THE EFFECT OF NUTRITIONAL HYPOPROTEINEMIA ON
THE ELECTROLYTE PATTERN AND CALCIUM
CONCENTRATION OF SERUM

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Previous work (1) showed that when the concentration of plasma
proteins is reduced by plasmapheresis, the concentration of serum
protein varied inversely with the chloride and directly with the
calium, while no relation could be demonstrated between protein
and total base or bicarbonate. The experiments were open to the
serious objection that plasmapheresis involves the injection of a
solution of sodium chloride as well as repeated bleeding. Hence
changes in electrolyte were referable to these procedures as well as
to variations in serum protein concentration. While an attempt
to control the effect of the injection of physiological saline solution
was made, the experimental method was not that best adapted to
a study of the relation of the concentrations of electrolyte and
serum protein.

In this paper similar data are presented from dogs in which
serum protein was lowered by diets deficient in protein.

Methods

The chemical data discussed in this paper were obtained from
venous serum taken about 9 a.m. at approximately weekly inter-
vals. Two dogs weighing about 8 kilos were fed a diet consisting
of dextrin, sucrose, vitavose, brewers' yeast, cod liver oil, and a
salt mixture.¹ In Experiment I, the animals were kept on the
diet till death seemed imminent and were then given the same diet
except that 20 per cent commercial casein was substituted for the

¹The added salt of the diet consisted of 2.5 per cent bone ash and
1.25 per cent salt mixture (Cowgill, G. R., J. Biol. Chem., 56, 725 (1923)).
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dextrin. This led to prompt recovery. The first diet (No. 29) contained less than 0.01 gm. of sodium chloride per day. Experiment II was carried out on the same dogs after they had received a normal diet for 6 months. The diet (No. 31) was the same as that used in Experiment I except that about 7 gm. per day of sodium chloride were added. The experiment was terminated by killing the dogs when death seemed likely to occur in a few days. The diets yielded about 5 per cent of the total calories in protein, which was derived from the yeast and vitavose. Otherwise the diets were considered adequate. The number of calories offered was that recommended by Cowgill (2). After about 40 days on the low protein diet, some of the food was refused.

The nutritional aspects will be discussed separately when more experiments can be carried out to study this phase. The electrolyte data are presented now, since this phase of the study is not connected with the other questions brought up by the experiments.

The chemical methods are the same as those used previously (1) except that sodium (Barber and Kolthoff (3)) and potassium (Shohl and Bennett (4)) were determined instead of total base. Concentrations are expressed in milli-equivalents per liter estimated as in the previous study (1). The statistical methods are those suggested by Dunn (5).

The statistical analysis of the data is presented in Table I which gives the average values ± the standard deviation. In Experiment I, sufficient analyses were made on each animal to permit averages for each, but in Experiment II, both animals are considered together. The values are substantially the same for the two experimental periods. In the case of potassium a slight variation in technique was thought to be the cause of the higher values in Experiment II.

Chart I shows the distribution of bicarbonate, chloride, and sodium as related to protein. All data are grouped together, the dogs on the higher sodium chloride intake being represented by crosses. No significant correlation is revealed between protein and these ions.

The data were further analyzed to determine whether individual experiments revealed correlations that were masked by considering data from the different experiments together. In Experiment II, a negative correlation between protein and chloride (−0.6
Chart I. The relation of the concentration of serum protein to that of serum electrolyte.

± 0.14)² was found, but no correlation in the other instances. In this same experiment a positive correlation between protein and bicarbonate (± 0.062 ± 0.14)² was found.

² The figures give the correlation coefficient ± the standard deviation of the coefficient.
### TABLE I

Average Electrolyte Concentration ± Standard Deviation

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Diet No.</th>
<th>Protein</th>
<th>HCO$_3^-$ per cent</th>
<th>Cl m.-eq. per l.</th>
<th>H$_2$PO$_4^-$+HPO$_4^-$ m.-eq. per l.</th>
<th>Na m.-eq. per l.</th>
<th>K m.-eq. per l.</th>
<th>Ca m.-eq. per l.</th>
<th>Determination No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>4.81±0.82</td>
<td>21.68±1.26</td>
<td>109.55±2.94</td>
<td>2.02±0.13</td>
<td>144.35±2.80</td>
<td>3.73±0.62</td>
<td>5.01±0.55</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>4.45±0.84</td>
<td>22.66±1.07</td>
<td>109.91±2.22</td>
<td>2.53±0.34</td>
<td>144.46±3.59</td>
<td>3.91±0.57</td>
<td>5.21±0.61</td>
<td>19</td>
</tr>
<tr>
<td>1, 2</td>
<td>29</td>
<td>4.63±0.85</td>
<td>22.41±1.19</td>
<td>109.72±2.65</td>
<td>2.27±0.52</td>
<td>144.41±2.53</td>
<td>3.82±0.50</td>
<td>5.11±0.54</td>
<td>36</td>
</tr>
<tr>
<td>1, 2</td>
<td>31</td>
<td>4.57±0.52</td>
<td>22.70±1.80</td>
<td>110.74±3.29</td>
<td>2.56±0.45</td>
<td>142.55±1.43</td>
<td>4.89±0.45</td>
<td>4.93±0.30</td>
<td>19</td>
</tr>
</tbody>
</table>

### TABLE II

Effect of Injection of 0.9 Per Cent Sodium Chloride on Electrolyte of Serum*

<table>
<thead>
<tr>
<th>Period</th>
<th>No. of determinations</th>
<th>Protein</th>
<th>HCO$_3^-$ per cent</th>
<th>Cl m.-eq. per l.</th>
<th>Total base m.-eq. per l.</th>
<th>Na $^+$ m.-eq. per l.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8</td>
<td>4.75±0.10</td>
<td>22.38±0.42</td>
<td>110.25±1.03</td>
<td>142±1.70</td>
<td></td>
</tr>
<tr>
<td>Salt</td>
<td>8</td>
<td>4.21±0.09</td>
<td>21.50±0.50</td>
<td>111.75±0.67</td>
<td>141±1.20</td>
<td></td>
</tr>
<tr>
<td>Change†</td>
<td>8</td>
<td>-0.54±0.09</td>
<td>-0.88±0.04</td>
<td>+1.50±1.22</td>
<td>-1±2.08</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>8</td>
<td>6.04±0.14</td>
<td>23.68±0.44</td>
<td>109.38±0.90</td>
<td>159.16±1.46</td>
<td></td>
</tr>
<tr>
<td>Salt</td>
<td>11</td>
<td>5.90±0.15</td>
<td>22.37±0.34</td>
<td>110.42±0.77</td>
<td>156.95±0.71</td>
<td></td>
</tr>
<tr>
<td>Change†</td>
<td></td>
<td>-0.14±0.20</td>
<td>-1.31±0.56</td>
<td>+1.04±1.19</td>
<td>-2.21±1.62</td>
<td></td>
</tr>
</tbody>
</table>

* Average values ± standard deviation.
† Difference ± standard deviation of difference.
These figures were interpreted to indicate no fundamental relation between chloride or bicarbonate and protein. Apparently some disturbance in the concentration of chloride or bicarbonate occurred while the decrease in serum protein was being brought about by the low protein diet. Under these circumstances, the usual reciprocal relation between bicarbonate and chloride held, and no inference concerning the relation of bicarbonate or chloride and protein can be made. No other correlations were of a degree that could be deemed significant. Chart I is, therefore, regarded as representing the distribution of bicarbonate, chloride, and sodium in relation to protein in dogs with nutritional hypoproteinemia.

The relation of protein to calcium is represented in Chart II. The central line represents the regression equation bounded on either side by a line 1 standard deviation distant. The correlation coefficient of calcium and protein is +0.74. The standard deviation of the correlation coefficient is ±0.06. The regression equation is Ca = 0.467 protein + 2.89. The standard deviation
of the slope or regression coefficient is ±0.057 and the standard deviation of the calcium computed from protein ±0.213. Calcium is expressed in milli-equivalents per liter and protein in percent. The similar equation obtained by plasmapheresis experiments (1) was Ca = (0.47 ± 0.57) protein + (3.72 ± 0.32). These equations do not differ from each other significantly except perhaps in the intercept.

The negative correlation between protein and chloride in plasmapheresis experiments was deemed significant, although a gradual raising of chloride by the repeated injection of 0.9 percent sodium chloride could not be ruled out. Furthermore, in the plasmapheresis experiments, no correlation between protein and bicarbonate was found. In normal dogs, the daily injection of about 500 ml. of physiological salt solution did not lead to significant deviations in the protein, bicarbonate, chloride, or total base. In order to test whether a low serum protein concentration would alter the results, Dogs 1 and 2 on the 65th to 68th days of Experiment II were subjected to daily intravenous injections of 500 ml. of 0.9 percent sodium chloride and daily estimations of electrolyte were made on blood withdrawn just before the infusion.

Table II gives the averages ± the standard deviations of the average. In each dog, the withdrawal of four serum samples was preceded within 22 to 24 hours by the injection of salt solution, and four other analyses which were carried out within 2 weeks before or after the infusions are used as controls. The similar data obtained previously on normal dogs (1) are reproduced for comparison. Although the dogs had definitely low serum proteins, the results are essentially the same in both experiments, except that with hypoproteinemia the serum protein is significantly reduced by the injection of salt solution. While the experiments in both instances do not demonstrate that no change takes place, they do indicate that more extensive data would be unlikely to show larger differences than those found ± 2 standard deviations of the differences.

**DISCUSSION**

The present data probably give a correct impression of the electrolyte picture of the serum in dogs with nutritional hypoprotein-
emia. The undernutrition accompanying the hypoproteinemia in these experiments may alter the electrolyte picture so that changes produced by alteration in protein concentration are masked. However, such distortions are probably not great and the data indicate that low serum protein is not the cause of deviations in the electrolyte pattern found in nephrosis. In other words the present data afford experimental substantiation of the conclusion of Peters et al. (6) that low serum protein does not explain the high chloride or low total base of nephrosis.

The data confirm the direct relation between protein and calcium pointed out previously (7–10). Attention should be called to the fact that the slope of the curve expressing the relation between protein and calcium differs in dog and man. Our data indicate the slope for the dog to be 0.47, while Peters and Eiserson (9) found the slope for man to be 0.27, when the equation is expressed in milli-equivalents per liter. The proteins of dog and man may exhibit such a difference in their calcium-combining power. On the other hand, the selection of cases in deriving the human curve which for the lower protein values was largely based on cases of nephritis, may have obscured the true relationship. Nutritional hypoproteinemia seems less likely to be complicated by deviations in calcium concentration due to factors other than serum protein. This seems especially true of the dogs, which presumably received adequate calcium, as bone ash was present in their food. Data showing the relation of protein to calcium in nutritional states might settle this point. Stearns and Knowlton's (10) figures show a relation between protein and calcium in babies. As pointed out previously (1), this relationship substantiates the slope of the curve of Peters and Eiserson. For the present it seems safe to assume that dog serum and human serum combine with calcium in different amounts and the equation of Peters and Eiserson expresses the relation in man. However, as pointed out previously, the constant (or intercept) will vary with disturbances in calcium metabolism, since it measures the factors, other than protein, which affect the concentration of serum protein.

**SUMMARY**

Electrolyte concentration during the course of protein starvation was determined on dogs.
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No clear cut relationship between the variation in serum protein and serum chloride, bicarbonate, sodium, or potassium was found.

The direct relationship between serum protein and serum calcium was found to be expressed by the following equation: Ca = 0.47 protein + 2.89. Ca is expressed in milli-equivalents per liter, protein in per cent.

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