THE ACID-BASE EQUILIBRIUM OF THE BLOOD IN ECLAMPSIA.

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(Received for publication, September 9, 1929.)

The most outstanding chemical findings, so far reported, in patients suffering from eclampsia are the decreased CO₂-combining power and the increased uric and lactic acids in the blood. The CO₂-combining power is often in the neighborhood of 20 volumes per cent, and it is not unusual to observe uric acid values above 10 mg. and lactic acid above 100 mg. per 100 cc. of blood (1-3). The hydrogen ion concentration of the blood has been determined in a few isolated cases of eclampsia (4, 5), but there has been no complete study of the acid-base equilibrium in this disease.

It seemed to us that the markedly lowered CO₂-combining power, often observed in the eclamptic patient, may be evidence of a true acidosis. In this connection, one is sometimes impressed with the exceedingly short duration of the disease, ending in death. In this clinic, we have observed eclamptic patients dying 2 to 3 hours after the first convulsion; furthermore, all such patients had exceedingly low CO₂-combining power. These deaths may be due to a rapidly developing acidosis, and it is because of this probability that we undertook to make a complete study of the acid-base equilibrium in eclampsia.

Collection of Blood.

All specimens of blood, with the exception of those of eclamptic patients, were obtained in the morning before breakfast. Each blood sample was secured in two fractions, the first being drawn under oil and the second into 50 cc. centrifuge tubes. The former was employed for the determinations of hydrogen ion concentra-
Acid-Base Equilibrium

This particular fraction of the blood was always taken without the use of a tourniquet, and with the patient resting in bed. The greatest possible care was exercised to prevent CO$_2$ loss, and to this end the following procedure was employed: The blood is drawn from the patient's median basilic vein into a 30 cc. syringe, into which have previously been introduced 5 cc. of sterile light oil, of tested neutrality, the bore of the needle being also completely filled with this fluid. The blood is immediately transferred under oil to two 15 cc. centrifuge tubes in such a manner that the tubes retain only a thin layer of supernatant oil. A vaccine stopper, through which a thin bore needle has been introduced, is now inserted into the centrifuge tubes. As this stopper is pushed downwards, the thin layer of oil and a few drops of blood escape through the needle, which is now immediately withdrawn and the blood in this way effectively protected from the air. The blood is then centrifuged, and as it is no longer in contact with oil, the error due to escape of CO$_2$ from blood to oil is obviated. The centrifugation is carried out at 1000 R.P.M. for 10 minutes. The blood is again covered with oil by means of introducing through the vaccine stopper a needle attached to a small syringe, both needle and syringe being filled with oil. It is not necessary to force the oil downwards, as it is drawn into the tube by the vacuum produced by raising the stopper out of the tube. The serum can now readily be drawn off for hydrogen ion and CO$_2$ determinations.

The second fraction is taken with minimum stasis, allowed to clot in the 50 cc. centrifuge tubes, and centrifuged at 1000 R.P.M. for 10 minutes. The serum from this fraction is used for all other determinations.

Methods.

The pH was measured electrometrically, with a Michaelis U electrode (6) and a Leeds and Northrup potentiometer type K. Triplicate determinations were made on each blood sample with a precision of 0.01 pH.

The carbon dioxide content was determined by the Van Slyke and Neill method (7) in a calibrated constant volume Van Slyke pipette.

Total Base.—Serum was ashed by the method of Van Slyke,
Hiller, and Berthelsen (8), and benzidine precipitation and titration were carried out in accordance with the procedure of Stadie and Ross (9).

Chlorides were determined by the Whitehorn method (10).

Proteins were estimated by macro Kjeldahl determination on 1 cc. specimens, determined non-protein nitrogen being deducted.

Non-protein nitrogen was determined by the Folin-Wu method (11).

Sulfates were determined by the Denis and Reed nephelometric method (12).

Acetone bodies were estimated by the method of Van Slyke and Fitz (13).

Organic acids in blood were determined by the method of Perlzweig and Delrue (14).

Organic acids in urine were determined by the Van Slyke and Palmer method (15).

Calculations.

In order to express all values in millimolar equivalents, the following formulae were employed:

$$BHCO_3 = \frac{\text{CO}_3}{\text{antilog} (\text{pH} - \text{pK}) + 1} \times 10 \quad (\text{Peters, et al. (16)})$$

$$BP = 0.104 \times \text{gm. protein per 100 cc.} \times (\text{pH} - 5.08) \times 10 \quad (\text{Van Slyke, et al. (17)})$$

$$BCl = \frac{\text{mg. NaCl per 100 cc.}}{58.46} \times 10$$

$$BPO_4 = \frac{\text{mg. P per 100 cc.} \times 0.58}{(\text{Henderson (18)})}$$

$$BSO_4 = \frac{\text{mg. S per 100 cc.} \times 0.6}{(\text{Peters, et al. (16)})}$$

Results.

In Table I are given our results for normal non-pregnant women. In this group of cases we did not determine the blood organic acids, and these are, therefore, represented in the column "undetermined acid." Table II gives the findings in normal pregnancy. In Table III, which presents the results in eclampsia, are given the
values found during the period of convulsions and while the patients were severely ill. A more detailed report covering the changes throughout the disease and during convalescence will appear in a later publication.

From a comparison of the values expressed in Tables I and II, it is manifest that normal pregnancy is accompanied by a reduction in fixed base, as well as a decrease in the serum anions, protein, and bicarbonate. The reduction in total base of the serum in normal pregnancy averages 8 mM. Gestation is accompanied by a normal hydrogen ion concentration, averaging pH 7.37.

The findings in eclampsia, as shown in Table III, are very striking when compared with the normal pregnancy values. The

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Non-protein nitrogen</th>
<th>Proteina.</th>
<th>BP</th>
<th>CO₂</th>
<th>BHCO₃</th>
<th>NaCl</th>
<th>ECl</th>
<th>Phosphorus</th>
<th>BPO₄</th>
<th>Sulfur</th>
<th>HSO₄</th>
<th>Total acid.</th>
<th>Total base</th>
<th>Un determined</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>24410</td>
<td>mg. per 100 cc. per cent</td>
<td>mmol per 100 cc.</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
<td>mmol</td>
</tr>
<tr>
<td>24239</td>
<td>28.9</td>
<td>6.7</td>
<td>16.0</td>
<td>60.7</td>
<td>25.8</td>
<td>609</td>
<td>104</td>
<td>2</td>
<td>2.1</td>
<td>3</td>
<td>0.8</td>
<td>0.5</td>
<td>147.6</td>
<td>154.7</td>
<td>7.1</td>
</tr>
<tr>
<td>23187</td>
<td>27.7</td>
<td>6.9</td>
<td>15.9</td>
<td>58.2</td>
<td>24.3</td>
<td>627</td>
<td>107.2</td>
<td>2.3</td>
<td>3.1</td>
<td>3</td>
<td>1.0</td>
<td>0.6</td>
<td>149.3</td>
<td>151.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Average</td>
<td>25.8</td>
<td>7.0</td>
<td>16.4</td>
<td>60.2</td>
<td>25.4</td>
<td>624</td>
<td>106.6</td>
<td>2.2</td>
<td>3</td>
<td>0.8</td>
<td>0.5</td>
<td>150.2</td>
<td>155.3</td>
<td>5.2</td>
<td>7.34</td>
</tr>
</tbody>
</table>

The total base amounts to about 3 mM more than in normal pregnancy, but is below the normal non-pregnant limits. Nevertheless, there is a definite reduction in BHCO₃, which is more than counter-balanced by the marked increase in organic acids. The most outstanding changes noted in Table III are the very low pH readings, the definitely increased organic acids, and the reduction in BHCO₃.

The millimolecular BHCO₃ concentration and pH values for our normal non-pregnant, pregnant, and eclamptic women are plotted in Chart I, in which we have employed the graph devised by Van Slyke (19). It will be noted that our normal non-pregnant values all fall within Area 5, which represents a normal acid-base balance. Normal pregnancy values fall close to the boundary separating
## TABLE II.

**Acid-Base Equilibrium in Normal Pregnancy.**

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>24038</td>
<td>23.0</td>
<td>6.4</td>
<td>15.2</td>
<td>45.1</td>
<td>20.4</td>
<td>620</td>
<td>106.0</td>
<td>2.1</td>
<td>1.2</td>
<td>1.7*</td>
<td>0.7</td>
<td>144.9</td>
<td>144.9</td>
<td>7.38</td>
<td></td>
</tr>
<tr>
<td>24547</td>
<td>20.0</td>
<td>6.1</td>
<td>13.4</td>
<td>47.2</td>
<td>20.1</td>
<td>596</td>
<td>102.0</td>
<td>1.9</td>
<td>1.1</td>
<td>8.2</td>
<td>0.9</td>
<td>145.9</td>
<td>143.8</td>
<td>7.41</td>
<td></td>
</tr>
<tr>
<td>T-41929</td>
<td>31.6</td>
<td>5.8</td>
<td>13.6</td>
<td>51.2</td>
<td>21.6</td>
<td>610</td>
<td>104.3</td>
<td>1.8</td>
<td>1.0</td>
<td>6.8</td>
<td>0.7</td>
<td>147.5</td>
<td>152.5</td>
<td>7.33</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>24.9</td>
<td>6.1</td>
<td>14.1</td>
<td>48.8</td>
<td>20.7</td>
<td>608</td>
<td>104.1</td>
<td>1.9</td>
<td>1.1</td>
<td>5.6</td>
<td>0.8</td>
<td>146.1</td>
<td>147.0</td>
<td>7.37</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated.

<table>
<thead>
<tr>
<th>Duration of pregnancy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 days ante partum.</td>
</tr>
<tr>
<td>5½ mos.</td>
</tr>
<tr>
<td>At term.</td>
</tr>
</tbody>
</table>
### TABLE III.

**Acid-Base Equilibrium in Eclampsia.**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Non-protein Nitrogen</th>
<th>Protein</th>
<th>BP</th>
<th>CO₂</th>
<th>BHCO₃</th>
<th>NaCl</th>
<th>BCl</th>
<th>Phosphorus</th>
<th>FCO₃</th>
<th>Organic acid.</th>
<th>Sulfur</th>
<th>Total acid</th>
<th>Total base</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>23300</td>
<td>61.8</td>
<td>5.3</td>
<td>10.2</td>
<td>29.1</td>
<td>11.5</td>
<td>631</td>
<td>107.8</td>
<td>1.9</td>
<td>1.1</td>
<td>18.0</td>
<td>1.5</td>
<td>0.9</td>
<td>154.1</td>
<td>151.3</td>
</tr>
<tr>
<td>23925</td>
<td>33.3</td>
<td>6.8</td>
<td>14.3</td>
<td>35.6</td>
<td>14.4</td>
<td>621</td>
<td>106.2</td>
<td>1.9</td>
<td>1.1</td>
<td>14.5</td>
<td>0.9</td>
<td>0.5</td>
<td>151.3</td>
<td>154.6</td>
</tr>
<tr>
<td>25222</td>
<td>25.0</td>
<td>6.4</td>
<td>13.4</td>
<td>42.7</td>
<td>17.5</td>
<td>597</td>
<td>102.0</td>
<td>1.8</td>
<td>1.0</td>
<td>20.5</td>
<td>155.0</td>
<td>152.8</td>
<td>7.13</td>
<td></td>
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<tr>
<td>S-81929</td>
<td>32.1</td>
<td>6.9</td>
<td>13.6</td>
<td>40.2</td>
<td>15.9</td>
<td>596</td>
<td>101.9</td>
<td>2.3</td>
<td>1.7</td>
<td>13.7</td>
<td>147.5</td>
<td>153.4</td>
<td>6.98</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>38.0</td>
<td>6.4</td>
<td>12.9</td>
<td>36.9</td>
<td>14.8</td>
<td>611</td>
<td>104.5</td>
<td>2.1</td>
<td>1.2</td>
<td>16.7</td>
<td>1.2</td>
<td>0.7</td>
<td>150.8</td>
<td>153.0</td>
</tr>
</tbody>
</table>

**Time specimen taken.**

- In coma. 45 sec. after 4th convulsion.
- In coma. 30 sec. after 4th convulsion.
- In coma. About 30 min. after 4th convulsion.
- In coma. 5 min. after 10th convulsion.

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Areas 5 and 6. In other words, there is a tendency in normal pregnancy towards the compensated alkali or CO₂ deficit area. This is due to the lowered BHCO₃ concentration.

All our eclamptic cases fall in Area 9, which represents an uncompensated alkali deficit. This true acidosis, which we have found in all our cases of severe eclampsia, seems to be due to the marked accumulation of organic acids (probably chiefly lactic) in the blood, and to a concomitant reduction in BHCO₃. We may state that so far we have found normal values for blood acetone bodies in eclampsia, and ketosis therefore probably does not play a rôle in the production of this acidosis. In this connection it is interesting to note that the organic acids in the urine in eclampsia

![chart](http://www.jbc.org/)

CHART I. Variations of the BHCO₃ and pH in serum of normal non-pregnant, normal pregnant, and eclamptic women.
are usually markedly increased. The following are our findings for the patients represented in Tables I to III.

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Type</th>
<th>Average 0.1 N organic acid. cc. per 24 hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Normal non-pregnant.</td>
<td>338</td>
</tr>
<tr>
<td>2</td>
<td>&quot; pregnant.</td>
<td>775</td>
</tr>
<tr>
<td>3</td>
<td>Eclampsia, severe.</td>
<td>1168</td>
</tr>
</tbody>
</table>

**DISCUSSION.**

*Normal Pregnancy.*—Oard and Peters have recently given an excellent review of the literature on serum electrolytes in normal pregnancy (20). These authors made a very complete study of the concentration of acid and base in the serum of normal pregnancy, and showed that the total base in pregnancy is lowered about 8 mm from the normal, and that there is also a concomitant and equal reduction of the anion content of the serum in pregnancy. This reduction they found to be in serum protein, serum bicarbonate, and organic acid. Our own results are in full agreement with those of Oard and Peters, except that we were unable to note a reduction in organic acids. It should be noted, however, that Oard and Peters calculated the organic acids as "undetermined acid," while we measured it electrometrically by the method of Perlzweig. It should also be stated that while this method gave very good results when we were dealing with fairly large quantities of organic acids, as in eclampsia, our results were not so satisfactory when the amounts to be determined were less than 8 mm of acid. This may perhaps explain the slight discrepancy between the results of Oard and Peters and our own figures.

Our pH determinations show that normal pregnancy is not accompanied by any change from the normal non-pregnant value. We have been unable to find in the literature electrometric pH determinations in pregnancy with which to compare our results. The term "acidosis of pregnancy," as pointed out by Oard and Peters, is misleading, as normal pregnancy is not associated with an increase of abnormal acids, but rather with a reduction of alkali reserve and a decrease in total base. We agree with these authors that the reduction in fixed-base in the serum in pregnancy cannot readily be explained on the basis of fetal requirements,
acid production and excretion, or hyperventilation. At present, we are unable to give a satisfactory explanation for this serum base decrease which accompanies normal pregnancy.

Eclampsia.—The literature contains no complete study of the acid-base equilibrium in the serum of eclamptic women. It is well known, however, that the CO₂-combining power of the blood is often markedly lowered in severely ill eclamptic patients. Furthermore, Zweifel (21), Bokelmann (22), Kienlin (23), Loeser (24), Schultze (25), and Stander and Radelet (3), demonstrated an increase in lactic acid in the blood of eclamptic women. Hasselbalch and Gammeltoft examined four eclamptic patients and noted in two cases an increase in the fixed acidity of the blood, while in the other two cases, the pH of the blood was normal. From these considerations, one may suspect that the coma of eclampsia is associated with a true acidosis. Our total electrolyte studies on the sera of five eclamptic patients fully confirmed this hypothesis. All our patients, while in coma, showed an acid-base balance falling in Van Slyke’s Area 9, which represents an acidosis resulting from an uncompensated alkali deficit. The alkali reserve has been lowered below the extreme normal limit.

The total base in eclampsia is not lower than in normal pregnancy—on the contrary, it is slightly higher (3 mM). A previous study (26) on the cations of the blood in eclampsia gave the following averages, as compared with normal pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Normal pregnancy</th>
<th>Eclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mg or mM)</td>
<td>325</td>
<td>332</td>
</tr>
<tr>
<td>K (μg)</td>
<td>21.2</td>
<td>21.3</td>
</tr>
<tr>
<td>Ca (μg)</td>
<td>9.6</td>
<td>10.7</td>
</tr>
<tr>
<td>Mg (μg)</td>
<td>2.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Total</td>
<td>153.4</td>
<td>157.4</td>
</tr>
</tbody>
</table>

These figures agree very satisfactorily with our determinations on total base, as eclampsia gave a value 3.2 mM more than normal pregnancy, and from the above calculations based on our previous study, eclampsia shows 4.0 mM more than normal pregnancy.

Certain anion concentrations are markedly altered in eclampsia. BHCO₃⁻ and serum protein are reduced, while organic acids are markedly increased. We have not determined the nature of these organic acids, although our evidence so far indicates that they are not ketones, but probably mainly lactic acid. The outstanding
changes on the acid side are the accumulation of organic acid and the decrease in \( \text{BHCO}_3 \). Chlorides, phosphates, and sulfates are within normal limits. The pH of the eclamptic blood is at the very lower limit of the "maximum tolerated pH range," being 7.04.

From these figures it is evident that the uncompensated acidosis in eclampsia is so marked that it in itself may cause the death of the patient. Whether the eclamptic convulsions cause this low pH, or are the result of it, cannot be determined until more work has been done on the etiology of this acidosis.

Our electrolyte studies on eclamptic sera lead us to the main conclusion that many patients undoubtedly succumb to this disease because of the marked acidosis due to an uncompensated alkali deficit, and that a certain number of these may be saved by the rigorous use of antiacidosis treatment, such as bicarbonate.

CONCLUSIONS.

1. Normal pregnancy is associated with a reduction in total serum base, amounting to about 8 mm.

2. This reduction in total base is accompanied by a decrease in serum protein and serum bicarbonate. The other anion concentrations are within the normal non-pregnant limits.

3. There is no increase in organic acids, nor an accumulation of abnormal acids during normal pregnancy.

4. The pH of the blood in uncomplicated gestation is within the normal range.

5. Severe eclampsia is associated with a true acidosis, due to an uncompensated alkali deficit.

6. A marked increase in organic acids in the blood accompanies eclampsia.

7. The pH of the blood in severe eclampsia is decidedly lowered, averaging about 7.04.

8. The marked \( \text{BHCO}_3 \) decrease, with its accompanying acidosis, observed in eclampsia, deserves special attention in the treatment of the disease.

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