CELL SODIUM, POTASSIUM AND WATER IN URAEMIA
AND THE EFFECTS OF REGULAR DIALYSIS AS STUDIED IN THE LEUCOCYTE

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SUMMARY

1. The leucocyte has been used as a model for the study of intracellular sodium, potassium and water in uraemia. The advantages of this cell are described.

2. In undialysed patients with advanced renal failure leucocyte sodium and water contents were significantly greater than normal. Leucocyte potassium content (mmol/kg of dry solids) and concentration (mmol/l of cell water) were reduced.

3. In patients receiving regular dialysis leucocyte water was significantly reduced. Leucocyte potassium content was also reduced in this group, but leucocyte potassium concentration in cell water had returned to normal.

4. In the normal subjects and also in the dialysed patients leucocyte water correlated better with potassium than with sodium content. In contrast, in the undialysed uraemic patients leucocyte water correlated better with sodium than with potassium content, indicating that the increased cell sodium was an important determinant of the increased cell water in this group.

Key words: uraemia, dialysis, leucocyte, sodium, potassium, water.

The sodium content of the erythrocyte is increased and active sodium efflux from this cell diminished in some patients with advanced chronic renal failure (Welt, Sachs & McManus, 1964; Welt, 1969). This defect in the erythrocyte is associated with reduced activity of the membrane ouabain-sensitive adenosine triphosphatase (Welt, Smith & Dunn, 1967), is not caused by substrate deprivation (Lightman & Miller, 1970), and can be induced in normal cells by incubation in uraemic plasma (Cole, Balfe & Welt, 1968). However, the erythrocyte is a highly specialized cell and it cannot be assumed that uraemia produces similar defects in cation transport in other cells. Moreover, the erythrocyte is unsatisfactory as a model for the study of the effects on cell volume of alterations in sodium and potassium transport. Thus

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erythrocyte potassium is inversely related to haemoglobin content (Maizels, 1936), and the possession of a considerable amount of chloride is probably an important factor in the unusual regulation of cell volume seen in the erythrocyte (Gary-Bobo & Solomon, 1968).

The leucocyte lacks the above drawbacks while sharing with the erythrocyte the advantages of easy accessibility and of an isolated cell preparation for analysis of intracellular constituents (Baron, 1969; Patrick & Bradford, 1972). We have previously reported a reduction in leucocyte potassium content in uraemia (Patrick, Jones, Bradford & Gaunt, 1972) and in the present paper we report measurements of leucocyte sodium and water in patients with renal failure. The relationship between measured intracellular cations and water content of the leucocyte is described. This relationship is important in the determination of cell volume, which is increasingly recognized as a factor of great potential importance in the pathophysiology of disease (Ames, Wright, Kowada, Thurston & Majno, 1968; Leaf, 1970; Flores, DiBona, Beck & Leaf, 1972). A preliminary account of the present work has been published (Jones & Patrick, 1972).

**METHODS**

Thirty measurements were made on nineteen patients with advanced chronic renal failure ('no-dialysis group'). Plasma creatinine varied from 0.46 to 2.57 mmol/l, mean 1.33 mmol/l (15 mg/100 ml), and exceeded 0.89 mmol/l (10 mg/100 ml) in all patients except one. The replicate measurements made on eleven patients were separated by at least 1 month and in the interval plasma creatinine had increased by at least 0.27 mmol/l (3 mg/100 ml).

One set of measurements was also made on each of fifteen patients ('dialysis group'), who had received regular haemodialysis for 3–26 months (mean 14.3 months). Haemodialysis was performed for 30 h each week by using Kiil dialysers and Cuprophane membranes. The potassium concentration in the dialysis fluid was 1 mmol/l. Blood samples from patients in this group were obtained immediately before dialysis.

The control values were obtained from fifty-nine measurements on normal hospital staff and medical students.

The method of harvesting and analysing the leucocytes from 20 ml of venous blood was described in detail by Patrick et al. (1972.) It is based on the technique described by Boyum (1968), in which whole blood is layered on to a mixture of Hypaque (28.33 g/100 ml sodium diatrizoate, 56.67 g/100 ml meglumine diatrizoate, 0.02 g/lOO ml calcium edetate) and methyl cellulose, with a density of 1.07 g/ml. Erythrocytes are aggregated at the interface, the leucocyte-rich plasma layer is collected and remaining erythrocytes are removed by carefully controlled hypotonic lysis. Viability and ultramicroscopic integrity of the leucocytes collected by this method exceed 95% as judged by Trypan Blue exclusion and electron microscopy.

This study was approved by the Hospital Ethical Committee.

**RESULTS**

*Sodium*

The range of sodium content was much wider in undialysed uraemic patients than normal, and in twelve of the thirty measurements leucocyte sodium content [mmol/kg of dry solids (DS)] exceeded the normal mean by more than one standard deviation. The mean leucocyte
**Table 1. Leucocyte analyses in control subjects, undialysed uraemic patients and patients receiving regular haemodialysis**

NS, not significant; DS, dry solids.

<table>
<thead>
<tr>
<th>Leucocyte component</th>
<th>Control (59 subjects)</th>
<th>Uraemia (30 patients)</th>
<th>Dialysis (15 patients)</th>
<th>Control versus uraemia(1)</th>
<th>Control versus dialysis(1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
</tr>
<tr>
<td>Sodium (mmol/kg DS)</td>
<td>104</td>
<td>4</td>
<td>123</td>
<td>8</td>
<td>85</td>
</tr>
<tr>
<td>Sodium (mmol/l of cell water)</td>
<td>40</td>
<td>1</td>
<td>43</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>Potassium (mmol/kg DS)</td>
<td>377</td>
<td>4</td>
<td>332</td>
<td>9</td>
<td>324</td>
</tr>
<tr>
<td>Potassium (mmol/l of cell water)</td>
<td>142</td>
<td>2</td>
<td>117</td>
<td>3</td>
<td>141</td>
</tr>
<tr>
<td>Water (l/kg DS)</td>
<td>2.64</td>
<td>0.03</td>
<td>2.86</td>
<td>0.07</td>
<td>2.31</td>
</tr>
<tr>
<td>Sodium + potassium (mmol/kg DS)</td>
<td>483</td>
<td>5</td>
<td>460</td>
<td>14</td>
<td>409</td>
</tr>
</tbody>
</table>

(1) To allow for unequal variances between the groups the P values were calculated by Welch's modification of Student's t-test.
sodium content in this uraemic group was 123 mmol/kg DS compared with a control value of 104 mmol/kg DS: this increase was just significant at the 5% level (Table 1). In contrast, in six of the fifteen dialysed patients leucocyte sodium content was lower than the normal mean by more than 1 SD. The mean leucocyte sodium content in the dialysis group was 85 mmol/kg DS compared with the control value of 104, but this difference did not achieve significance.

In four patients studied before and after regular haemodialysis was started leucocyte sodium content fell by 57, 63, 87 and 98 mmol/kg DS respectively. The concentration of sodium in cell water did not differ significantly between the three groups (Table 1).

Fig. 1. Relationships between leucocyte potassium content [mmol/kg of dry solids (DS)] and leucocyte water content in (a) normal subjects ($r = 0.71; t = 7.54; P < 0.001$), in (b) uraemia ($r = 0.41; t = 2.40; P < 0.05$) and in (c) regular dialysis patients ($r = 0.84; t = 5.49; P < 0.001$).
Leucocyte electrolytes in uraemia

Fig. 2. Relationships between leucocyte sodium content (mmol/kg of dry solids) and leucocyte water content in (a) normal subjects \( (r = 0.41; t = 3.44; P < 0.01) \), in (b) uraemia \( (r = 0.71; t = 5.21; P < 0.001) \) and in (c) regular dialysis patients \( (r = 0.60; t = 2.73; P < 0.05) \).

Potassium

As previously reported (Patrick et al., 1972), leucocyte potassium was significantly reduced in the uraemic patients, both when referred to cell dry solids and to cell water (Table 1). In the 'dialysis' group the potassium content of leucocytes related to cell dry solids remained significantly below normal. This finding differs from the normal value previously found in patients having regular dialysis (Patrick et al., 1972), and results in part from a small increase in the mean value for potassium content in the normal group, compared with the earlier series, and in part from the slightly lower value for potassium content obtained in the present 'dialysis'
FIG. 3. Relationships between leucocyte sodium and potassium content (mmol/kg of dry solids) and leucocyte water in (a) normal subjects ($r = 0.79; t = 9.87; P < 0.001$), in (b) uraemia ($r = 0.74; t = 5.74; P < 0.001$) and (c) in regular dialysis patients ($r = 0.84; t = 5.69; P < 0.001$).

group patients. However, as in the earlier study the concentration of potassium in cell water in the 'dialysis' group was significantly higher than in the 'no-dialysis' group and did not differ from normal.

Water

The water content of leucocytes was significantly increased in the undialysed uraemic patients and was significantly below normal in the 'dialysis' group of patients (Table 1). This effect of
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regular dialysis on cell water was seen in each of four patients studied before and after regular dialysis was started.

In the normal subjects leucocyte water content correlated well with cell potassium content \((r = 0.71)\), less well with cell sodium content \((r = 0.41)\) and the best correlation was with sodium + potassium \((r = 0.79)\) (Figs. 1–3). In contrast, in the uraemic patients leucocyte water correlated better with sodium content \((r = 0.71)\) than with potassium content \((r = 0.41)\), whereas the correlation between water and sodium + potassium was comparable with that in the control group (Table 1).

The relationships between leucocyte water and sodium and potassium contents in patients receiving regular dialysis resembled those in the normal subjects rather than the uraemic patients, leucocyte water correlating better with potassium content \((r = 0.84)\) than with sodium content \((r = 0.60)\) (Table 1; Figs. 1–3).

DISCUSSION

The results indicate that in chronic renal failure leucocyte sodium and water contents are increased whereas leucocyte potassium content is reduced. Whereas in the normal subjects leucocyte water correlated better with potassium than with sodium content the converse was true in the uraemic patients. This suggests that the increased cell sodium content in uraemia is an important determinant of the increase in cell water. However, the sum of leucocyte sodium and potassium contents was not increased in uraemia. The increase in cell water might be caused by an increase in other intracellular osmotically active solutes. Alternatively, if some of the potassium lost from the cells in uraemia had been bound in a state rendering it osmotically inactive then its replacement by sodium might increase total osmotically active cation, and hence cell water.

These findings imply that the decrease in sodium transport previously reported in the erythrocyte (Welt et al., 1964) may be a widespread consequence of uraemia. This is of particular interest in view of Bricker's hypothesis that this defect arises from the presence in increased amounts of the factor responsible for the decrease in tubular sodium reabsorption, which characterizes the remaining nephrons in badly damaged kidneys (Bricker, 1972). This alteration in tubular reabsorption of sodium as the nephron population decreases would be beneficial, but if achieved by the increased release of a factor which also affects sodium transport in other cells then the control of cell volume might be disturbed in many organs.

In the undialysed uraemic patients neither leucocyte water nor sodium content correlated well with the plasma urea, creatinine, sodium or bicarbonate levels, and leucocyte potassium content did not correlate with plasma potassium level. However, these observations were made only on patients in whom renal failure was advanced, the plasma creatinine exceeding 0.89 mmol/l (10 mg/100 ml) in every case except one; it is possible that examination of patients with less-severe renal failure might disclose relationships between leucocyte cation and water contents and abnormalities in blood chemistry. On clinical assessment, those of our patients who were most ill appeared to have the highest leucocyte sodium contents. The difficulties of quantifying ‘illness’ defeated attempts to define this relationship more precisely, but it is of interest that Welt and his colleagues also observed that elevations of erythrocyte sodium in uraemia were found in ‘the sickest patients’.

In the four patients studied before and after regular dialysis therapy was started large falls
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in leucocyte water and sodium contents occurred after dialysis had commenced. Leucocyte water content was significantly less than normal in the 'dialysis group'. It is of interest that the undialysed uraemic patients, with increased leucocyte sodium and water contents, were all hypertensive, whereas the blood pressure had fallen to normal or near-normal values in the 'dialysis group' patients with decreased leucocyte sodium and water. The complexities of the uraemic state and variations in anti-hypertension therapy prevented a clear assessment of this apparent relationship between blood pressure and leucocyte sodium and water, but this question is currently under study.

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REFERENCES


