 GU renin/g in dog renal tissue (25). Thus, only 0.007% of the total renin in dog kidneys is released per minute compared to 0.11% for human renal tissue.

Appendix
MATHEMATICAL EVALUATION
We designate t = time of infusion (minutes), R = total amount of renin present in the blood at time t (GU), C = rate of infusion of renin (GU/min), K = fraction of the total amount of renin removed (minutes^-1), and t_50 = time required for removal of 50% of the renin from the blood.

It follows that

\[ K \times R = \text{rate of removal of renin (GU/min)}, \]
\[ C \times t = \text{total amount of renin infused (GU)}, \]
\[ \frac{dR}{dt} = C - KR. \]  \hspace{1cm} (1)

In the integrated form

\[ R = \frac{C}{K} (1 - e^{-Kt}). \]  \hspace{1cm} (2)

The constant K in Eq. 2 has been calculated as follows from the experimental results of Table 1, i.e., from the retention of renin (average = 54%), at t = 60 minutes and for values of C ranging between 0.0667 GU/min and 0.0042 GU/min. Under these conditions \[ R = 60 \times 0.54 \times C. \]  \hspace{1cm} (3)

Substituting these values for R and t in Eq. 2 we obtain

\[ 32.4 = \frac{1}{K} (1 - e^{-0.0}K). \]  \hspace{1cm} (4)

And K = 0.0232 minutes^-1.

With the same procedure, but calculated from the retention of renin in each of the 15 experiments of Table 1, we obtained a similar value, \[ K = 0.0238 \pm 0.00186 \text{ (se) minutes^-1,} \] for the fraction of the total amount of renin removed.

The validity of Eq. 2, using \[ K = 0.0232 \text{ minutes^-1,} \] has been tested (Table 2) by calculating the percent recovery of renin for various values of C and t. There was good agreement between the experimentally determined recovery and the calculated values (Table 2) for rates of infusion varying between 0.0667
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GU/min and 0.0042 GU/min and for periods of infusion from 30 to 120 minutes.

The validity of our experimental and mathematical procedures for the determination of the constant $K = 0.0232$ minutes$^{-1}$ was tested further under a considerably different set of experimental conditions, i.e., by a rapid (15-second) injection of a single relatively large dose ($R_0 = 1$ GU) of renin. After 60 minutes, 25% of the original dose ($R = 0.25$ GU) was recovered in the dog's serum. Under these conditions the following equations applied.

$$\frac{dR}{dt} = K \cdot R,$$

and integrating

$$K = \frac{1}{t} \cdot \log_e \frac{R_0}{R}.$$

Therefore, $K = \frac{1}{60} \cdot \log_e \frac{1.00}{0.25} = 0.0231$ minutes$^{-1}$.

Thus, a uniform value of $K$ was obtained under a variety of experimental and mathematical procedures.

From this value we have calculated (Eq. 7) the time required for the disappearance of 50% of the renin from the blood.

$$t_{50} = \frac{\log_2 \frac{1}{2}}{K} = 0.693 \times \frac{1}{0.0232} = 30$$ minutes.

For large values of $t$, e.g., 120 and 240 minutes, the exponential term in Eq. 2 becomes insignificant, 0.06 and 0.004, respectively, and it can be neglected. After such prolonged infusion, the total amount of renin present ($R$) approaches a steady state (at which the rate of removal is equal to the rate of infusion); the amount of renin present is directly proportional to the rate of renin infusion ($C$) and independent of the total amount of renin infused.

$$R = \frac{C}{0.0232}.$$

The recovery of renin after long periods of infusion approaches zero (Eq. 9 and Table 2).

Percent recovery of renin = $\frac{100}{0.0232} \times \frac{1}{t}$. 

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