THE RED CORPUSCLES IN ACIDOSIS AND ALKALOSIS

BY

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As far back as 1895, Gurber, Hambürg and v. Limbeck showed that the addition of carbon dioxide to the blood caused increase in the volume of the red cells. Price-Jones in his investigations into the diameter of the red corpuscles found that there is a diurnal variation, the cells being smaller in the morning and larger later in the day, when the alkalinity is less. He further noted that violent exercise, by increasing the accumulation of lactic acid, and thereby causing lessened alkalinity of the blood, is accompanied by increase of cell diameter, and that in the converse state of increased blood alkalinity, produced by hyperventilation, which drives off carbon dioxide from the blood, there is a diminution of cell diameter. Experiments in vitro, blood being made more or less alkaline, produced corresponding results.

In these instances the change in acid-base equilibrium was transient. Similar findings, however, have been described when the disturbance was of longer duration. Földes, Holler and Kulka noted an increase in the volume of the red corpuscles in diabetic coma, the first showing that treatment with alkali caused a return to normal. Wiechmann observed an increase in cell volume with return to normal during treatment with insulin. Increased cell volume, with decreased cell diameter, was however described by Holler and Kulka, the cells apparently becoming globular in shape, and Horwitz made similar observations in experimental acidosis produced by calcium chloride. Increase of cell diameter occurs in the deep sleep induced by the administration of morphine (Wiechmann and Shürmeyer). The same workers describe diminution of mean diameter of the red corpuscles after administration of sodium bicarbonate.

An increase in red cell count in diabetic coma is described by Grawitz (quoted by Horwitz) and by Földes, the latter being of the opinion that the erythrocytosis is directly proportional to the severity of the acidosis. Detre and Zárday found erythrocytosis in experimental acidosis produced in dogs. The former observed an increase in the red cell count after strenuous work. This did not occur when alkali was given.

In the following study, Price-Jones curves were constructed from cases of acidosis and alkalosis occurring in children. The blood of ten children was examined. Four of these were examples of acidosis, two...
with diabetic coma and two with acidosis produced by calcium chloride. Six were examples of alkalosis and included two of subacute nephritis undergoing treatment with massive doses of sodium bicarbonate, and four of congenital hypertrophic pyloric stenosis. The technique followed in construction of the curves was that described by Price-Jones. Blood films, made on slides and dried by air, were fixed with Jenner's stain and counter-stained with watery eosin. A projection apparatus was used in drawing the cells, the magnification being 1,000 diameters. The cells were measured in two directions at right angles, the square root of the product, to the nearest 0.25 \( \mu \), being taken as the mean diameter of the corpuscle. In the construction of a curve five hundred cells were measured.

The blood in acidosis.

Table 1 summarizes the results found in acidosis. It will be seen that in all four cases there was an increase in corpuscular diameter (shift to the right), but that this was not proportional to the diminution of blood carbon dioxide. Furthermore, the shape of the curves was not changed, the whole being moved en masse to the right in each case. Examples of this are shown in fig. 1 and 2. In three of the four cases it was found that the coefficient of variation was decreased during acidosis. Erythrocytosis occurred in diabetic coma, but in neither of the cases of calcium chloride acidosis.

### Table 1.

**The effect of acidosis on the red corpuscles.**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Nature of Case</th>
<th>Hb. per cent.</th>
<th>R.B.C. in millions per c.mm.</th>
<th>M.C.D. (( \mu ))^*</th>
<th>Shift to right (( \mu ))</th>
<th>Blood CO₂ (Vol. per cent.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>During Acidosis</td>
<td>On Recovery</td>
<td>During Acidosis</td>
<td>On Recovery</td>
<td>During Acidosis</td>
</tr>
<tr>
<td>1</td>
<td>Diabetic coma</td>
<td>106</td>
<td>95</td>
<td>5.64</td>
<td>4.96</td>
<td>7.439</td>
</tr>
<tr>
<td>2</td>
<td>Diabetic coma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.752</td>
</tr>
<tr>
<td>3</td>
<td>Calcium chloride acidosis</td>
<td>78</td>
<td>76</td>
<td>4.46</td>
<td>4.38</td>
<td>7.468</td>
</tr>
<tr>
<td>4</td>
<td>Calcium chloride acidosis</td>
<td>50</td>
<td>50</td>
<td>4.00</td>
<td>3.94</td>
<td>6.731</td>
</tr>
</tbody>
</table>

*M.C.D. = Mean corpuscular diameter.
FIG. 1.—Price-Jones curves in a case of diabetes, during coma (broken line) and on recovery (continuous line). Mean diameter during coma 7.752\(\mu\). Mean diameter on recovery 7.146\(\mu\).

FIG. 2.—Price-Jones curves in a case of acidosis produced by administration of calcium chloride. Mean diameter during acidosis (broken line) 7.468\(\mu\); mean diameter on recovery (continuous line) 7.078\(\mu\).
The blood in alkalosis.

The findings in alkalosis produced by the administration of sodium bicarbonate in nephritis are found in table 2. Here there was a diminution in red cell diameter during alkalosis, though the general characters of the Price-Jones curve were unchanged, as shown in fig. 3. In these cases the coefficient of variation was increased in the alkalotic period.

No change in the erythrocyte count was noted in either case.

Cell volume was estimated in case 6. Blood, oxalated by the method described by Wintrobe in America and by Vaughan and Goddard in England, was centrifugalized in graduated centrifuge tubes, and not in the haematocrit as was done by these workers. Mean corpuscular volume (M.C.V.) of the red cells is given in cubic \( \mu \), mean corpuscular haemoglobin content (M.C.H.) in micro-microgrammes of haemoglobin (\( \gamma \)) and mean corpuscular haemoglobin concentration (M.C.H.C.), i.e., the haemoglobin per unit volume of red corpuscle, as a percentage. Table 3 shows that the volume of the red cells in alkalosis was reduced and, though the total amount of haemoglobin remained unchanged, its concentration was increased, i.e., fluid had been removed from the cells.

In pyloric stenosis it is well recognized that there is a state of alkalosis. Clinically this is manifested by the slow respiratory rate, which has been shown to bear a close relationship to the blood carbon dioxide. In the four cases examined there was a definite diminution in the mean cell diameter, but this did not appear to be proportional to the degree of alkalosis as gauged by the respiratory rate. The data are given in table 4, where the normal cell diameter for the age, as determined by van Creveld is also shown. The Price Jones curve has the characteristic broad base of curves at this age (fig. 4). Marked erythrocytosis was present in all four cases.
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Diameters in μ.

Fig. 3.—Price-Jones curves during alkalosis produced by the administration of sodium bicarbonate. Mean diameter during alkalosis (broken line) 6·041μ; mean diameter on recovery 7·242μ.

Diameters in μ.

Fig. 4.—A Price-Jones curve in a case of pyloric stenosis in a child aged five weeks, mean diameter 6·68μ. The normal mean diameter at this age (7·94μ) is also shown.
**TABLE 3.**

The influence of alkalosis on the volume and the haemoglobin of the red cells.

<table>
<thead>
<tr>
<th>Case</th>
<th>R.B.C. in millions per c.mm.</th>
<th>Hb. in gm. per cent.</th>
<th>Vol. of packed R.B.C. per cent.</th>
<th>M.C.V. in c.μ</th>
<th>M.C.H. in y.y</th>
<th>M.C.H.C. per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>4.87</td>
<td>12.69</td>
<td>38.5</td>
<td>68.78</td>
<td>26.05</td>
<td>37.88</td>
</tr>
<tr>
<td>7</td>
<td>4.61</td>
<td>11.59</td>
<td>39.0</td>
<td>84.59</td>
<td>25.14</td>
<td>29.72</td>
</tr>
</tbody>
</table>

M.C.V. = Mean corpuscular volume.
M.C.H. = Mean corpuscular haemoglobin.
M.C.H.C. = Mean corpuscular haemoglobin concentration.

**TABLE 4.**

The influence of the alkalosis of pyloric stenosis on the red corpuscles.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>M.C.D. (μ)</th>
<th>Normal M.C.D. for age (μ)</th>
<th>Shift to left (μ)</th>
<th>Respiratory rate per min.</th>
<th>Blood count.</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>7.28</td>
<td>7.94</td>
<td>0.66</td>
<td>32</td>
<td>Hb. 100 per cent. R.B.C. 4,800,000</td>
</tr>
<tr>
<td>8</td>
<td>7.68</td>
<td>7.94</td>
<td>0.26</td>
<td>28</td>
<td>Hb. 105 per cent. R.B.C. 5,300,000</td>
</tr>
<tr>
<td>9</td>
<td>6.68</td>
<td>7.94</td>
<td>1.26</td>
<td>22</td>
<td>Hb. 135 per cent. R.B.C. 6,800,000</td>
</tr>
<tr>
<td>10</td>
<td>7.33</td>
<td>7.72</td>
<td>0.39</td>
<td>28</td>
<td>Hb. 110 per cent. R.B.C. 5,500,000</td>
</tr>
</tbody>
</table>

M.C.D. = Mean corpuscular diameter.

**Discussion.**

Detre was of the opinion that acid stimulated erythropoiesis, but Horwitz⁹ points out that there is no evidence of this, as the number of reticulocytes is normal throughout acidosis and states that though on account of the reduction of blood volume in diabetic coma there may be an apparent erythrocytosis, the total number of red cells in the body is the same as when acidosis is absent. The increased red cell count in acidosis is therefore probably due to blood concentration, but erythrocytosis is not an invariable finding, as it occurred in neither of our cases of acidosis due to calcium chloride. In diabetes progressing to coma there is always great loss of fluid, while this is not a notable feature in cases of acidosis produced by calcium chloride, a fact which would explain the absence of erythrocytosis in our two cases of the latter.
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All the results obtained by separating corpuscles from plasma, by centrifugalizing oxalated blood, are in agreement that in acidosis the ratio of red cells to plasma is increased. Horwitz, and Holler and Kulka, who hold that there is no increase in the mean diameter, maintain on the basis of this finding that the individual cell undergoes a change of size and shape, becoming more globular. The data on which Horwitz based this conclusion are more readily explained by the presence of anhydraemia due to loss of fluid. It would be necessary before concluding that the red cells enlarge by assuming a globular shape without increase in diameter to prove that the increase of the volume of packed cells in the centrifugalized blood was greater than could be explained by decreased plasma volume.

In our series, however, an increase of cell diameter occurred in both diabetic coma and acidosis from calcium chloride administration, and in the latter no change in red cell count was present, proving that while the blood plasma may or may not be decreased, there is certainly an increase of corpuscular size, though the shape of the cell is not apparently changed.

These results are parallel with the findings of Price-Jones in transient non-gaseous acidosis, and Wiechmann and Shürmeyer in gaseous acidosis, and show in contrast to the results of other workers, that in prolonged pathological non-gaseous acidosis the same changes occur. It may be that in addition to the anhydraemia the increased size of the corpuscle increases the viscosity of the blood, and so plays a part in the circulatory failure which so frequently accompanies grave acidosis.

We have been unable to demonstrate any correlation between the extent of increase of cell diameter and the diminution of blood carbon dioxide, although the latter is not necessarily an exact measurement of the degree of acidosis.

It is of interest to note that case 4 had a marked microcytic, hypochromic anaemia, which did not modify the behaviour of the cells in acidosis.

Alkalosis has the reverse effect on the red corpuscle, causing a reduction in its volume, and its mean diameter. The haemoglobin content remains unchanged, but the concentration of haemoglobin per unit volume of red cell rises. This effect is doubtless due to the removal of water from the corpuscle. There is no change in the erythrocyte count in alkalosis produced by sodium bicarbonate.

Price-Jones found that the coefficient of variation was increased in acidosis and suggested that possibly some cells were more sensitive to change in acid-base equilibrium than others. In three of our four cases the coefficient of variation was decreased in acidosis. These apparently
conflicting results might be explained for, if, as Price-Jones suggests, some cells are more sensitive than others it would take longer for the less sensitive cells to be affected and it would only be when they had been subjected to acidosis for some time that an increase in size would occur.

In the two cases of alkalosis produced by sodium bicarbonate the variability was increased. This may be due to unequal sensitivity of the cells, and to the fact that conditions necessitating withdrawal of cellular fluid were not so urgent as those demanding the converse movement, which occurs in acidosis. For lack of data regarding the normal variability in the distribution of the cells of young infants, it is impossible to say whether there was any variation from normal in the cases of pyloric stenosis examined. In pyloric stenosis there is increase in the cell count from blood concentration, due to vomiting and inadequate intake of fluid.

In early infancy the diameter of the red cells is much greater than in older children and adults. The red cells probably attain normal size about the sixth month and certainly in the first year. In spite of these differences, a microcytosis occurs in alkalosis, but there again there is little correlation between the degree of alkalosis as estimated by the respiratory rate, which is recognized to be proportional to the amount of carbon dioxide in the blood.

Price-Jones has suggested that carbon dioxide is the immediate factor in producing changes in cell size. Since increase in cell diameter occurs both in gaseous and in non-gaseous acidosis, and decrease both in gaseous and non-gaseous alkalosis, it cannot be either the free or the total carbon dioxide which is the factor, but rather the ratio of the free to the combined carbon dioxide, i.e., the cell size varies as the pH of the blood, increasing with decreased pH and vice versa.

**Summary and conclusions.**

In acidosis, whether occurring in disease or induced by drugs, the red corpuscles are enlarged, the cell apparently retaining its normal shape. This may be accompanied by an increase in the red cell count, which, when it occurs, is probably due to blood concentration.

It is suggested that the increase in cell size in addition to the anhydremia may be a further cause of increased blood viscosity, and may contribute to the tendency to circulatory failure in acidosis.

Alkalosis causes a reduction in the size of the corpuscles, without change in shape, or haemoglobin content. There is probably no change in the red cell count due to alkalosis per se.

The corpuscles in early infancy, in spite of their different features, react to alkalosis in the same way as those of the older individual.

I have pleasure in recording my gratitude to Prof. G. B. Fleming and Dr. N. Morris for their valuable criticism and advice, and to the Rankin Medical Research Fund for financial assistance.
REFERENCES.