The Effect of Salt Loading and Salt Depletion on Renal Function and Electrolyte Excretion in Man

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With the Technical Assistance of Martha Barrett and Bernice Dumas

Glomerular filtration rate (GFR), renal plasma flow (RPF), and electrolyte excretion were studied in 17 patients subjected to salt depletion and loading. Salt depletion led to maximal renal salt conservation with the average GFR and RPF slightly decreased. Salt loading produced increased excretion of sodium and chloride with the average GFR and RPF slightly increased. Since the decreased electrolyte excretion with salt depletion and increased electrolyte excretion with salt loading were essentially independent of the direction of change in GFR and RPF, it is inferred that tubular absorptive activity is a more significant factor in achieving electrolyte balance than are GFR changes.
ing a period in which the patient was maintained on the routine ward diet. Subsequently, the patient was salt depleted by the restriction of salt intake and the intravenous administration of 2 cc. of Mercuzanthin per day for three days. On the fourth day the measurements were repeated. The patient was then salt loaded by the intravenous administration of 3 liters of 0.9 per cent saline each day for three days. Again on the fourth day the measurements were repeated. In all, 5 patients were subjected to the complete series of three tests. Four additional patients were subjected to the control test and either the depletion or loading procedure. Throughout all control, salt depleting or salt loading periods water intake was unrestricted. Each test consisted of three clearance periods approximately 20 minutes in length. All were performed in the postabsorptive state 14 to 18 hours after the last meal and were preceded by the ingestion of 1 liter of water to ensure an adequate flow of urine. Inulin and paraaminohippurate were administered by intravenous drip.

In the second series of experiments, changes in renal function in response to rapid salt loading were assessed in the following manner. Control levels for filtration rate, plasma flow and clearance of sodium, potassium and chloride ions were established in three initial clearance periods, following which 1800 cc. of either 0.9 per cent saline or balanced salt solution* were administered intravenously at a rate of approximately 30 cc. per minute. During this infusion interval three additional clearance periods were obtained. Subsequent to the loading procedure a third group of three clearance periods completed the experiment. This routine was applied in 8 patients, on one of whom two experiments were performed, the first with saline, the second with the balanced salt solution.

Methods employed include that of Harrison for inulin, that of Bratton and Marshall for paraaminohippurate, that of Sendroy for chloride, that of Van Slyke and Neill for bicarbonate, and that of Phillips and associates for plasma protein. Hematocrits were measured in Wintrobe tubes and analyses of sodium and potassium were performed with an internal standard flame photometer accurate to ±2 per cent.

**Results**

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The clearance data on the 5 patients in which the full series of control, depletion and loading tests were completed are summarized in table 1. The control values for glomerular filtration rate, renal plasma flow and filtration fraction in these patients averaged 128 cc. per minute, 596 cc. per minute and 0.22, respectively. With the possible exception of those cited for patient Y. M., all renal variables lie within the generally accepted ranges of normal.

As a result of salt depletion by three successive daily doses of Mercuzanthin, body weight decreased significantly in each subject, the average weight loss amounting to 8.3 pounds. It is apparent from the mean increase in plasma protein concentration of 0.47 Gm. per hundred cc. that only a small fraction of the lost fluid was derived from the blood plasma; the major fraction must have been derived from the interstitial and intracellular reservoirs. On an average, glomerular filtration rate decreased 4 cc. per minute and renal plasma flow decreased 44 cc. per minute. These changes are rather insignificant, especially in view of the fact that in 2 subjects (Y. M. and N. S.) filtration rate actually increased and in only one (L. B.) was the decrease appreciable.

Significant decreases in the plasma concentrations of chloride and sodium were noted in all subjects. Since chloride fell somewhat more than sodium, a rise in plasma carbon dioxide content would be anticipated and was actually observed in the 2 instances in which it was measured. Most striking, however, was the negligible clearance of chloride and of sodium, the marked conservation of these ions constituting an effective renal compensation for depleted reserves and reduced plasma levels.

As a result of salt loading by the administration of 3 liters of saline intravenously per day on three successive days, body weight increased appreciably over the control value in all but one subject, L. B. The average increase amounted to 6.7 pounds. As indicated by the decrease in protein concentration, plasma volume was somewhat increased. On an average, glomerular filtration rate increased 6.1 cc. per minute and renal plasma flow increased 26 cc. per minute. These changes are of minor significance in view of the fact that both variables actually decreased in two subjects. Further-
more, subject N. S. accounted for most of the average change.

Increases in the plasma concentration of sodium and chloride were noted in all subjects, a fact which accounts for the small weight gain in response to saline infusion, added dietary salt and free access to water.

The data relating sodium excretion to filtra-

**Table 1.—Clearance Data for Control, Salt Depletion, and Slow Salt Loading Periods**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Regimen</th>
<th>Blood Press.</th>
<th>Urine Flow</th>
<th>Glom. Filtr. Rate</th>
<th>Plasma Concentration</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mm. Hg</td>
<td>cc. per min.</td>
<td>m.Eq. per liter</td>
<td>Na</td>
<td>K</td>
</tr>
<tr>
<td>Y. M. F.</td>
<td>Psychoneurosis</td>
<td>Control</td>
<td>112/75</td>
<td>151</td>
<td>7.17 39.2</td>
<td>389 0.24</td>
<td>142 64.35</td>
</tr>
<tr>
<td>49 yrs.</td>
<td></td>
<td>3 × 2 cc. Mercuzan</td>
<td>122/81</td>
<td>143</td>
<td>2.89 101.4</td>
<td>373 0.27</td>
<td>134 54.49</td>
</tr>
<tr>
<td>M. W. F.</td>
<td>Cirrhosis</td>
<td>Control</td>
<td>116/89</td>
<td>111.5</td>
<td>4.18 123.5</td>
<td>578 0.21</td>
<td>134 23.95</td>
</tr>
<tr>
<td>32 yrs.</td>
<td></td>
<td>3 × 2 cc. Mercuzan</td>
<td>140/103</td>
<td>123</td>
<td>3.40 125.2</td>
<td>521 0.24</td>
<td>141 13.64</td>
</tr>
<tr>
<td>H. S. F.</td>
<td>Peptic ulcer</td>
<td>Control</td>
<td>113/95</td>
<td>193</td>
<td>11.9 148.7</td>
<td>701 0.21</td>
<td>142 52.41</td>
</tr>
<tr>
<td>36 yrs.</td>
<td></td>
<td>3 × 2 cc. Mercuzan</td>
<td>106/82</td>
<td>178</td>
<td>7.87 138.2</td>
<td>626 0.22</td>
<td>136 64.09</td>
</tr>
<tr>
<td>N. S. F</td>
<td>Peptic atonia</td>
<td>Control</td>
<td>117/72</td>
<td>179</td>
<td>9.46 152.5</td>
<td>789 0.19</td>
<td>140 63.60</td>
</tr>
<tr>
<td>43 yrs.</td>
<td></td>
<td>3 × 2 cc. Mercuzan</td>
<td>113/77</td>
<td>125.5</td>
<td>1.36 131.0</td>
<td>594 0.22</td>
<td>136 83.32</td>
</tr>
<tr>
<td>L. B. F.</td>
<td>Pneumonia</td>
<td>Control</td>
<td>120/71</td>
<td>128.5</td>
<td>4.27 146.6</td>
<td>682 0.22</td>
<td>142 14.09</td>
</tr>
</tbody>
</table>

**Fig. 1. Relationship of sodium clearance to glomerular filtration rate and renal plasma flow (salt loading).**

Since chloride increased more than sodium, a fall in plasma carbon dioxide content would be expected and was actually observed in the 2 subjects in which it was measured. The clearances of chloride and of sodium were increased in all subjects, a fact which accounts for the small weight gain in response to saline infusion, added dietary salt and free access to water.
control value is plotted against the change in glomerular filtration rate and against the subjects, independent of change in filtration rate or plasma flow. The sodium clearance was

**Table 2.**—Clearance Data for Two Experiments on Patient E. B. for Control and Rapid Salt Loading Periods

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>E. B.</td>
<td>Convalescent Pneumonia. Mild Cirrhosis</td>
<td>31–51</td>
<td>130/88</td>
<td>10.20</td>
<td>150.2</td>
<td>610</td>
<td>0.25</td>
<td>138.3</td>
<td>4.23</td>
<td>109.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51–71</td>
<td>125/90</td>
<td>7.80</td>
<td>141.4</td>
<td>541</td>
<td>0.27</td>
<td>140.0</td>
<td>4.23</td>
<td>109.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>145.8</td>
<td>576</td>
<td>0.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. B.</td>
<td>Convalescent Pneumonia. Mild Cirrhosis</td>
<td>82–147</td>
<td>1800 cc</td>
<td>0.9 per cent Sodium Chloride at 27.7 per min.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>142–167</td>
<td>130/90</td>
<td>10.82</td>
<td>131.8</td>
<td>583</td>
<td>0.23</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>167–187</td>
<td>140/90</td>
<td>5.20</td>
<td>125.4</td>
<td>492</td>
<td>0.26</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>187–207</td>
<td>140/90</td>
<td>3.80</td>
<td>126.5</td>
<td>493</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>127.9</td>
<td>523</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. B.</td>
<td></td>
<td>32–55</td>
<td>115/75</td>
<td>7.18</td>
<td>152.0</td>
<td>628</td>
<td>0.24</td>
<td>139.6</td>
<td>4.52</td>
<td>107.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55–76</td>
<td>115/75</td>
<td>5.52</td>
<td>140.0</td>
<td>556</td>
<td>0.25</td>
<td>139.6</td>
<td>4.36</td>
<td>107.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>146.0</td>
<td>592</td>
<td>0.24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. B.</td>
<td></td>
<td>78–134</td>
<td>1800 Balanced Salt Solution at 32.2 cc. per min.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>143–164</td>
<td>140/95</td>
<td>3.90</td>
<td>112.0</td>
<td>446</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>164–186</td>
<td>140/95</td>
<td>2.77</td>
<td>125.0</td>
<td>522</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>186–207</td>
<td>150/95</td>
<td>2.88</td>
<td>146.0</td>
<td>664</td>
<td>0.22</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>128.0</td>
<td>544</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

change in renal plasma flow. The data clearly fall into two groups. The sodium clearance was reduced relative to normal in all saline loaded subjects, independent of change in filtration rate or plasma flow. Obviously, the differences increased relative to normal in all saline loaded subjects, independent of change in filtration rate or plasma flow. Obviously, the differences
in sodium clearance between the states of dehydration, normal hydration and saline loading cannot in these experiments be related primarily to changes in either filtration rate or plasma flow. They must be due in large part to alterations in completeness of tubular absorption of sodium. However, in the data obtained after saline loading there appears to be a relationship between the magnitude of the increase in sodium clearance and both filtration rate and plasma flow, imperfect though the correlation may be.

The Effect of Rapid Hydration on Renal Function and Electrolytic Excretion.

The nine experiments in which patients were rapidly hydrated with 1800 cc. of either normal saline or balanced salt solution confirm the above expressed view that major changes in electrolyte clearance may be effected by alterations in tubular activity independent of changes in renal plasma flow and filtration rate. Two experiments on one subject, E. B., are summarized in table 2. It is apparent from both plasma protein concentration and hematocrit that rapid hydration with saline (experiment 1) produced a significant degree of hemodilution. During the infusion a slight increase in renal plasma flow occurred; filtration rate actually dropped. However, both variables were reduced below the normal in the posthydration period. Despite these facts the clearance of sodium and chloride increased, although the increase was not especially striking. Essentially the same response was observed in experiment 2, in which the balanced salt solution was administered. Two differences are, however, worthy of note. Sodium and chloride clearances increased slightly more with the infusion of the balanced salt solution than with the saline.

![Figure 2](http://circ.ahajournals.org/)

**Fig. 2.** Relationship of sodium clearance to glomerular filtration rate and renal plasma flow (rapid salt loading).

Although the differences are small, they have been observed repeatedly in both man and dog. The potassium clearance in the experiment with the balanced salt solution which contained 5 millimols per liter of potassium chloride, was much increased, indeed to such an extent that an actual fall in plasma potassium concentration resulted.

The data relating sodium excretion to filtration rate and plasma flow in all nine experiments in which 1800 cc. of fluid were rapidly infused are summarized in figure 2. The change in sodium clearance during and after the infusion relative to the average of the three control values is plotted against the change in glomerular filtration rate or plasma flow. It is apparent that the sodium clearances in all infusion and postinfusion periods with two exceptions were significantly elevated over the control values independent of change in filtration rate.
tion rate or plasma flow. The two instances in which no change in clearance occurred were both initial infusion periods. Obviously, the increase in sodium clearance in these experiments cannot be related directly to change in filtration rate or renal plasma flow, but must be assigned in large part to change in tubular absorptive activity. However, as was suggested in the previous series of experiments, there appears to be a significant relationship between the magnitude of the increase in sodium clearance and both filtration rate and plasma flow, imperfect though the correlation may be.

**Discussion**

According to Wesson and his co-workers, variations in filtration rate play a prominent role in maintenance of electrolyte balance under differing salt loads. This view is based on their concept that a fixed proportion of the filtered sodium amounting to 87.5 per cent is absorbed in the proximal tubular system. The 12.5 per cent delivered into the distal tubule is ordinarily slightly more than enough to saturate the fixed and limited reabsorptive capacity of this segment. The excess is excreted. If salt load is low, the circulating blood volume is reduced and filtration rate declines. The delivery of 12.5 per cent of this reduced filtered moiety into the distal segment less than saturates its absorptive capacity and essentially all of the sodium is conserved. If salt load is high, the circulating blood volume is expanded and filtration rate increases. The delivery of 12.5 per cent of the increased filtered moiety into the distal segment more than saturates absorptive capacity and the rate of excretion of sodium rises. As salt and fluid are lost, blood volume contracts and filtration rate declines to the more normal range. Sodium excretion again returns to normal.

In support of this concept, Ladd and Raisz have demonstrated in the dog a positive correlation between salt load, salt excretion and filtration rate. Furthermore, Merrill and others claim that a reduction in filtration rate without a corresponding reduction in tubular absorptive capacity underlies the sodium retention observed in chronic congestive heart failure and acute glomerulonephritis. Our data support this concept in part in that they indicate that under salt loading the magnitude of the increase in sodium clearance is greater if filtration rate increases. The fact that filtration rate ordinarily increases but little in man whereas in the dog it increases markedly may explain the relative inability of the former to eliminate rapidly a large salt load.

However, our experiments more directly confirm the view of Leaf and associates and Kattus and Sinclair-Smith and co-workers that achievement of electrolyte balance under high salt load or exercise depends primarily upon a reduction in tubular absorptive capacity. It would appear that the rate of secretion of adrenal cortical hormone varies inversely with salt load. High salt load, low rate of hormone secretion and increased absorptive capacity lead to salt conservation. There is evidence suggesting that exaggeration of this latter hormonal response is the cause of salt retention in those diseases characterized by the formation of edema. Actually, our results indicate only that variations in completeness of tubular absorption play a more significant role in determining electrolyte balance in man than do variations in filtration rate. They have no bearing on the mechanism by which this end is achieved. In the salt depleted state, the decreases in plasma sodium and chloride concentration must in themselves largely condition the nearly complete renal conservation of these ions.

**Summary**

Glomerular filtration rate, renal plasma flow and electrolyte excretion have been studied in a series of 17 convalescent patients subjected to salt depleting and salt loading procedures in an attempt to assess the relative roles of changes in glomerular filtration and tubular absorptive activity in the maintenance of electrolyte balance. When patients were salt depleted by a low salt diet and the administration of 2 cc. of Mercuzanthin per day for three days, rates of excretion of sodium and chloride were reduced nearly to zero. Glomerular filtration rate and renal plasma flow were on an average slightly decreased, but independent of the direction of change in these renal variables,
both ions were maximally conserved. The plasma levels of sodium and chloride were reduced by such salt depleting measures and the filtered ion loads decreased. It is inferred that a lower filtered load favors more complete absorption. When patients were salt loaded gradually by the administration of 3 liters of saline per day for three days or rapidly by the infusion of 1800 cc. of saline in one hour, sodium and chloride excretion were increased. Although glomerular filtration rate and plasma flow were on an average slightly increased, sodium and chloride clearances were elevated independent of the direction of change in these renal variables. It is inferred that a decrease in tubular absorptive activity under salt loading is a more significant factor in achieving electrolyte balance than is an increase in glomerular filtration rate. However, the magnitude of the increase in electrolyte excretion which results from salt loading appears to be related directly to filtration rate.

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Circulation. 1951;3:275-281
doi: 10.1161/01.CIR.3.2.275

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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