Further Observations on the Potentiation of Postnephrectomy Hypertension of the Dog by Dietary Protein

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An assay procedure for the evaluation of dietary factors in renoprival hypertension over a short period is described. By means of this procedure dietary protein was found to potentiate renoprival hypertension of the dog. In the absence of dietary protein 2.5 mEq. sodium per kilogram per day was attended by a slight but significant elevation in the arterial pressure. The same level of hypertension was observed with fluid and sodium loading alone, dietary protein plus a lesser sodium intake, and dietary protein plus a greater sodium intake.

The relationship of dietary protein to hypertensive cardiovascular disease has been of interest for some time. Handler and Bernheim reviewed this subject and demonstrated a potentiation of experimental renal hypertension by dietary protein. It is now established that the removal of both kidneys of experimental animals under certain conditions is associated with a high incidence of hypertensive cardiovascular disease. Two conditions have been found to aggravate renoprival hypertension, namely, prolonged survival made possible by in vivo dialysis and a high intake of sodium salts and water in short-term experiments. Later it was demonstrated that an intake of sodium salts in high concentration without overt hydration also aggravates renoprival hypertension. Thus sodium appears to be a major factor in potentiating hypertension in the absence of kidneys.

Earlier observations from this laboratory suggested a potentiating influence of dietary protein on the hypertension following nephrectomy in dogs. Kolff and Page reported similar findings in rats but they observed only a slight increase in the severity of renoprival hypertension of the dog as a consequence of a high protein diet. Thus the role of dietary protein on renoprival hypertension of the dog remains unsettled. We wish to present additional data on this question.

During the past 5 years the relationship of dietary protein to renoprival hypertension of the dog has been studied in this laboratory. These experiments have utilized a single assay procedure in which variables other than dietary protein have been controlled. These variables include the caloric intake, the water intake, the sodium intake, and in vivo dialysis. This report reviews the data from 102 nephrectomized dogs (55 receiving protein and 47 controls). The material represents an expansion of that previously published as an abstract.

Methods

Trained mongrel dogs of both sexes were used. Mean arterial pressure was measured once or twice daily by means of direct femoral artery puncture (19 gauge needle) and a mercury manometer. This was done in the intact animals for 4 to 7 days before nephrectomy. During this preliminary period the animal was fed Purina dog food and water ad libitum. The control mean arterial pressure for all animals varied between 95 and 135 mm. Hg.

The kidneys were removed during ether anesthesia. In the first 28 dogs the kidneys were removed posteriorly, first one kidney and then 5 to 7 days later the other kidney. During the interval between nephrectomies the mean arterial pressure remained steady in all 28 examples.
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this reason in the remaining 74 dogs both kidneys were removed at the same time by the anterior approach. The special diet was commenced on the day of the bilateral nephrectomy or the removal of the second kidney. It was given once daily for four days. Aliquots of the semi-solid formula were placed on the side of the mouth next to the tongue, thus stimulating swallowing. All animals on diet were force-fed in this manner. Vomiting did not occur in these 102 dogs. Eighteen other dogs which vomited were omitted from the study, regardless of the changes in the arterial pressure. This procedure seemed warranted in view of the adverse influence on the blood pressure of salt deficiency after bilateral nephrectomy of the dog.

The diets were composed basically of dialyzed peanut oil, chemically pure dextrose, electrolyte-free casein and a vitamin mixture previously described. Six variations of the basic dietary mixture were used; 3 lacked protein and 3 contained protein. The diets are described in table 1. The caloric intake by diet for each group is given in table 2. The dietary formulas were arranged so that the two major groups (protein, no protein) were subdivided into groups receiving a lower and groups receiving a higher caloric intake. Dogs subjected to peritoneal irrigation absorbed an amount of dextrose from the irrigating fluid which usually added 2 to 4 calories Kg./day to the caloric intake. The protein intake for all groups averaged 3 Gm./Kg./day.

Most animals were weighed each day, prior to the feeding, on a scale yielding a tolerance of ± 0.2 Kg. with known weights. The control weight was the average of the daily weights during the 4 to 7 days prior to complete nephrectomy. The weight on the third or fourth postoperative day was compared to the control weight.

Peritoneal irrigation was carried out as previously described. The concentration (mEq./L.) and composition of the irrigating fluid were:

\[ \text{Na} = 141, \text{Ca} = 3.6, \text{Mg} = 1.5, \text{K} = 2.7, \text{Cl} = 108 \text{ and } \text{HCO}_3 = 41. \]

Irrigation was done intermittently, usually 1 to 2 L. of the fluid remaining in the peritoneal cavity for 4 to 16 hours. The irrigating fluid also contained Terramycin 100 mg./L. and one per cent dextrose. Immediately after nephrectomy the animal received 20,000 units of penicillin intramuscularly.

The amount of fluid entering and leaving the peritoneal cavity was measured on each occasion. The irrigated groups were divided into a subgroup having minimal or no fluid load during the irrigation, and a subgroup which was allowed to retain a substantial positive fluid and sodium load. The fluid balance over 4 days was expressed in terms of milliliters of fluid retained per kilogram of body weight per day. For purposes of this study a minimal fluid load was considered to exist when the positive fluid load over 4 days was 8 ml./Kg./day or less. (In 5 dogs the fluid balance was zero; in 7 dogs it varied between +2 and +8 ml./Kg./day; in 2 dogs it was +16 to 18 ml./Kg./day). The subgroups not in fluid balance had a positive fluid load varying between 20 and 60 ml./Kg./day (± 20 ml./Kg./day in 4 dogs, +25 to 40 ml. in 5 dogs, and +50 to 60 in 4 dogs).

Eleven of the 14 dogs in the minimal fluid load subgroup had the input and output of sodium through the peritoneal cavity measured as previously described. The average positive sodium load in this group was 2 mEq. sodium/Kg./day.

The control value for mean arterial pressure was obtained over 4 to 7 days as described above. Following renal ablation the mean arterial pressure was measured twice daily with 6 to 8 hours between the observations. The diet was fed once daily. The weight was obtained once daily before feeding, after removal of the peritoneal fluid in the irrigated groups and before the infusion in the infused groups.

The groups not irrigated were given about 2.5 mEq. sodium/Kg. body weight/day parenterally in a volume of about 16 ml./Kg./day. This addition of sodium was based on our experience indicating that nephrectomized dogs subjected to peritoneal dialysis tend to gain sodium and lose potassium and that such animals, when maintained in fluid balance, gain an average of 25 mEq. sodium per day if their average weight is near 10 Kg. When the protein-containing dietary formula was given to an earlier group of dogs without the use of dialysis or the addition of saline, vomiting became troublesome. Addition of sodium and water in the amounts listed above appeared to improve the clinical well-being of the animals for the 4 days of observation. Finally, as indicated subsequently, the use of these quanti-

### Table 1.—The Dietary Formulas Used in This Study

<table>
<thead>
<tr>
<th>Diet no.</th>
<th>Volume (ml.)</th>
<th>Calories (%)</th>
<th>CHO (%)</th>
<th>Fat (%)</th>
<th>Protein (%)</th>
<th>Protein (Gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>130</td>
<td>48</td>
<td>32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>250</td>
<td>26</td>
<td>27</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>3a</td>
<td>120</td>
<td>500</td>
<td>32</td>
<td>48</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>3b</td>
<td>120</td>
<td>700</td>
<td>35</td>
<td>45</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>4a</td>
<td>120</td>
<td>290</td>
<td>47</td>
<td>53</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4b</td>
<td>120</td>
<td>500</td>
<td>70</td>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*The volume and composition are for one arbitrary unit. The animals received one or two of these units, depending on their weight.*
Table 2.—Data Relating to a General Description of the Various Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Peritoneal Irrigation</th>
<th>Protein (av. 3 Gm./Kg./day)</th>
<th>Calories/ Kg./day</th>
<th>Mean weight KG±SD</th>
<th>No. of dogs</th>
<th>No. BP 25 mm Hg</th>
<th>No. of dogs with gross lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>No diet</td>
<td>0</td>
<td>9.2±1.7</td>
<td>21</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>1</td>
<td>12.1-14</td>
<td>10.5±2.0</td>
<td>5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15-24</td>
<td>10.5±2.0</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>4a</td>
<td>35.49</td>
<td>12.9±1.8</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>50-60</td>
<td></td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>No diet</td>
<td>0</td>
<td>9.0±1.3</td>
<td>6</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>2</td>
<td>15-24</td>
<td>9.5±2.2</td>
<td>11</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23-35</td>
<td></td>
<td>17</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td>+</td>
<td>2</td>
<td>15-24</td>
<td>11.2±2.0</td>
<td>8</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>6b</td>
<td>+</td>
<td>2</td>
<td>15-26</td>
<td></td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>7a</td>
<td>+</td>
<td>3a</td>
<td>15-25</td>
<td>12.8±2.0</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>7b</td>
<td>+</td>
<td>3b</td>
<td>40-60±</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*The diets are described in Table 1. The next to last column on the right relates the number of dogs in each group displaying an elevation of the mean arterial pressure of 25 mm. Hg or more above the control value, while the last column relates the incidence of hemorrhagic lesions in each group.

Tissues of physiologic saline did not appreciably alter the arterial pressure of control groups of animals not receiving protein.

The observations on the blood pressure were terminated after 4 days. In most experiments the animals were killed at this time. The viscera were inspected closely for hemorrhagic foci, which in our experience indicate arteriolar necrosis and necrosis of muscle in the heart, gastrointestinal tract, and urinary bladder. Tissues were placed in 10 per cent formalin and prepared for microscopic study.

The various groups (test groups receiving dietary protein, and control groups receiving no diet or a diet devoid of protein) are described in Table 2.

Statistical Analysis. A scatterplot was made of the changes in the mean arterial pressure against time for the groups analyzed. A linear regression line ($y = a + bx$) was fitted to the data of the animals not subjected to dialysis, and a correlation coefficient was calculated. Comparison of the correlation coefficient of each of the groups was accomplished by means of a Z test. The correlation coefficients and $p$ values are given in Table 3.

In the groups subjected to peritoneal dialysis the changes in the mean arterial pressure appeared to describe a nonlinear relationship with time. In the latter groups the regression line fitted to the data was an exponential one ($y = b \log x + a$). A similar fit was applied to control group 4 (dialysis and no diet). A Z test was used to compare these data.

Whether or not the slope of the regression line of each group differed significantly from zero was determined by a t test. The $p$ values are given in Table 3.

The end point arterial pressure of the test animals was compared to that of the control groups by the t test. Similarly the end point value for the control groups was compared to the projected zero value (Table 3).

**RESULTS**

**Control Mean Arterial Pressure**

The over-all mean control for the 102 dogs was 118 mm. Hg. Eighty-six per cent of the control values fell in the range of 105 to 125 mm. Hg.

Once the animal was accustomed to the procedure, the control value remained fairly steady. Thus the variations in individual cases subsequent to the first observation following training were ± 5 mm. Hg in 96 per cent of the examples, and varied ± 15 mm. Hg only twice.
The average of the arterial pressure taken over 4 to 7 days was considered as the control baseline pressure to which all pressures subsequent to the bilateral nephrectomy were related. The mean control arterial pressure and the standard deviation for each group in this study are given in table 4.

**After Nephrectomy**

*Control Groups (No Dietary Protein). No Diet and 16 Ml./Kg./Day of Saline (Group 1).* Of the 21 dogs in this group, 4 displayed an elevation of the mean arterial pressure which exceeded the control value by 25 mm Hg or more (table 2). There was a slight rise in the mean pressure curve for all of the dogs that amounted to 7.2 mm Hg on the fourth day (table 3).

*Diet of Low Caloric Content, Devoid of Protein, and 16 Ml./Kg./Day of Saline (Group 2).* Of the 10 dogs in this group only one displayed an elevation of the mean arterial pressure which exceeded the control value by 25 or more mm Hg. The mean arterial pressure was elevated by an average of 10.8 mm Hg on the fourth day.

*Diet of Higher Caloric Content, Devoid of Protein, and 16 Ml./Kg./Day of Saline (Group 3).* Of the 10 dogs in this group none developed an elevation in mean arterial pressure which exceeded the base line value by 25 or more mm Hg. Only 1 of the 20 dogs in groups 2 and 3 (diet without protein) revealed an elevation in pressure which exceeded the base line by 25 mm Hg, and the over-all mean curve for these 2 groups showed a minimal rise of 2 mm Hg by 4 days.

*Peritoneal Dialysis Attended by No or Minimal Fluid Load (Group 4).* None of the 6 dogs in this group showed an elevation of the mean arterial pressure which exceeded the base line value by 25 or more mm Hg. The average change at 4 days was 4.1 mm Hg above the control of 112 mm Hg (+10, +5, -10, +5, +10, +5 mm. Hg). From the fifth through the eighth day after the renal ablation a positive fluid load was allowed to develop via the peritoneum (+36 to +68 ml. fluid/Kg./day, av. +60 ml./Kg./day). During this time 4 of the 6 dogs developed an elevation of the mean arterial pressure which exceeded the control value by 25 or more mm. Hg (+30, +40, +5, 0, +45, +60, av. +25 mm. Hg). Thus, a minimal or no fluid load without a protein intake was attended by negligible changes in the arterial pressure, while in the same group an excessive load of fluid containing mainly sodium was associated with a definite eleva-
TABLE 4.—The Control Mean Arterial Pressure for Each Group and Its Variations

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of dogs</th>
<th>Mean control BP (mm. Hg)</th>
<th>SD control BP (mm. Hg)</th>
<th>Fraction control between 105 &amp; 125 (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &amp; 4</td>
<td>27</td>
<td>118</td>
<td>±9</td>
<td>0.80</td>
</tr>
<tr>
<td>2 &amp; 3</td>
<td>20</td>
<td>126</td>
<td>±8</td>
<td>0.70</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>115</td>
<td>±7</td>
<td>0.84</td>
</tr>
<tr>
<td>6 &amp; 7</td>
<td>27</td>
<td>118</td>
<td>±6</td>
<td>0.97</td>
</tr>
</tbody>
</table>

tion in arterial pressure even in the absence of dietary protein. These manipulations support further the earlier observations made by Orbison, Peters and Christian, and by Leonard and Heisler.

Statistical Analysis of the Inter-Relationships of the Control Groups Which Received No Protein by Diet (Groups 1, 2, 3, and 4, 47 Dogs, Table 3). Comparison of the linear fits of the data revealed no significant difference when group 1 was compared with group 2, when group 1 was compared with group 3, and when group 2 was compared with group 3 (table 3, p values 0.11-0.36). Thus, these groups which received no protein may be treated as a single population.

Gross analysis of the groups which received no dietary protein (groups 1, 2, 3, 4) used as a single population yielded only 5 examples (of the 47) with an elevation of the mean arterial pressure of 25 or more mm. Hg above the control value (fig. 1). The mean curve of these values indicated an elevation of +7 mm. Hg in 4 days (fig. 1). The linear fit of these data indicated a mean elevation in pressure at the rate of 1.7 mm. Hg/day. This slope, when compared to the zero line, gave a p value of 0.025. It would appear from the latter analysis that a tendency toward elevation of the mean arterial pressure above the control value existed in our nephrectomized dogs when some saline was given in the absence of a diet, or in the presence of a diet lacking in protein. This may be taken to support the concept of an inherent tendency toward elevation of the arterial pressure following renal ablation. Additional variables which elevate the arterial pressure prominently may be considered to do so by potentiating a basic defect rather than initiating it de novo.

A comparison of the linear fit of the data of the group subjected to peritoneal dialysis and given no diet (group 4) with that of a combination of the other groups not receiving protein (groups 1, 2 and 3) revealed no significant difference between these groups handled in this fashion (p 0.43). Thus, the interposition of peritoneal dialysis per se did not alter significantly the state of the arterial pressure as long as a substantial fluid load (sodium and water) did not accrue.

Test Groups (Dietary Protein)

Protein-Containing Diet of Low Caloric Content and 16 Ml./Kg./Day of Saline (Group 5). Of the 28 dogs in this group, 19 yielded an elevation of the mean arterial pressure which exceeded the control value by 25 or more mm. Hg (table 2). The average elevation at 4 days amounted to +38 mm. Hg. The caloric intake in the range of 15 to 24 calories/Kg./day gave results similar to those when the range was 25 to 35 calories/Kg./day.

Protein-Containing Diet of Low or Moderate Caloric Content and Peritoneal Dialysis (Group 6, 17 Dogs). All but one of these dogs revealed an elevation in the arterial pressure which exceeded the control value by 25 or more mm. Hg. The average elevation at 4 days amounted to +32 mm. Hg. The caloric intake in the range of 15 to 34 calories/Kg./day and no major fluid load gave results similar to those when the caloric intake was in the range of 15 to 26 calories/Kg./day plus a high positive fluid load.

Protein-Containing Diet of Higher Caloric Content and Peritoneal Dialysis (Group 7). Of the 10 dogs in this group all developed an elevation in the mean arterial pressure which exceeded the control by 25 mm. Hg or more. The average elevation at 4 days was +39 mm. Hg. The results when the caloric content was in the range of 15 to 25 calories/Kg./day while a minimal or no fluid load accrued were the same as with the development of a fluid load and the caloric content in the range of 40 to 60+ calories/Kg./day.
Statistical Analysis of Test Groups. A comparison of the logarithmic fit of the data of the groups subjected to peritoneal dialysis (groups 6a and 6b; 7a and 7b; 6a and 7a; 6b and 7b) revealed no significant difference between these groups (p values 0.2-0.5). Thus these groups and subgroups (peritoneal dialysis plus protein-containing diet) may be considered to have come from the same population (table 3).

A comparison of the linear fits of the data of the group receiving dietary protein and saline (group 5) versus the groups given no protein (groups 1, 2, and 3 combined) yielded a highly significant difference (p 0.001). This comparison indicates an unequivocal potentiation of the hypertension by dietary protein in the absence of dialysis. When group 5 was compared with these groups individually the significance persisted. Thus a comparison of the group receiving saline and a diet minus protein (group 2) and the group receiving saline and a diet containing protein (group 5) gave a p value of 0.00005.

A comparison of the logarithmic fit of the data of groups 6 and 7 combined (peritoneal dialysis and protein-containing diet) with group 4 (peritoneal dialysis, no diet) gave a p value of 0.04. This level of significance again indicates the potentiating influence of dietary protein. It may be inferred that the level of significance was not greater because of the small population of group 4 (6 dogs). The latter interpretation is supported by the comparison of group 4 with the subgroups of
FIG. 2. The changes in the mean arterial pressure for groups 5, 6, and 7 combined are shown. These are the test groups (55 dogs) which received protein in the diet. The same scheme as in figure 1 is used.

groups 6 and 7 individually. Thus group 6a versus group 4 yielded a $p$ value of 0.03; 6b versus 4 gave a $p$ value of 0.02; 7a versus 4 gave a $p$ value of 0.08; and 7b versus 4 gave a $p$ value of 0.02. A more definite difference existed with all subgroups except with subgroup 7a (dialysis, minimal or no fluid load; protein in diet) with which the $p$ value was not significant.

A test of whether the slope of regression differed significantly from zero (control value projected) yielded additional information (table 3). Significant values were obtained for the control groups given no diet or a diet minus protein (groups 1 and 2), indicating again a trend toward an elevated arterial pressure inherent in the experimental preparation even in the absence of dietary protein. The values for the dialyzed group given no diet (group 4) and the other control group given saline and a diet minus protein (group 3) were not significant. Highly significant $p$ values were obtained when this type of analysis was applied to all groups receiving dietary protein (table 3).

It should be emphasized that the statistical comparison thus far used in these analyses deals with a comparison of slopes (regression lines) and not with the end point of rise in mean arterial pressure. This is further displayed by a comparison of the slopes of the nondialyzed and the dialyzed groups (5 versus 6 and 7) insofar as the rate of rise in pressure is concerned. Group 5 (saline, protein in diet) shows a greater rate of elevation of arterial pressure than the combined groups 6 and 7 (dialysis, protein in diet) while the end point of the rise for each of these 3 groups is essentially the same.
Statistical Analysis of End Point Elevation of the Arterial Pressure. This analysis is given in Table 3. The comparisons are both to zero and between the pertinent groups.

As compared to zero, the end point pressures of the control groups 1, 2, and 3 were not significantly elevated (Table 3). The p value for group 3 is significant in a negative manner. Group 2 revealed an end point elevation significantly greater than zero.

Group 1 received no diet. The major difference between groups 2 and 3 was in the caloric intake derived from carbohydrate and fat. Since group 3 had a distinctly higher caloric intake the analysis suggests that this factor may interfere with the expression of the hypertension.

All of the dietary protein groups (5, 6, 7) revealed a highly significant elevation of the end point arterial pressure when it was compared to zero. The nondialyzed group (group 5) yielded the same level of significance as the irrigated groups (6 and 7). A substantial fluid load plus dietary protein did not improve the level of significance over the group receiving protein and accruing a minimal or no fluid load.

An analysis of the end point pressures indicated no significant differences when the groups receiving no protein in the diet were compared with each other, with the exception of group 3. Since group 3 showed a general downward trend in pressure, it differed significantly from groups 2 and 4, which tended to be slightly elevated. This, therefore, was in part a negative correlation.

A comparison of the end point pressure of the nondialyzed groups receiving a diet with and without protein (groups 2 versus 5) indicated a highly significant end point elevation for the protein group (group 5). Similarly, groups 6 and 7 (protein plus dialysis) when compared to group 4 (dialysis plus no protein) demonstrated a highly significant elevation of the end point mean arterial pressure.

Weight Change. The body weight on the third or fourth day when compared with the control weight showed a tendency toward a slight decrease irrespective of the group. The change in body weight varied between zero to minus 0.4 Kg. as follows for various groups: For 23 of 32 dogs receiving dietary protein plus saline or peritoneal irrigation (groups 5, 6, and 7); for 18 of 25 dogs receiving no diet and saline or peritoneal irrigation (groups 1 and 3); for 15 of 17 dogs receiving a diet without protein plus saline (groups 2 and 4). For all groups minimal or no weight change occurred in 56 of 74 dogs. Weight gain was definite only in 6 dogs of the irrigated groups.

Gross Hemorrhagic Lesions (Table 2). Excluding group 4, which eventually received a high fluid load, the control groups combined (groups 1, 2, and 3, no protein) displayed gross hemorrhagic lesions at autopsy in 7 of 41 cases. On the other hand, of the 55 dogs receiving protein, 20 displayed gross hemorrhagic lesions at autopsy. In the groups receiving protein, approximately the same incidence of gross vascular lesions was encountered in the nondialyzed group (5) as in the dialyzed groups (6 and 7). It would appear that the inclusion of protein in the diet not only aggravated the hypertensive state but also increased the incidence of gross hemorrhagic (vascular) lesions.

Discussion

The prescribed amount of sodium in these experiments (2.5 mEq./Kg./day) given in isotonic saline did not of itself effect a major elevation of the arterial pressure of the control groups not receiving dietary protein during the 4 days of observation. Forty-five of 55 dogs receiving protein under similar conditions developed an elevation of the mean arterial pressure which exceeded the control value by 25 mm. Hg or more. That the trend toward an elevated arterial pressure was evident within 24 hours after the nephrectomies may be meaningful.

Statistically there was no difference between the dialyzed groups (6a and 6b; 7a and 7b) which received dietary protein, indicating no difference in arterial pressure in groups maintained in or near fluid balance and groups which were subjected to positive fluid and sodium load. A fluid and sodium load alone
aggravated the hypertension (group 4) but a fluid and sodium load added to dietary protein did not appear to potentiate the hypertension beyond that level which was achieved by either factor alone. In the dialyzed groups an insufficient caloric intake (groups 6a, 6b, and 7a) gave the same levels of hypertension as a sufficient caloric intake (group 7b). A low water intake (diet 2) gave the same results as an adequate water intake (diets 3a and 3b) as long as protein was fed.

A tendency toward elevation of the mean arterial pressure in the nephrectomized animals of control group 1 and 2 (no protein) was indicated when the slope of regression was compared to zero. Thus, a tendency toward elevation of the arterial pressure appeared to be an intrinsic feature of the renal ablation plus the amount of sodium given. The highly significant results with all test groups (protein) using the same type of analysis plus differences between control and test groups demonstrated that dietary protein acted as a potentiating factor toward the hypertension. Similar results were obtained when the end point (4 day) elevation was analyzed. Moreover, there is some indication that dietary protein aggravates the hemorrhagic lesions of the viscera observed following nephrectomy.

The differences between the results herein recorded and those previously reported by Kolff and Page\textsuperscript{13} may be due to differences in management of the animals and differences in methods of analysis. Our approach depended primarily on a standardized 4 day period for all groups of animals, a similar protein intake for all groups, a standardized intake of sodium, and the discarding from consideration all dogs which overtly vomited. The number of discards was as great in groups not receiving protein as in the dietary protein groups (total reject 15 per cent).

The present experiments provide a partial separation of two factors which aggravate renoprival hypertension, namely, dietary protein, and fluid and sodium loading. Dietary protein appears to be most effective when coupled with a degree of sodium intake which alone does not substantially aggravate the hypertension for the four days of observation. Thus, although dietary protein has a potentiating role, this role seems to have a relationship to the sodium intake or sodium metabolism.

In rats the importance of dietary protein, calories, and salt on experimental hypertension induced by partial nephrectomy was demonstrated by Handler and Bernheim.\textsuperscript{2} In their observations a lowered caloric intake appeared to be a factor in lowering the blood pressure when it was extended over a prolonged period of time, whereas in the present experiments for the short period of observation the caloric intake did not appear to be a major factor.

As reviewed by Floyer\textsuperscript{19} and Kolff,\textsuperscript{20} the literature discloses the possibility of overlapping mechanisms in the pathogenesis of experimental renal and renoprival hypertension. The indication that both renal\textsuperscript{2} and renoprival hypertension as observed in animals are affected similarly by sodium and dietary protein may be taken to add to a possible basic relationship between these two states.

**SUMMARY**

Procedure for the evaluation of dietary factors on renoprival hypertension is proposed. This consists essentially of the determination of the control pressures over 4 to 7 days, the removal of both kidneys, the injection of 16 ml./Kg. of isotonic saline intravenously per day, force feeding the diet tested once daily, and the measurement of arterial blood pressure twice daily.

By means of this procedure, dietary protein was found to potentiate postnephrectomy hypertension in the dog, as determined by comparing protein-containing diets with diets without protein and with no dietary intake. In the absence of protein in the diet there was a minimal elevation in the arterial pressure following nephrectomy. This appeared to indicate an inherent tendency of the nephrectomized dog to develop an increased arterial pressure. Dietary protein is thus consid-
ered to be a potentiating and not an initiating factor in the hypertension.

In the absence of dietary protein, variations in the caloric intake and slight variations in the water intake, and a low intake of sodium did not effect a major elevation in the arterial pressure following nephrectomy.

Peritoneal dialysis without a sodium load did not potentiate the hypertension following nephrectomy. Peritoneal dialysis with a minimal fluid and sodium load plus protein in the diet potentiated the postnephrectomy hypertension. The same level of hypertension was observed with fluid and sodium loading alone, dietary protein plus a minimal sodium intake, and dietary protein plus a fluid and sodium excess.

SUMMARIO IN INTERLINGUA
Es proponite un procedimento pro le evaluation de factores dietari in le disvelopamento de hypertension postnephrectomic. Le procedimento consiste essentemente in stablir presiones de controlo in le curso de un periodo de inter 4 e 7 dies, le ablation de ambe renes, le injection intravenose de 16 ml/Kg/die de isotonic solution salin, le administration fortiate del dieta experimental un vice per die, e le mesuration del pression de sanguine arterial duo vices per die.

Per medio de iste procedimento il esseva constatate que proteina dietari resulta in canes in un potentiation del hypertension postnephrectomic. Iste conclusion es basate super le comparation de mesurationes post dieta a contenu de proteina e le mesurationes post dieta sin contenu de proteina e post nulle dieta del toto. In le absentia de proteina in le dieta, nephrectomia esseva sequite per elevaciones minimal in le pression del sanguine arterial. Isto pareva indicar un tendentia, inherente in canes nephrectomisate, a disveloppar un augmentate pression arterial. Assi proteina dietari es considerate como un factor potentiatori e non initiatori in le disveloppamento de hypertension.

In le absentia de proteina dietari, nulle major elevation del pression arterial postnephrectomic esseva evocate per variationes in le ingestion caloric, per leve variationes in le ingestion de aqua, o per un basse ingestion de natrium.

Dialyse peritonee sin carga de natrium non potentiava le hypertension postnephrectomic. Dialyse peritonee con carga minimal de fluido e natrium in le presenta de proteina in le dieta effectuava un potentiation del hypertension postnephrectomic. Le mesma nivello de hypertension esseva observate con carga de fluido e de natrium sol, con proteina dietari in le presenta de un ingestion minimal de natrium, e con proteina dietari in le presenta de un excesso de fluido e de natrium.

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Circ Res. 1959;7:68-78
doi: 10.1161/01.RES.7.1.68

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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