Sodium Gradient and Renoprival Hypertension in the Rat

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Following nephrectomy in the rat blood pressure rises while the extracellular fluid volume increases, sodium concentration falls and potassium rises. These changes (without the potassium rise) can be mimicked by simple hyperosmotic loading while the reverse can be induced by dehydration. The rise in blood pressure is not due to either expansion of the extracellular space or the fall in sodium concentration alone but probably to the resultant decrease in the Na\textsubscript{o}/Na\textsubscript{i} gradient.

The effects of renal extirpation have long been of critical importance to theories of the hypertensive process. Indeed, Goldblatt's original thinking was conditioned by his failure to observe any rise in pressure in the nephrectomized dog.\textsuperscript{1} Later, however, Braun-Menendez and von Euler\textsuperscript{2} noted that blood pressure did in fact rise in the nephrectomized rat and subsequently, Grollman et al.\textsuperscript{3} showed that this was also true in the nephrectomized dog kept alive by peritoneal lavage. There is now no argument about the fact, but two opinions as to its explanation. One opinion is that the case for an antipressor function of the kidney in the hierarchy of renal pressor materials has been made.\textsuperscript{4} The other suggests that in the absence of renal regulation, salt and water undergo a basic redistribution which is causally related to the hypertension.\textsuperscript{5} As yet, no specific renal material has been isolated to prove the first case, nor has any electrolyte change been pinpointed to prove the latter.

Our immediate interest in the problem stems from the demonstration that smooth muscle tone in general and peripheral vascular tone in particular is directly related to the extra/intracellular gradient of sodium,\textsuperscript{6} a view also reached by Raab and co-workers,\textsuperscript{7} from different evidence. The sodium gradient is a dynamic equilibrium, or steady state, which can be altered in several basic ways, first and probably most simply by a shift of water between the cell and its environment in accord with osmotic requirements, second by an alteration in Donnan forces, third by a change in membrane permeability affecting either inward or outward movement of sodium or both, and fourth, by changes in the metabolically driven sodium transport (extrusion). Seemingly, no matter how caused, a fall in the gradient Na\textsubscript{o}/Na\textsubscript{i} results in an increase in tone.

In the present report the problem of renoprival hypertension has been restudied and evidence is presented to show that the rise in blood pressure is again a function of a fall in sodium gradient. The emphasis on sodium does not exclude potassium, calcium or other ions, but represents only our present limited point of attack.

METHODS

Adult male albino rats of an inbred Wistar strain were used throughout. The basic methods for deriving data concerning the gross extracellular distribution of Na, K and water have been described elsewhere.\textsuperscript{8} Briefly, inulin is injected intravenously in the bilaterally nephrectomized rat and allowed 2 hours for equilibration. An arterial (usually femoral) blood sample is then drawn and the concentrations of inulin, Na, and K in the sample are measured. The product of the extracellular fluid volume (ECFV = volume distribution of inulin) and Na concentration yields a measure of total extracellular Na (EC Na) and ECK is similarly derived. In some experiments, a second procedure, e.g., infusion or gavage, was carried out at this time and a second blood sample taken after a measured interval in order to determine the degree and direction of changes. Groups of at least 8 animals...
Table 1.—Effect of Nephrectomy on Blood Pressure and on Extracellular Fluid Volume, Na and K

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>24 hrs</th>
<th>48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct B.P., mm. Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>94 ± 4</td>
<td>115 ± 4†</td>
<td>127 ± 2†</td>
</tr>
<tr>
<td>diastolic</td>
<td>56 ± 3</td>
<td>70 ± 3†</td>
<td>88 ± 3†</td>
</tr>
<tr>
<td>ECFV ml./100 Gm.</td>
<td>22.7 ± 0.7</td>
<td>24.4 ± 0.3‡</td>
<td>25.8 ± 0.4†</td>
</tr>
<tr>
<td>Na conc., mEq./L.</td>
<td>144.4 ± 1.1</td>
<td>142.3 ± 1.5</td>
<td>135.4 ± 2.2†</td>
</tr>
<tr>
<td>K conc., mEq./L.</td>
<td>4.17 ± 0.12‡</td>
<td>5.90 ± 0.16†</td>
<td>7.62 ± 0.21†</td>
</tr>
<tr>
<td>EC, Na, mEq./100 Gm.</td>
<td>3.27 ± 0.11</td>
<td>3.48 ± 0.06‡</td>
<td>3.49 ± 0.07‡</td>
</tr>
<tr>
<td>EC, K, mEq./100 Gm.</td>
<td>94 ± 4</td>
<td>144 ± 4‡</td>
<td>194 ± 6‡</td>
</tr>
<tr>
<td>Average body wt., Gm.</td>
<td>246 ± 3</td>
<td>241 ± 4</td>
<td>246 ± 5</td>
</tr>
<tr>
<td>No. of animals</td>
<td>9</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Water intake, ml./rat/24 hours</td>
<td>33 ± 3</td>
<td>8 ± 1</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Wt. change following nephrectomy, Gm.</td>
<td>-4 ± 1</td>
<td>0 ± 2</td>
<td>0 ± 2</td>
</tr>
<tr>
<td>Gk</td>
<td>6.8</td>
<td>6.5</td>
<td>6.0</td>
</tr>
<tr>
<td>G-approx</td>
<td>13.6</td>
<td>15.0</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*± standard error.
†p<0.02.
‡p<0.05.

were used throughout. All calculations were made separately for each animal and then averaged; this is particularly important in the case of the derived data. Inulin was determined by the method of Higashi and Peters,9 Na and K by flame photometry and blood pressure by direct electromanometry using either a Statham or Sanborn transducer. All operative procedures were performed under light ether anesthesia. Additional procedures are described as they arise.

The method used to estimate relative changes in Na gradient, shown in the tables as Gk and G-approx. will be discussed separately.

RESULTS

Experiment 1. Effect of Nephrectomy on Salt and Water Distribution and on Blood Pressure

This experiment is presented as typical of the changes that occur in the nephrectomized rat. Group 1 consisted of 9 animals serving as control, i.e., nephrectomized at the time of inulin injection 2 hours before blood sampling. Group 2 consisted of 14 rats nephrectomized 24 hours before inulin injection and the 14 animals of group 3 were nephrectomized 48 hours previously (table 1).

After nephrectomy, blood pressure increases steadily, accompanied by an increase in the extracellular fluid volume. There is frequently, as here, a small increase in total extracellular sodium which is probably real, but this is more than diluted out by the increase in fluid volume so that sodium concentration falls slightly at 24 hours, markedly at 48 hours. By contrast, there is a large increase in extracellular potassium which, doubling itself in 48 hours, is more than sufficient to offset the increase in fluid volume and hence K concentration rises steadily. These findings are in general agreement with those of other authors.10 They cannot be explained by fluid intake11 since the nephrectomized animals greatly reduced their water intake to just about match their insensible water loss and did not eat. There was a small loss of weight.

The calculated relative Na gradient decreased as blood pressure rose.

Experiment 2. Effect of Nephrectomy on Salt and Water Distribution in the Absence of Neurohypophysial or Adrenal Function

Two experiments bearing on the problem of whether the neurohypophysis or adrenal play an active role in the changes in salt and water distribution following nephrectomy are pre-
SODIUM GRADIENT IN HYPERTENSION

Table 2.—Effect of Dehydration on Blood Pressure and on Extracellular Fluid Volume, Na and K

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Dehydration 24 hrs</th>
<th>Dehydration 48 hrs</th>
<th>Dehydration 72 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct B.P., mm. Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>119 ± 5</td>
<td>103 ± 6*</td>
<td>86 ± 7†</td>
<td>97 ± 9*</td>
</tr>
<tr>
<td>diastolic</td>
<td>66 ± 2</td>
<td>56 ± 3†</td>
<td>50 ± 4†</td>
<td>55 ± 4†</td>
</tr>
<tr>
<td>mean</td>
<td>82 ± 3</td>
<td>72 ± 5*</td>
<td>64 ± 5†</td>
<td>69 ± 6*</td>
</tr>
<tr>
<td>ECFV ml./100 Gm.</td>
<td>19.5 ± 0.5</td>
<td>17.5 ± 0.4†</td>
<td>16.4 ± 0.4†</td>
<td>16.3 ± 0.3†</td>
</tr>
<tr>
<td>Na conc., mEq./L</td>
<td>143.5 ± 0.6</td>
<td>150.0 ± 1.4†</td>
<td>150.2 ± 0.8†</td>
<td>152.4 ± 1.1†</td>
</tr>
<tr>
<td>K conc., mEq./L</td>
<td>3.71 ± 0.15</td>
<td>3.73 ± 0.11</td>
<td>3.49 ± 0.08</td>
<td>3.84 ± 0.08</td>
</tr>
<tr>
<td>EC Na, mEq./100 Gm.</td>
<td>2.80 ± 0.08</td>
<td>2.61 ± 0.05*</td>
<td>2.46 ± 0.05†</td>
<td>2.48 ± 0.04†</td>
</tr>
<tr>
<td>EC K, μEq./100 Gm.</td>
<td>72 ± 3</td>
<td>65 ± 3*</td>
<td>57 ± 2†</td>
<td>62 ± 1†</td>
</tr>
<tr>
<td>Average body wt., Gm.</td>
<td>273 ± 7</td>
<td>273 ± 6</td>
<td>254 ± 4</td>
<td>258 ± 4</td>
</tr>
<tr>
<td>No. of animals</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Gk</td>
<td>6.9</td>
<td>7.7</td>
<td>7.65</td>
<td>7.75</td>
</tr>
<tr>
<td>G-approx</td>
<td>13.8</td>
<td>16.4</td>
<td>15.3</td>
<td>15.5</td>
</tr>
</tbody>
</table>

*P<0.05.
†P<0.02.

In the first experiment 8 animals served as intact control and 10 as diabetes insipidus control, 2 parallel groups of 8 and 9 animals respectively being nephrectomized 24 hours before the experiment. Diabetes insipidus was produced and verified as previously described. The second experiment was similar except that adrenalectomy rather than diabetes insipidus was tested and all groups had 9 animals. Although the same measurements as in the first experiment were made, only the essential findings are summarized in figure 1 for direct comparison with those of the first experiment.

It is clear that the change in salt and water distribution which follows nephrectomy cannot be ascribed to any active role on the part of either the neurohypophysis or adrenal for it occurs equally well in the absence of these glands. The rat with diabetes insipidus ordinarily shows an increase in extracellular fluid volume and an increase in total sodium. The 24 hour adrenalectomized rat ordinarily shows a decrease in fluid volume, a minor decrease in Na and a clear rise in K concentration. The effects of nephrectomy appear superimposed on these expected changes. Thus the increase in fluid volume is accentuated in the rats with diabetes insipidus and the rise in K in the adrenalectomized animals.

No attempt was made to compare effects on blood pressure in these 2 experiments. Since both glands are active in the normal maintenance of the blood pressure the effect of nephrectomy could only be studied in therapeutically maintained animals.

In a series of experiments not reported here, aldosterone and pitressin alone or in various combinations did not reverse the salt and water redistribution following nephrectomy.

Experiment 3. Effect of Simple Dehydration on Salt and Water Distribution and on Blood Pressure

The possibility that the increase in blood pressure following nephrectomy is a direct outcome of the alteration in fluid and salt balance was next explored. In seeking information on this point we attempted to determine the effects on blood pressure of controlled alterations in salt and water distribution in the normal rat. In the first of these experiments 4 groups of 8 animals were used, the first group serving as control, the others deprived of water for 24, 48 or 72 hours. The findings are shown in table 2 and are in general agreement with known facts.
TABLE 3.—Effect of an Oral Hyperosmotic Glucose Load on Blood Pressure and on Extracellular Fluid Volume, Na and K

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hydrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct B.P., mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>112 ± 6</td>
<td>138 ± 4*</td>
</tr>
<tr>
<td>diastolic</td>
<td>66 ± 5</td>
<td>84 ± 3*</td>
</tr>
<tr>
<td>mean</td>
<td>83 ± 5</td>
<td>106 ± 3*</td>
</tr>
<tr>
<td>ECFV ml./100 Gm.</td>
<td>21.7 ± 0.3</td>
<td>24.6 ± 0.5*</td>
</tr>
<tr>
<td>Na conc., mEq./L.</td>
<td>146.1 ± 1.1</td>
<td>144.1 ± 0.9</td>
</tr>
<tr>
<td>K conc., mEq./L.</td>
<td>3.64 ± 0.09</td>
<td>3.85 ± 0.12</td>
</tr>
<tr>
<td>EC Na, mEq./100 Gm.</td>
<td>3.16 ± 0.05</td>
<td>3.51 ± 0.09*</td>
</tr>
<tr>
<td>EC K, mEq./100 Gm.</td>
<td>79 ± 2</td>
<td>95 ± 4*</td>
</tr>
<tr>
<td>Average body wt., Gm.</td>
<td>264 ± 6</td>
<td>262 ± 6</td>
</tr>
<tr>
<td>No. of animals</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

*p<0.02.

FIG. 1 Top. Changes in extracellular fluid volume, plasma Na and K in the nephrectomized but otherwise intact rat compared with changes in the absence of neurohypophyseal or adrenal function.

FIG. 2 Bottom. Effect of an oral hyperosmotic load on blood pressure in the 48 hour nephrectomized rat.

The effect of the dehydration is manifest in a gradual and progressive decrease of extracellular fluid volume with a consequent increase in plasma sodium concentration. Total extracellular Na and K both decrease. These changes are essentially the reverse of those found in the nephrectomized rat and are accompanied by a significant decline in blood pressure. The calculation of relative gradient shows an increase as blood pressure falls with continuing water deprivation.

Experiment 4. Effect of a Simple Oral Hyperosmotic Load on Salt and Water Distribution and on Blood Pressure

The second experiment of this series was designed as the converse of the preceding. Two groups of 10 animals were used. Group 1 served as control while the animals of group 2 were given 5 per cent glucose in saline by stomach tube in an amount equal to 5 per cent of their body weight. Half of this was given at the time of insulin injection and half one hour later (table 3).

Blood pressure rose in the hyperhydrated group. This observation has been repeated and is in general agreement with the findings of others. The rise in blood pressure is accompanied by an increase in fluid volume. Total extracellular sodium is usually increased, as in this experiment, but this is more than diluted out so that sodium concentration falls. Although there is no rise in plasma K the diluting effect of the increase in fluid volume is obviated by a real increase in ECK. The picture is remarkably similar to that observed following nephrectomy.

It would thus be anticipated that the administration of a hyperosmotic load to the nephrectomized rat would accentuate whatever rise of pressure might already have occurred. This was readily demonstrated by giving the load as described above to 48 hour nephrectomized rats with the well defined results shown in figure 2 and agrees with the findings in the dog.14

The relative change in gradient cannot be
TABLE 4.—Effect of an Intravenous Hyperosmotic Glucose Load on Blood Pressure and on Extracellular Fluid Volume, Na and K in Normal and in Dehydrated Rats

<table>
<thead>
<tr>
<th></th>
<th>Normal Preinfusion</th>
<th>Normal Postinfusion</th>
<th>Dehydrated Preinfusion</th>
<th>Dehydrated Postinfusion</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct B.P., mm. Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>91 ± 8</td>
<td>104 ± 7</td>
<td>+13*</td>
<td>58 ± 4</td>
<td>+24*</td>
</tr>
<tr>
<td>diastolic</td>
<td>55 ± 4</td>
<td>60 ± 4</td>
<td>+ 5*</td>
<td>37 ± 3</td>
<td>+ 5*</td>
</tr>
<tr>
<td>EGFPV ml./100 Gm.</td>
<td>20.7 ± 0.6</td>
<td>24.1 ± 0.5*</td>
<td>+ 3.3*</td>
<td>17.7 ± 0.4</td>
<td>+ 2.9*</td>
</tr>
<tr>
<td>Na conc, mEq./L.</td>
<td>144.3 ± 1.3</td>
<td>127.6 ± 2.4*</td>
<td>−16.7*</td>
<td>151.6 ± 2.8</td>
<td>−16.8*</td>
</tr>
<tr>
<td>K conc., mEq./L.</td>
<td>3.29 ± 0.08</td>
<td>3.33 ± 0.06</td>
<td>+ 0.04</td>
<td>3.29 ± 0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>EC Na, mEq./100 Gm.</td>
<td>2.90 ± 0.06</td>
<td>3.07 ± 0.05</td>
<td>+ 0.08</td>
<td>2.65 ± 0.06</td>
<td>+ 0.08</td>
</tr>
<tr>
<td>EC K, mEq./100 Gm.</td>
<td>68 ± 1</td>
<td>80 ± 2*</td>
<td>+12*</td>
<td>58 ± 1</td>
<td>+ 8*</td>
</tr>
<tr>
<td>Average body wt., Gm.</td>
<td>275 ± 7</td>
<td>303 ± 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of animals</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gk</td>
<td>7.1</td>
<td>6.0</td>
<td></td>
<td>7.9</td>
<td>6.8</td>
</tr>
<tr>
<td>G-approx</td>
<td>14.2</td>
<td>12.0</td>
<td></td>
<td>15.8</td>
<td>13.6</td>
</tr>
</tbody>
</table>

*p<0.02.

calculated without knowing how much fluid was actually absorbed from the load.

Experiment 5. Effect of an Intravenous Hyperosmotic Load on Salt and Water Distribution and on Blood Pressure

This experiment was arranged to provide data for estimating gradient change by injecting the load as a measured volume of warmed 5 per cent glucose in saline intravenously. The continuous infusion syringe delivered 3.7 ml in 2 min. The experiment was internally controlled and made use of 2 basic types of experiment animal, the first fully nourished, the second deprived of water for 72 hours. Two groups of 8 rats each were thus used. Basal measurements were made as usual after 2 hours of inulin equilibration, the 2 min. infusion was then given and a second sample taken less than 30 sec. after it was completed (table 4).

The initial measurements are as reported in experiment 3. Thus, in the dehydrated group, extracellular fluid is reduced and Na concentration increased. This is accompanied by a lower blood pressure and higher relative gradient than in the normal.

The infusion in both groups caused an increase in extracellular fluid greater than the amount actually injected as is expected with a hyperosmotic infusion. Sodium concentration fell in proportion to the dilution while K concentration remained unchanged. The gradient was reduced and blood pressure rose, moderately, but in every animal.

Experiment 6. Effect of Sodium on the Blood Pressure Response to an Expansion of the Extracellular Fluid Volume

While it is apparent from the preceding results that the response to hyperosmotic loading is similar to that which follows nephrectomy, the expansion of the extracellular space might perhaps be considered the basic change in both. Equally well, the fall in sodium concentration might be considered the important factor. Two experiments can be presented to demonstrate that neither of these interpretations alone is valid. In these, the effect of fluid volume expansion on the sodium concentration was balanced off by using an intravenous infusion of NaCl, slightly hypotonic in the one, 100 mEq./L., and slightly hypertonic in the other, 200 mEq./L. In each case 7 rats nephrectomized for 48 hours were available. The initial measurements were made as usual 2 hours after inulin injection and, following this, the NaCl solution, warmed, was infused at the rate of 2 ml./100 Gm. The second blood sample was taken 5 min. after the start of the infusion (table 5).
## Table 5.—Effect of Expansion of the Extracellular Space by Infusion of Hypo- and Hyperosmotic NaCl on Blood Pressure and on Extracellular Fluid Volume, Na and K in 48-hour Nephrectomized Rats

<table>
<thead>
<tr>
<th>NaCl 100 mEq/L</th>
<th>NaCl 200 mEq/L</th>
<th>Change Preinfusion Postinfusion</th>
<th>Change Preinfusion Postinfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct B.P., mm Hg</td>
<td>Direct B.P., mm Hg</td>
<td>Change Preinfusion Postinfusion</td>
<td>Change Preinfusion Postinfusion</td>
</tr>
<tr>
<td>systolic</td>
<td>126 ± 9</td>
<td>122 ± 8</td>
<td>4</td>
</tr>
<tr>
<td>diastolic</td>
<td>86 ± 9</td>
<td>81 ± 7</td>
<td>5</td>
</tr>
<tr>
<td>ECFV ml/100 Gm.</td>
<td>23.9 ± 0.7</td>
<td>26.4 ± 1.0</td>
<td>2.5*</td>
</tr>
<tr>
<td>Na conc., mEq/L.</td>
<td>154.7 ± 1.6</td>
<td>151.1 ± 2.5</td>
<td>3.5*</td>
</tr>
<tr>
<td>EC Na, mEq/100 Gm.</td>
<td>3.60 ± 0.09</td>
<td>3.98 ± 0.12</td>
<td>0.29*</td>
</tr>
<tr>
<td>Average body wt., Gm.</td>
<td>189 ± 6</td>
<td>223 ± 3</td>
<td>34</td>
</tr>
<tr>
<td>No. of animals</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Gk</td>
<td>7.13</td>
<td>6.89</td>
<td>0.24</td>
</tr>
<tr>
<td>G-approx</td>
<td>14.3</td>
<td>10.1</td>
<td>14.0</td>
</tr>
</tbody>
</table>

*p < 0.02.

Both infusions increased the extracellular fluid volume, neither caused a rise in blood pressure. Further, while hyposmotic infusion lowered the plasma sodium concentration, blood pressure remained unchanged. Hyperosmotic infusion in this case raised the concentration and caused a fall in blood pressure.

The calculation of relative change in gradient in these experiments (described later) allows for the added sodium and water in both cases. Gradient, like blood pressure, was essentially unchanged by the hyposmotic infusion. In the case of the hyperosmotic infusion gradient rose and blood pressure fell.

The specific effect of the sodium ion is implicit in the fact that the infusion of a glucose solution of comparable osmotic activity (compare experiment 5) raised the blood pressure.

### DISCUSSION

We have presented evidence elsewhere to show that the sodium gradient, that is, the relation of extracellular to intracellular sodium, is itself a determinant of the tone of smooth muscle in general and of the peripheral vasculature in particular. This view is in general harmony with concepts of the role of sodium in excitable tissues but differs in ascribing for smooth muscle less importance to acute depolarization and repolarization and more importance to the steady or equilibrium state.

The general factors involved in determining the sodium gradient may be formulated:

Let

- \( c_i \) = intracellular concentration of Na
- \( c_e \) = extracellular concentration of Na
- \( v_i \) = intracellular fluid volume
- \( v_e \) = extracellular fluid volume

Then

\[ c_i v_i = \text{total effective intracellular Na} = n_i \]
\[ c_e v_e = \text{total effective extracellular Na} = n_e \]

Total body fluid

\[ V_i = v_i + v_e \]

Total body Na

\[ N_i = n_i + n_e + n_s \]

where \( n_s \) represents slowly mobilizable stones.

By direct transposition

\[ c_i = \frac{n_i}{v_i} = \frac{N_i - n_e - n_s}{V_i - v_e} = \frac{N_i - v_e}{V_i - v_e} \]

and the gradient

\[ G = \frac{c_e}{c_i} = \frac{c_e (V_i - v_e)}{N_i - v_e} \]

This formulation implies that whatever fluid or sodium moves out of one compartment is necessarily found in the other. This is true for sudden permeability changes where \( V_i, N_i \), and \( n_e \) are all unchanged. Here the gradient change depends on changes in \( c_e v_e \). Since a decrease of this product in the numerator also increases the denominator...
small changes in permeability obviously have large effects on the gradient. This fits our data for acute pressor and depressor agents very well and explains why our best correlation was between blood pressure and the product c_{ev}.

As is well known, however, the effective intracellular sodium is relatively quite a small quantity and where there is no abrupt change in permeability cannot be expected to change very much. In brief, the denominator in equation (1) \( N_i - c_{ev} - n_s \) is the expanded expression for \( n_i \) in effect a constant so that the equation reduces to

\[
G = \frac{c_{ev}(V_i - v_e)}{k}
\]

This equation would apply to slowly developing equilibrium states such as follow nephrectomy and dehydration, assuming \( Y_t \) is either unchanged or known. The relative gradient, \( G_k \), where \( k \) is unresolved, was calculated for our data in these two states (experiments 1 and 2) using values for \( V_i \) taken from the data of Aach, Rolf and White, although the results in these cases are similar if \( Y_t \) is taken as unchanged. In both these experiments the blood pressure is inversely related to the direction of gradient shift. A numerical approximation of \( G \) can be made by setting \( k \) equal to 0.5 mEq./100 Gm. based on 50 ml. of intracellular water/100 Gm. containing sodium at an average concentration of 10 mEq./L. This value is shown in the tables as \( G_{approx} \).

It seems likely that a similar explanation is true for renalprival hypertension in the dog. Here the problem is complicated by the fact that the animal is usually maintained in approximate balance by one or another type of vivadialysis. Nonetheless, several investigators have felt that the rise in blood pressure did in fact depend on some masked alteration in salt and water balance. Causal emphasis was at first placed on an expanded plasma volume and later on an expansion of the extracellular fluid volume. The demonstration that blood pressure rises even if plasma volume is held constant made this explanation doubtful. A rise in plasma sodium concentration has been looked for since this has been considered of possible importance in hypertensive states, but definitive evidence has been presented to show that blood pressure rises even if sodium does not rise. In point of fact, these same experiments usually show a fall in plasma sodium, as might be expected from the preceding analysis. Orbison et al. have
emphasized, however, that a tenuous equilib-
rium does exist even where the dog is in ap-
parent balance, by showing that an extreme
pressor response may be obtained by ex-
panding the extracellular space. This tallies
with our findings in the rat. The claim that
implanting the ureters into the vena cava
does not raise blood pressure is not convinc-
ing since a small rise in pressure is shown
and the toxic nature of the procedure ac-
knowledged.3

Although our analysis of gradient changes
is in the early stages of development and is
necessarily crude, it does demonstrate that 3
important quantities at least—body water,
freely mobile sodium and stored sodium—each
of which may vary independently, are in-
volved. The rise of blood pressure which fol-
lows nephrectomy can easily be mimicked in
the rat by a simple hyperosmotic load which
decreases plasma sodium and increases extra-
cellular fluid. It has also been shown, how-
ever, that the rise in blood pressure is not
related to any of these quantities considered
alone, but rather to their interrelation as de-
finied by the sodium gradient.

These experiments suggest that renoprival
hypertension can be explained on the same
basis as other pressor and depressor phenom-
ena which we have studied. In this case no
specific hormone alters permeability or ion
binding or metabolism. Instead, the accumu-
lation of unexcreted metabolites tends to shift
water out of the cells and to lower the sodium
gradient. In the general sense of a final
common pathway, renoprival hypertension is
pertinent to the problem of essential hyper-
tension. Etiologically, it does not seem to
have common ground.

Summary

The rise in blood pressure following
nephrectomy in the rat is accompanied by an
increase in extracellular fluid volume and,
despite a small increase in extracellular so-
dium, a fall in sodium concentration in the
plasma. There is also a marked increase in
extracellular potassium which more than off-
sets the diluting effect of the increase in fluid
volume so that plasma potassium rises. The
basic pattern of salt and water shift follow-
ing nephrectomy is not due to active inter-
vention on the part of either the neurohy-
pophysis or adrenal glands since it occurs
equally well in the absence of both these func-
tions.

An orally or intravenously administered
hyperosmotic load mimics the effects of
nephrectomy insofar as extracellular fluid
volume, sodium and blood pressure are con-
cerned. Water deprivation produces the re-
verse patterns accompanied by a fall in blood
pressure. In both cases the blood pressure is
inversely related to the Na\textsubscript{2}/Na\textsubscript{1} gradient,
which is a direct determinant of smooth mus-
cle tone. Since the accumulation of metabolites
following nephrectomy is analogous to the
introduction of an hyperosmotic load, this
alone is sufficient cause for the postnephrec-
tomy rise in blood pressure.

A basic formulation of the factors involved
in the sodium gradient is presented.

Summario in Interlingua

Le augmento del tension de sanguine post
nephrectomia in rattos es accompaniante de un
augmento del volumine de liquido extracel-
lar e—in despecto de un leve augmento del
natrium extracellular—de un reduction del
concentration de natrium in le plasma. Il oc-
curre etiam un marcate augmento del kalium
extracellular que non solmente compensa le
effecto dilutori del augmentate volumine de
liquido sed de facto effectua un augmento del
nivello de kalium in le plasma. Le configura-
tion fundamental del migration de sal e aqua
post nephrectomia non resulta de un inter-
vention active per le neurohypohyse o per
le corpore suprarenal, proque illo remane sin
alteration quando iste duo functiones es
eliminate.

Un carga hyperosmotice administrate per
via oral o intravenose imita le effectos de
nephrectomia con respecto al volumine de
liquido extracellular, al concentration de
natrium, e al tension de sanguine. Depriva-
tion de aqua produce un configuration contrari, accompaniate de un reduction del tension de sanguine. In ambe casos le tension de sanguine es relationate inversemente al gradiente Na⁺/Na⁻, le qual es un determinante directe del tono de musculo lisie. Viste que le accumulation de metabolitos post nephrectomia es analoge al introduction de un carga liyperosmotie, isto per se es sufficiente pro causar le augmento post-nephrectomia in le tension de sanguine.

Es presentate un formulation fundamental del factores que es interesate in le gradiente de natrium.

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