In order to study in detail the effect on the total acid-base equilibrium of certain conditions that might be expected to influence the water content and the electrolyte distribution of the blood a series of special experiments was carried out on the single subject JP and compared with individual studies of other normal persons and patients. The general methods of procedure which were followed in these experiments have been described in the first paper of this series (21).

Effect of Venous Stasis.

The first three experiments on JP (see protocols and Table I) illustrate the effects of prolonged venous stasis.

Experiment of March 11, 1923. Subject JP (See Protocols of Paper I).—In all the experiments of this series blood was withdrawn about an hour or an hour and a half after a light breakfast. For 20 or 30 minutes before the venipunctures the subject sat quietly in a chair with one or both hands and forearms immersed in warm water.

A tourniquet was applied to the arm with sufficient force to obstruct the venous return without obliterating the radial pulse. The pressure was maintained until the forearm and hand had developed a marbled cyanotic appearance and were quite painful. A specimen of blood was then withdrawn from the vein of the arm without disturbing the tourniquet. Another sample of venous blood was simultaneously secured from the other arm, without stasis. In the experiments of March 18 and April 18 the same procedure was followed. The experiment of May 13 was similar to those of March 11 and 18 and April 18, except that the blood samples were withdrawn immediately after the tourniquet had been removed. For data of these experiments see Table I.
### TABLE I.

*Effect of Venous Stasis on the Total Acid-Base Equilibrium of Plasma.*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Date</th>
<th>Oxygen capacity</th>
<th>Cell volume</th>
<th>Protein</th>
<th>CO₂</th>
<th>Cl</th>
<th>Total acid.</th>
<th>Total base.</th>
<th>Organic acid.</th>
<th>pH</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>JP</td>
<td></td>
<td></td>
<td></td>
<td>(1)</td>
<td>(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>vols.</td>
<td>vols.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>per cent</td>
<td>per cent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mar. 11</td>
<td></td>
<td>18.6</td>
<td>42.7</td>
<td>6.71</td>
<td>60.8</td>
<td>370</td>
<td>143.5</td>
<td></td>
<td></td>
<td>7.34</td>
<td>V. cont.</td>
</tr>
<tr>
<td>“ 18</td>
<td></td>
<td>22.5</td>
<td>51.2</td>
<td>9.13</td>
<td>65.4</td>
<td>349</td>
<td>143.1</td>
<td></td>
<td></td>
<td>7.29</td>
<td>“ “</td>
</tr>
<tr>
<td>“ 18</td>
<td></td>
<td>22.7</td>
<td>52.1</td>
<td>8.95</td>
<td>49.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.34</td>
<td>“ “</td>
</tr>
<tr>
<td>Apr. 18</td>
<td></td>
<td>18.5</td>
<td>42.8</td>
<td>54.6</td>
<td>368</td>
<td></td>
<td>140.0</td>
<td>155.1</td>
<td>15.1</td>
<td>7.36</td>
<td>“ “</td>
</tr>
<tr>
<td>“ 18</td>
<td></td>
<td>22.8</td>
<td>53.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.34</td>
<td>“ “</td>
</tr>
<tr>
<td>May 13</td>
<td></td>
<td>19.1</td>
<td>45.2</td>
<td>6.34</td>
<td>54.3</td>
<td>366</td>
<td>139.0</td>
<td>155.8</td>
<td>19.8</td>
<td>7.36</td>
<td>“ “</td>
</tr>
<tr>
<td>“ 18</td>
<td></td>
<td>20.5</td>
<td>47.9</td>
<td>7.64</td>
<td>52.5</td>
<td>362</td>
<td>139.2</td>
<td>155.7</td>
<td>19.5</td>
<td>7.34</td>
<td>“ “</td>
</tr>
</tbody>
</table>

In this and all succeeding tables *A* and *V* in Column 13 indicate arterial and venous blood respectively; *cont.*, that the specimen was analyzed as drawn; *cap.*, that it was brought into equilibrium with 40 mm. of CO₂ in air at 38°C. before analysis.

*Remark.*

Without stasis.

After prolonged venous stasis.

Without stasis.

After prolonged venous stasis.

Before stasis.

1 min. after removal of tourniquet.
Dautrebande, Davies, and Meakins (8) have shown that such a procedure results in the passage of water and electrolytes to the tissues from the blood in consequence of which the blood becomes dehydrated. This is amply confirmed by the experiments of March 11, March 18, and April 18, if plasma protein, hemoglobin, and cell volume can be interpreted as an indication of the water concentration of the blood. The plasma on both occasions lost some 30 per cent of its water. Under these circumstances both protein and bicarbonate rose, while chloride fell. The fall in chloride was sufficient to compensate exactly the increase in the other elements. The "total" acid of March 11 did not change as much as a millimol and the total base of April 18 increased only about 1 millimol.

In these experiments an abnormal acid load was placed on the blood, first of all by the increase of protein and secondly by the accumulation of carbon dioxide. Under ordinary circumstances the organism might have responded by increasing the blood flow and the respirations. By these means the load of CO$_2$ could have been removed and base freed for combination with the additional protein. The presence of the tourniquet precluded such a reaction and forced the body to meet the emergency in some other manner. It is clear from the experiment of March 18 that, under these circumstances, the carbon dioxide absorption curve falls. It is possible, then, for the organism to reduce the level of the carbon dioxide capacity of the blood without the mediation of the respiratory mechanism. The importance of this fact from the standpoint of maintaining the reaction of the blood at a constant level and facilitating the escape of carbon dioxide when the blood again has access to the lungs has been discussed in another connection (20). The constancy of base and total acid in the different experiments renders it unlikely that abnormal acids have entered the blood in appreciable amounts and forces the conclusion that bicarbonate has yielded base to the proteins.$^1$ The production of CO$_2$ by the tissues, however, ex-

$^1$ It may be objected that the acid values for protein are so uncertain that this argument is invalid. In that case one must suppose that the increase of protein took up only a fraction of the base freed by bicarbonate and chloride and the remainder combined with organic acid. The constancy of the acid values before and after stasis must then be looked upon.
ceeds the drop in bicarbonate. The only recourse then, is for chloride to give up some of its base. That such weak acids as proteins and bicarbonate should be able to displace as strong an acid as hydrochloric at first seems incomprehensible. The reaction, however, has long been known to occur in the equilibria between plasma and blood cells.

The experiment of May 13 differed somewhat from the three preceding ones in that the second sample of blood was withdrawn after the tourniquet had been removed. It was hoped that it might show a reversal of the process observed in the earlier experiments; i.e., that the blood from the arm just relieved from stasis would be more dilute than the normal blood. In this respect it proved a disappointment, possibly because the venipuncture followed too closely the removal of the tourniquet. The changes observed are less marked than those of the previous studies, but are of the same nature. Evidently the effects of stasis on the tissues persist for a certain time after stasis is relieved. Whether a reversal of the phenomena could be demonstrated at a later period was not determined.

Studies of the oxygen content of the stasis blood revealed a high grade of anoxemia. Under these circumstances a certain amount of lactic acid might have been expected to accumulate in the blood. If it did it appeared in undemonstrable quantities. The muscles were, of course, kept at rest during the experiment, so that the lactic acid production was presumably quite small.

**Effects of Exercise.**

The effect of exercise on JP (see protocols and Table II) offers a striking contrast to that of simple venous stasis.

*Experiments of March 27 and April 3, 1924, and June 5, 1925. Subject JP.*

—These experiments were carried out about an hour or an hour and a half after a light breakfast. For 20 or 30 minutes before the venipunctures the subject sat quietly in a chair with one or both hands and forearms immersed in hot water. With the forearm supported on a table the hand and wrist as a mere coincidence. These coincidences throughout the whole work recur with such frequency that one can hardly escape the impression that the protein calculations are not greatly in error, at least from a relative point of view.


<table>
<thead>
<tr>
<th>Subject</th>
<th>Date</th>
<th>Oxygen capacity</th>
<th>Cell volume</th>
<th>Plasma</th>
<th>Nature and treatment of blood</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>JP</td>
<td>Apr. 3, 1924</td>
<td>18.3 vols. per cent 38.1 vols. per cent</td>
<td>6.41 per cent 57.0 mg. per 100 cc.</td>
<td>137.8 mm</td>
<td>V. cont.</td>
<td>Before exercise.</td>
</tr>
<tr>
<td></td>
<td>June 5, 1925</td>
<td>18.7 vols. per cent 41.4 vols. per cent</td>
<td>6.48 per cent 62.2 mg. per 100 cc.</td>
<td>138.3 mm</td>
<td>‘’ ‘’</td>
<td>‘’ ‘’ During “</td>
</tr>
<tr>
<td></td>
<td>Mar. 27, 1924</td>
<td>18.2 vols. per cent 42.6 vols. per cent</td>
<td>6.43 per cent 51.5 mg. per 100 cc.</td>
<td>137.5 mm</td>
<td>‘’ ‘’ cap.</td>
<td>‘’ ‘’ Before “</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.7 vols. per cent 43.3 vols. per cent</td>
<td>45.6 per cent 381 mg. per 100 cc.</td>
<td>141.2 mm</td>
<td>‘’ ‘’</td>
<td>‘’ ‘’ During “</td>
</tr>
<tr>
<td></td>
<td>Jan. 22, 1923</td>
<td>21.0 vols. per cent 42.9 vols. per cent</td>
<td>6.72 per cent 55.4 mg. per 100 cc.</td>
<td>147.1 mm</td>
<td>V. cap.</td>
<td>Without stasis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.0 vols. per cent 42.9 vols. per cent</td>
<td>7.62 per cent 42.3 mg. per 100 cc.</td>
<td>139.3 mm</td>
<td>‘’ ‘’</td>
<td>‘’ ‘’ After stasis and exercise.</td>
</tr>
</tbody>
</table>

TABLE II.
Effect of Exercise on the Total Acid-Base Equilibrium of Plasma.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Date</th>
<th>Oxygen cap.</th>
<th>Cell vol.</th>
<th>Protein</th>
<th>CO₂</th>
<th>Cl</th>
<th>Inorg P</th>
<th>Total acid</th>
<th>Total base</th>
<th>pH</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>JP</td>
<td>Apr. 3, 1924</td>
<td>18.3</td>
<td>38.1</td>
<td>6.41</td>
<td>57.0</td>
<td>357</td>
<td>137.8</td>
<td>7.37</td>
<td>7.20</td>
<td>16-22</td>
<td>V. cont. Before exercise.</td>
</tr>
<tr>
<td></td>
<td>June 5, 1925</td>
<td>18.7</td>
<td>41.4</td>
<td>6.48</td>
<td>62.2</td>
<td>357</td>
<td>138.3</td>
<td>7.20</td>
<td>7.20</td>
<td>148.4</td>
<td>‘’ ‘’ During ‘’</td>
</tr>
<tr>
<td></td>
<td>Mar. 27, 1924</td>
<td>18.2</td>
<td>42.6</td>
<td>6.43</td>
<td>51.5</td>
<td>380</td>
<td>141.8</td>
<td>7.33</td>
<td>7.28</td>
<td>162.6</td>
<td>‘’ ‘’ Before ‘’</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.7</td>
<td>43.9</td>
<td>45.6</td>
<td>381</td>
<td>137.5</td>
<td>7.28</td>
<td>7.28</td>
<td>162.6</td>
<td>7.28</td>
<td>‘’ ‘’ During ‘’</td>
</tr>
<tr>
<td></td>
<td>Jan. 22, 1923</td>
<td>21.0</td>
<td>42.9</td>
<td>6.72</td>
<td>55.4</td>
<td>390</td>
<td>147.1</td>
<td>7.37</td>
<td>7.24</td>
<td>162.6</td>
<td>V. cap. Without stasis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.0</td>
<td>42.9</td>
<td>7.62</td>
<td>42.3</td>
<td>380</td>
<td>139.3</td>
<td>7.24</td>
<td>7.24</td>
<td>162.6</td>
<td>‘’ ‘’ After stasis and exercise.</td>
</tr>
</tbody>
</table>
were alternately flexed and extended with a weight of about 10 pounds suspended from the finger tips, until the exercise had produced a state of painful fatigue. At this point, while the exercise was continued, blood was drawn synchronously, without stasis, from the veins of both arms.

Experiments of January 22, 1923. Subject JP.—The first sample of blood was withdrawn about an hour after breakfast, without stasis, but without any preliminary rest or preparation. Immediately after the blood had been obtained a tourniquet was applied to the arm with sufficient force to obstruct the venous return without obliterating the arterial pulse. The hand was then opened and closed rapidly and forcibly until the exercise became quite painful, when the second specimen was drawn while the tourniquet was still in place and while the exercise was continued.

In the first place exercise produces little change in the water content of the serum. The hemoglobin and cell volume do indicate a certain amount of concentration, but this is not reflected in the plasma proteins and may well be due to the liberation of additional blood cells from the capillaries as a result of the increased blood flow and vascular dilation produced by the exercise. From the experiment of March 27 it is clear that the CO₂ capacity of the blood has diminished. This decrease is, however, more than offset by the increased carbon dioxide load, as is evidenced by the fact that the bicarbonate content of the blood (see experiment of April 3) is greater after exercise than before. Chloride in both experiments remains unaltered. The end-result is to increase the “total” acid slightly, from 137.8 to 138.3 mm.

Unless total base increases this “total” acid accession can only take place at the expense of the organic acid fraction. This is unlikely. In fact investigations of Barr and his associates (4) and of Lundsgaard and Möller (17) have demonstrated that exercise results in the discharge of lactic acid into the blood. This must augment the organic acid fraction of the serum. Base was not determined in the first experiments, but was estimated in a separate study carried out on June 5, 1925, under the same conditions as the earlier observations. As might have been expected base increased considerably. Attention must be called to the fact that on this occasion the preliminary sample of serum contained less base than any other specimens from the same subject. For this reason the experiment cannot be considered quantitatively comparable to the previous ones. Nevertheless it is probable that similar qualitative variations occurred in all of them.
The local reaction to short, fatiguing exercise, therefore, consists in the delivery to the blood of an excess of organic acid, presumably lactic. To meet this added acid load the blood responds to a slight extent by reducing the bicarbonate of the blood, but mainly by withdrawing base from the tissues. The plasma chlorides are not affected. It is worth remarking in passing that phosphate is not appreciably altered.

The experiment of January 22, 1923, illustrates the combined effects of stasis and exercise. This is, of course, comparable to exercise with insufficient oxygen. As might be expected under these circumstances, the reduction of bicarbonate is greater than that with stasis or exercise alone. Furthermore chloride is again forced to come to the aid of bicarbonate. "Total" acid, therefore, is greatly diminished. If this diminution is entirely due to the accumulation of lactic acid and protein the part played by each of these acids can be calculated. The total drop in acid = 7.8 millimols. Of this 0.9 millimols is caused by the protein and 6.9 millimols by lactic acid. Base was not determined. If base also rose this estimate of the amount of lactic acid produced is too small.

**Effects of Voluntary Hyperpnea.**

That tetany could be produced by overventilation was first demonstrated by Grant and Goldman (12) and Collip and Backus (6), who ascribed the condition to alkalosis. The observation has since been confirmed by numerous workers and the associated electrolyte changes have been extensively investigated to determine the degree of change of the hydrogen ion concentration and the bicarbonate of the blood. In these studies indirect methods have, for the most part, been employed and the interpretation of observed phenomena has usually been open to question. The experiments of April 10 and 16 (see protocols and Table III) were planned to throw some light on certain features of overventilation tetany that had not, in the opinion of the authors, been satisfactorily settled by previous studies and for the solution of which the present procedure was peculiarly adapted.

**Experiments of April 10 and 16. Subject JP.**—About an hour after a light breakfast blood was withdrawn from the arm vein of the subject, who had been sitting at rest for 20 or 30 minutes with his hands and forearms
immersed in hot water. Immediately after the venipuncture he began to
breath as rapidly and forcibly as possible, giving his major attention to
expediting and completing the expiratory phase of respiration. Symptoms
came on very shortly, beginning with dizziness and marked tingling of the
extremities. The hands became fixed in the position typical of carpopedal
spasm, although the wrists were held in a position of adduction and exten-
sion. To change the position of the hands, while not impossible, was diffi-
cult and somewhat painful. The feet felt as if the shoes were too tight and
as if the balls of the toes were pressed hard against the soles of the shoes.
Although the subject did not lose consciousness he became distinctly dazed
so that he did not discontinue overventilating at the end of the experiment
until he had been told to stop three times. For some time afterwards there
was almost complete apnea, but no marked cyanosis appeared. As soon as
definite carpopedal spasm had developed a sample of blood was withdrawn,
without stasis, from the same vein from which the preliminary sample had
been obtained. Forced breathing was not discontinued until the blood
had been secured. The whole experiment took only about 5 minutes.

Grant and Goldman (12), Davies, Haldane, and Kennaway (9),
and others have reported the appearance of carpopedal spasm
and other evidences of tetany only after hyperventilation had
been carried on for 10 minutes or more. In so long a period
certain secondary adjustments may take place that obscure the
primary changes of tetany. To reduce the time necessary for the
production of tetany as far as possible seemed desirable. It was
conclusively demonstrated in two experiments on JP (see proto-
cols) that a striking picture of tetany can be produced in 5 minutes
or less by forced breathing alone, if the latter is performed in
the proper manner. The ordinary individual when told to over-
ventilate finds no difficulty in increasing the speed and depth of
inspiration. Expiration, naturally a more passive movement, is
usually unduly prolonged and is not carried to completion unless
special emphasis is put upon it. By giving the major attention
to accelerating and completing each expiration the effectiveness
of the ventilation is greatly increased and the appearance of
tetanic symptoms expedited. There can be no doubt from the
description in the protocols that the symptoms and signs induced
were those of tetany. The results of blood examinations appear
in Table III.

The change of pH produced, only 0.2, was surprisingly small
compared with that reported by other observers. Davies et al.
(9), from comparison of alveolar CO₂ and carbon dioxide absorp-
### TABLE III.

*Effect of Overventilation on the Total Acid-Base Equilibrium of Plasma.*

| Subject | Date | Oxygen Capacity | Cell Volume | | Plasma | | Nature and Treatment of Blood | Remarks |
|---------|------|-----------------|-------------|------------------|------------------|-------------------------------|---------|
|         |      | (1) vols. per cent | (2) vols. per cent | (3) per cent | (4) mg. per 100 cc. | (5) mm | (6) mm | (7) mm | PH | V. cont. | Before overventilation. |
| JP      | Apr. 10 | 19.1 | 42.1 | 6.46 | 61.5 | 368 | 141.1 | | 7.39 | " " | During " tetany. |
|         | 18.8 | 41.2 | 6.48 | 55.4 | 366 | 136.3 | | 7.59 | " " | " cap. Before " |
| " 16   | 18.9 | 43.9 | 6.57 | 53.0 | 378 | 142.3 | 158.1 | 15.8 | 7.35 | " " | During " tetany. |
|         | 19.9 | 43.9 | 7.08 | 52.6 | 368 | 138.0 | 158.6 | 20.6 | 7.34 | | |

Nature and Treatment of Blood:
- PH of blood:
  - Before overventilation: 7.39
  - During " tetany: 7.35
  - Before " cap: 7.34
  - During " tetany: 7.34

Remarks:
- Before overventilation:
- During " tetany:
tion curves, estimated the change in one of their experiments as 0.38 of pH. It is more than possible that they underestimated the arterial CO₂ tension. One cannot assume that the respired air during extreme overventilation comes into gaseous equilibrium with the arterial blood.

Y. Henderson (15) holds that the organism will respond to overventilation by reducing the carbon dioxide capacity of the blood, a reaction which would tend to maintain the pH of the blood at a constant level. There is considerable evidence (3) that such a reaction does occur during the adjustment to oxygen-want at high altitudes. If hyperventilation were prolonged sufficiently it is likely that compensation would be effected in a similar manner. In these experiments (see experiment of April 16) the carbon dioxide capacity remained practically unaltered. An excessive amount of carbon dioxide was, however, removed from the blood by reduction of the carbon dioxide tension. That chloride should diminish was quite unexpected; the diminution is, however, unmistakable in both experiments. Such a reduction of chloride with relatively little change in the other acids and with no alteration of base implies an increase of organic acid.

The nature of this organic acid was not investigated. Davies and his coworkers (9) detected acetone in the urine after overventilation, and after the administration of alkali. Adlersberg (1), who has confirmed their observations, has suggested that ketosis is one of the means by which the body is enabled to prevent alkalosis. The ketonuria, and presumably the ketonemia, reported by all these observers was extremely mild and could hardly account for more than a small part of the 5 millimols of abnormal organic acid found in the blood. It is not improbable that some or all of the remainder is lactic acid. The spasms of tetany certainly entail muscular activity, which must result in the production of lactic acid. On April 10 the oxygen content of the blood was determined before and during tetany. In spite of the vigorous respiration the tetany blood contained 3 volumes per cent less oxygen than the preliminary normal specimen. Tetany is, therefore, attended by a relative anoxemia which would promote the tendency to lactic acid formation. This anoxemia may be due to a retarded circulation or to an accelerated oxygen consumption. Macleod and Knapp (18) and
Anrep and Cannan (2) have both shown that lactic acid production is increased by alkalosis induced by the administration of bicarbonate. This, the latter observers think, is entirely due to the alkalosis which develops. If this is so, there is further reason for believing that part of the organic acid found in the serum after hyperventilation is lactic acid.

**Effects of Anoxemia.**

If a large enough volume of air is rebreathed under conditions which preclude the accumulation of CO₂ by individuals who are not peculiarly susceptible to the effects of oxygen-want, hyperventilation occurs after the oxygen concentration of the inspired air has fallen below a certain level and increases gradually as the oxygen continues to fall. The minute volume, however, does not usually increase to the point where breathing itself is distressing. The ventilation of JP, for instance, in the experiment of June 18 (Table IV and protocols), even at the end of the experiment when the air in the spirometers contained only about 7 per cent of oxygen and the subject was dazed, did not approach the volume attained by the same subject at other times when breathing high concentrations of carbon dioxide, nor was the anoxemia experiment attended by as much respiratory distress and effort.

*Experiment of June 11, 1925. Subject JP.*—About an hour after breakfast, without any preliminary preparation the subject, in a sitting position, rebreathed through soda lime from an ordinary Sanborn model Tissot spirometer which had been filled in advance with about 65 liters of air. The tubes connecting the subject with the spirometer were so long that a considerable dead space free from carbon dioxide, but probably of low oxygen tension, was interposed.

There was also continuous respiratory resistance. Consequently dyspnea began early and within little more than 5 minutes acute dyspnea had developed, with considerable cyanosis. Blood was taken from the arm vein just before the experiment and again when dyspnea had reached a maximum and the subject was extremely uncomfortable. Part of the first sample clotted, unfortunately, so that determinations of oxygen capacity, oxygen content, and cell volume could not be made. There was also a moderate amount of hemolysis in part of the second specimen. CO₂, Cl, and protein were estimated in the non-hemolyzed fractions of serum. Tingling of the extremities and dizziness appeared, but no signs of tetany developed.

*Experiment of June 18, 1925. Subject JP.*—About an hour and a half
<table>
<thead>
<tr>
<th>Subject</th>
<th>Date</th>
<th>Oxygen capacity</th>
<th>Cell volume</th>
<th>Protein</th>
<th>CO₂</th>
<th>Inorganic P</th>
<th>Total acid</th>
<th>Total base</th>
<th>Organic acid</th>
<th>pH</th>
<th>CO₂ content of arterial blood</th>
<th>CO₂ tension of blood</th>
<th>Nature and treatment of blood</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>JP</td>
<td>June 11</td>
<td>1925 vols. per cent</td>
<td>100 cc.</td>
<td>6.74</td>
<td>354</td>
<td>3.8</td>
<td>154.1</td>
<td>16.1</td>
<td>5.5</td>
<td>55.5</td>
<td>60.7</td>
<td>74.8</td>
<td>Before rebreathing.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.64</td>
<td>351</td>
<td>3.7</td>
<td>136.8</td>
<td>148.2</td>
<td>11.4</td>
<td>7.25</td>
<td>55.6</td>
<td>60.0</td>
<td>55.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>18</td>
<td>43.6</td>
<td>365</td>
<td>4.3</td>
<td>143.2</td>
<td>158.4</td>
<td>15.4</td>
<td>7.29</td>
<td>59.465</td>
<td>55.3</td>
<td>16.0</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot; (oxygen-want).</td>
</tr>
<tr>
<td>&quot;</td>
<td>16.1</td>
<td>6.36</td>
<td>374</td>
<td>2.5</td>
<td>142.8</td>
<td>156.0</td>
<td>13.2</td>
<td>7.35</td>
<td>60.8</td>
<td>43.1</td>
<td>11.3</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot; (oxygen-want).</td>
</tr>
<tr>
<td>HAB</td>
<td></td>
<td>(17.4)</td>
<td>348</td>
<td>3.4</td>
<td>139.7</td>
<td>149.1</td>
<td>9.4</td>
<td>7.26</td>
<td>59.560</td>
<td>59.4</td>
<td>15.0</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot; (oxygen-want).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(17.5)</td>
<td>351</td>
<td>2.4</td>
<td>139.8</td>
<td>153.0</td>
<td>13.2</td>
<td>7.38</td>
<td>58.305</td>
<td>43.4</td>
<td>4.7</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot; (oxygen-want).</td>
</tr>
</tbody>
</table>
after breakfast, after a preliminary rest of more than 30 minutes and after both hands and forearms had been held immersed in hot water for about 20 minutes, the subject started rebreathing air from which the CO₂ was continuously extracted with soda lime. This time a Benedict-Sanborn apparatus was connected in series with the Tissot spirometer in such a way that a continuous circulation was maintained throughout both spirometers by means of the fan of the Benedict apparatus. The apparatus was filled in advance with about 62 liters of room air, besides what the tubing and connections contained. With this apparatus the subject was able to continue rebreathing without extreme discomfort for about 28 minutes. After about 10 minutes the respirations became somewhat irregular at intervals and after 20 minutes assumed an irregular periodicity. From time to time after this slight tingling of the face and extremities developed. Towards the end of the experiment dyspnea became quite marked, dizziness and confusion developed, but not syncope, and the mouth relaxed so that some expiratory air, but no inspiratory air, escaped about the mouthpiece. Blood was withdrawn from the arm vein just before and at the end of the experiment before the subject was disconnected from the apparatus. Parts of both samples of serum showed slight hemolysis. CO₂, Cl⁻, and proteins were determined in the non-hemolyzed fractions of the two specimens of serum.

Experiment of June 16. Subject H.A.B. (See Protocols of Paper I).—This experiment was quite similar to that of June 18 on JP, except for the fact that only 40 liters of air were placed in the spirometer at the beginning. Rebreathing was continued for almost 30 minutes. Although the respiratory rate increased comparatively early and the minute volume gradually grew larger, even at the very end of the experiment, when the subject was strikingly cyanotic, the hyperpnea was quite moderate. At intervals the respirations were counted for a minute at a time and an attempt was made to estimate the tidal air by observing the excursion of the Benedict spirometer. The respiratory rate at different times was: in the 7th minute, 21; in the 11th, 21; in the 14th, 24; in the 19th, 22; and in the 24th, 23. The tidal air rose from less than 400 cc. in the 7th minute to over 700 cc. in the 24th. The ventilation continued to increase at a more rapid rate after this, but was not measured.

Although dyspnea never became distressing, the subject was distinctly uncomfortable by the end of the experiment and felt somewhat dazed. No signs or symptoms of tetany developed.

At the end of the experiment the spirometer air was found to contain only 5.60 per cent of oxygen and 1.19 per cent of CO₂. Through an error the stop-cock of one of the tubes was left open for some time before the samples were withdrawn. This probably caused no considerable error because the air in the spirometer was under slight positive pressure and the tube between the open stop-cock and the spirometer was 5 or 6 feet long. The oxygen figures must, however, be considered as maximum values and the CO₂ as minimum. Apparently the soda-lime absorber was somewhat inefficient in this experiment.
In the first experiment pH was not determined. In the last two it was estimated by a gasometric technique devised by one of the authors. This consists of separating the serum or plasma from blood, as drawn, without contact with air, in the usual way. The CO₂ content of this serum is determined. Two small samples are then saturated at 38°C. in micro-torimeters filled with CO₂ mixtures of different known tensions. These samples are also analyzed for CO₂. By means of the following equation developed from the straight line formula of Peters (19) the CO₂ tension of the unknown blood may be calculated.

\[
\log p_x = \log p_A - \frac{(\log p_A - \log p_B)(\log C_A - \log C_2)}{(\log C_A - \log C_B)}
\]

where \( p \) and \( C \) represent the CO₂ tension in mm. of mercury and CO₂ content of the serum in volumes per cent respectively; the subscript \( x \) stands for the blood of unknown tension; and the subscripts A and B for the two samples saturated with known tensions of CO₂.

The rebreathing experiments of June 18 on JP and of June 26 on HAB represent the effects of increasing, but always moderate, involuntary hyperpnea carried on for a comparatively long period of time and were planned to supplement the voluntary overventilation studies just described. Certain technical defects in the apparatus used in the experiment of June 11 modified the results by introducing complicating factors. In the June 11 observation obstruction to respiration and an excessive instrumental dead space resulted in the rapid production of symptoms that forced the early termination of the experiment. Although CO₂ and hydrogen ion concentration had fallen, chlorides had not changed. Base had diminished somewhat.

In the longer experiment of June 18 bicarbonate decreased considerably, far more than it did in any of the voluntary hyperpnea studies. The associated change of pH was, however, only

---

2 A. J. Eisenman. This procedure has been employed in these experiments because of the uncertainty of colorimetric procedures. The Cullen procedure has been found by us and several other observers to give inaccurate results when applied to pathologic material because the temperature correction is variable. The more recent bicolorimetric method of Hastings, in which the pH is determined at 38°C., has been subjected to similar criticism by Austin and Stadie (personal communication). On the other hand, most observers agree that pK₁ of plasma and serum is remarkably constant. It has seemed best, therefore, in the absence of facilities for electrometric determinations, to use a gasometric technique until the accuracy of the colorimetric procedure is established.
0.06 instead of the 0.20 of the preceding series. A greater change of reaction could only be prevented by the fixation by some other acid of a certain amount of the base previously bound by carbonic acid. The increase shows that this is what happened. Chloride, presumably derived from the tissues has almost exactly replaced the CO₂ which was driven off by the overventilation and thus prevented a change of reaction that might have resulted in tetany.

The experiment of June 26 on HAB shows a different reaction. Attention has already been called to the fact that the subject developed little hyperpnea. This is especially noteworthy in view of the fact that the respiratory air contained an excess of CO₂. Evidently there is a large variation in the reaction of different individuals to oxygen-want. This is further illustrated in the oxygen contents of the blood of the two subjects. The final oxygen saturation of JP's blood was 70 per cent while HAB's fell to 27 per cent. Nevertheless HAB developed less hyperpnea than JP.

The reduction of CO₂ bears a direct relation to the duration and intensity of the hyperpnea. It was least marked in the short experiment of June 11 and most marked in the experiment of June 18. The compensatory reactions also seem to be dependent on the same factors. In the experiment on HAB, therefore, since CO₂ fell comparatively little, chloride was not significantly affected.

In both the last experiments protein rose, suggesting a concentration of the serum. In the study of HAB oxygen capacity and cell volume give similar indications, but the same is not true of JP, June 18. The increase of serum protein in the experiment of June 26 is almost exactly equivalent to the loss of CO₂.

The effects of the involuntary hyperpnea of oxygen-want then seem to depend on the duration and intensity of the overventilation produced. If the experiment is continued for 30 minutes the serum proteins increase slightly, the CO₂ falls to a variable extent, and the pH increases moderately. If CO₂ falls far enough to exceed the compensatory action of the protein increase, chloride is yielded by the tissues to combine with the base freed by carbonic acid. By this means the change of pH is minimized and, possibly, tetany is avoided.
Attention has already been called to the fact that base diminished slightly in the experiment of June 18. The change is so small that it is of doubtful significance. It may be that a diminution of base aids the chlorides in compensating for the fall of bicarbonate. In the experiment of June 26 on HAB base and organic acids both increase. The changes in the two elements are almost exactly equivalent. The degree of anoxemia attained in this instance may well have resulted in the appearance of lactic acid or some other acid metabolic products. This has led as it did in exercise, not to a displacement of other acids but to the transfer of base from the tissues. This is probably more strictly a response to anoxemia than is that exhibited by JP, which seems to have been determined rather by the overventilation.

The reduction of phosphate that appears in both the last experiments is as inexplicable as it was unexpected. As far as we know this has not yet been recognized as one of the effects of oxygen-want or overventilation.

*Hyperventilation without Tetany, a Case Study.*

Comparison of the voluntary hyperventilation and the oxygen-want experiments suggests that the differences in reaction are largely the results of the duration and intensity rather than the cause and nature of the hyperpnea which produced them. Thus short, comparatively mild overventilation on June 11 produced little change in the blood electrolytes; long, mild overventilation on June 18 increased pH slightly and reduced carbonic acid, but provoked little compensation; short, violent hyperpnea of the voluntary overventilation experiments resulted in a fall of carbonic acid, a striking increase of pH, and an appearance of organic acid that replaced chloride; the prolonged, moderate hyperpnea of June 18 reduced bicarbonate considerably, but the corresponding alteration of pH was prevented by the contribution of chloride from the tissues. In oxygen-want there are, however, certain elements that are lacking in voluntary hyperpnea, especially deficient oxidation of the tissues. It is quite possible that this modifies the results of overventilation and is the factor that causes the chlorides to replace the falling bicarbonate.

To settle the question it is, of course, necessary to study the
phenomena that follow long, moderate, voluntary hyperpnea. Experiments along this line were planned and will eventually be attempted. Meanwhile a patient with overventilation presented himself on the ward and afforded an opportunity to approach the subject indirectly.

Case 28976.—American, male, age 16, admitted to the hospital May 11, 1925. About 2 years before this he had a condition which was diagnosed as encephalitis lethargica, a period of 3 weeks during which he had fever and extreme lethargy. After this he was troubled with increasing weakness. In February, 1924, he developed shortness of breath of such severity that he was practically incapacitated. The next month he was sent to the hospital for examination and treatment. He presented at this time no evidence of localized lesions of the central nervous system. He had striking bilateral nystagmus. The respirations were much exaggerated during the greater part of the day, but he was able to hold his breath a long time and his breathing was comparatively normal when he was asleep. Blood Wassermann, spinal fluid, and other special examinations revealed no significant abnormalities. At the time of his second admission, May 11, 1925, the patient's condition was practically unchanged. He said that he had occasional attacks of tingling of the extremities and sometimes sudden seizures characterized by preliminary weakness and dragging down sensations that caused him to double up and sometimes resulted in vomiting. No more exact description of these attacks could be obtained and none occurred while he was in the hospital.

The patient appeared somewhat underdeveloped and rather thin. His color was good, his expression somewhat vacant. The eyes showed constant lateral nystagmus. The respirations were rapid and violent and he kept his mouth open constantly. The heart showed marked sinus arrhythmia. Further examination revealed no significant abnormalities.

Further study of the respiration showed that he could refrain from overventilation and even hold his breath for a considerable time by voluntary effort. During sleep and when his attention was diverted the breathing also diminished. There was a tendency for the abdomen and chest walls to move in opposite directions during the phases of respiration. This paradoxical motion became more marked as the breathing increased in violence. When he kept his mouth shut the overventilation diminished without causing him distress. The pulse, like the respirations, showed considerable variation in rate and was quite rapid. The temperature also showed more than the usual daily fluctuation, reaching 100°F. (rectal) almost every day. Impression: Encephalitis epidemica; late manifestations.

On May 15 a study of the respirations was made to determine how much of the overventilation was real and how much of it was only apparent. Before breakfast, and after the usual rest and preparation, the subject was connected with a Tissot spirometer in the usual manner employed for the determination of basal metabolism. The results of the examination are...
Acid-Base Equilibrium.  IV  

given below. During the first run he breathed quite violently. The exact respiratory rate was not determined for each minute, but for 5 representative minutes it was 30, 28, 32, 30, and 32, with an average of 30.4 per minute. At the end of only 5.5 minutes the expiratory volume had already reached

**TABLE V.**  
Respiratory Experiment of May 15, 1925. Subject 28976.  

<table>
<thead>
<tr>
<th>Weight</th>
<th>Height</th>
<th>Surface area</th>
</tr>
</thead>
<tbody>
<tr>
<td>53.5 kilos</td>
<td>169 cm</td>
<td>1.61 sq.m.</td>
</tr>
</tbody>
</table>

**First Run.**

- Total volume of air expired at 0°, 760 mm: 100.3 litres
- Time of run: 5.50 min.
- CO₂ of expired air: 1.88 per cent
- O₂ " " " : 19.17 " "
- Nitrogen of expired air: 78.95 " "
- O₂ absorbed: 1.76 " "
- CO₂ produced: 1.85 " "
- Minute volume of air expired: 18,240 cc.
- Respiratory rate (average of rate for successive min., 30, 28, 32, 30, 32): 30.4 per min.
- O₂ absorbed per min: 321 cc.
- CO₂ produced " " : 338 " "
- R. Q.: 1.05
- Total metabolism per hr. (R. Q. of 1.00 used for calculations): 94.4 cals.
- Metabolism per sq.m. per hr., 58.6 cals.; 36 per cent above normal.

**Second Run.**

- Total volume of air expired at 0°, 760 mm: 109.0 liters
- Time of run: 11.08 min.
- CO₂ of expired air: 1.68 per cent
- O₂ " " " : 18.75 " "
- Nitrogen of expired air: 79.57 " "
- O₂ absorbed: 2.33 " "
- CO₂ produced: 1.65 " "
- Minute volume of air expired: 9850 cc.
- Respiratory rate (too irregular to determine): 0.229 cc.
- CO₂ produced " " : 0.162 " "
- R. Q.: 0.71
- Total metabolism per hr.: 64.6 cals.
- Metabolism per sq.m. per hr., 40.1 " ; 6.7 per cent below normal.

100.3 litres, giving a minute volume of 18.2 litres. The CO₂ concentration in this air was 1.88 per cent. Part of the respiration, that portion which merely exchanges the dead space air, is, of course, of no functional significance for respiration. This may become of some importance when the
respiratory rate is unduly increased. If the dead space in this case were 150 cc. with a respiratory rate of 30.4, the effective minute volume must have been \(18,240 - (30.4 \times 150) = 13,680\) cc. This is about three times as much as normal. The high respiratory quotient, 1.05, indicates overventilation, and the result of the basal metabolism determination, which proved to be 36 per cent above normal, is probably exaggerated by the same factor.

**TABLE VI.**

Respiratory Experiment of May 22, 1925.

<table>
<thead>
<tr>
<th>Time, min.</th>
<th>Respirations</th>
<th>Volume of air expired, cc.</th>
<th>Tidal air, cc.</th>
<th>Effective minute volume, cc.</th>
<th>Effective tidal air, cc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>7400</td>
<td>322</td>
<td>3930</td>
<td>172</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>8300</td>
<td>377</td>
<td>4990</td>
<td>227</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>8700</td>
<td>417</td>
<td>6410</td>
<td>267</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>7000</td>
<td>333</td>
<td>3840</td>
<td>183</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>10,400</td>
<td>473</td>
<td>7110</td>
<td>323</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>10,400</td>
<td>416</td>
<td>6650</td>
<td>266</td>
</tr>
<tr>
<td>7</td>
<td>22</td>
<td>7000</td>
<td>318</td>
<td>3700</td>
<td>168</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>8700</td>
<td>414</td>
<td>5540</td>
<td>264</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>9600</td>
<td>400</td>
<td>6000</td>
<td>250</td>
</tr>
<tr>
<td>10.03</td>
<td>21</td>
<td>7800</td>
<td>371</td>
<td>4640</td>
<td>221</td>
</tr>
<tr>
<td>Total</td>
<td>225</td>
<td>85,300</td>
<td>50,750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>22.4</td>
<td>8500</td>
<td>379</td>
<td>5060</td>
<td>229</td>
</tr>
</tbody>
</table>

CO\(_2\) of expired air ........................................ 2.54 per cent

O\(_2\) .................................................. 18.05 " "

Nitrogen of expired air ...................... 79.41 " "

O\(_2\) absorbed .................................. 3.01 " "

CO\(_2\) produced .................................. 2.51 " "

O\(_2\) absorbed per min .................................. 256 cc.

CO\(_2\) produced .................................. 213 " "

R. Q. ........................................... 0.83

Total metabolism per hr., 74.6 cals.

Metabolism per sq.m. per hr., 46 cals.; exactly normal.

A second run gave entirely different results. The patient was directed this time to close his eyes and attempt to go to sleep. Under these circumstances the respirations became very irregular. At times there was complete apnea for as much as 1.75 minutes. These periods were terminated abruptly and were succeeded by short spells of obvious dyspnea. The low respiratory quotient in this period, 0.71, suggests that he was compensating for the earlier dyspnea. In spite of this his minute volume is abnormally
large. It is probable, then that the increased respiration was not, at this moment, entirely due to psychic factors. The basal metabolism proved to be 6.7 per cent below normal. (The experimental data of the two respiratory experiments appear in Table V.) A little later blood was withdrawn from the brachial artery and used for an electrolyte study. During the arterial puncture the patient had another attack of extreme dyspnea. The results of this and subsequent blood analyses appear in Table VIII.

### TABLE VII.

Respiratory Experiment of May 29, 1925.

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>Respirations</th>
<th>Volume of air expired cc.</th>
<th>Tidal air cc.</th>
<th>Effective minute volume cc.</th>
<th>Effective tidal air cc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>7080</td>
<td>253</td>
<td>2880</td>
<td>103</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>7920</td>
<td>307</td>
<td>4070</td>
<td>157</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>10,630</td>
<td>462</td>
<td>7180</td>
<td>312</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>16,830</td>
<td>648</td>
<td>12,930</td>
<td>498</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>8860</td>
<td>316</td>
<td>4660</td>
<td>166</td>
</tr>
<tr>
<td>6</td>
<td>33</td>
<td>9750</td>
<td>295</td>
<td>4900</td>
<td>145</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>7970</td>
<td>295</td>
<td>3920</td>
<td>145</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>10,630</td>
<td>532</td>
<td>7630</td>
<td>382</td>
</tr>
<tr>
<td>9</td>
<td>28</td>
<td>11,510</td>
<td>411</td>
<td>7310</td>
<td>261</td>
</tr>
<tr>
<td>10.06</td>
<td>30</td>
<td>7970</td>
<td>266</td>
<td>3470</td>
<td>116</td>
</tr>
</tbody>
</table>

Total........ 269

Average........ 26.7

CO₂ of expired air.......................... 2.40 per cent
O₂ “ “ ........................................ 17.80 “ “
Nitrogen of expired air...................... 79.73 “ “
O₂ absorbed.................................. 3.28 “ “
CO₂ produced................................ 2.37 “ “
O₂ absorbed per min.......................... 326.5 cc.
CO₂ produced “ “ ............................... 236 “ “
R. Q.......................................... 0.72

Total metabolism per hr., 92.2 cals.
Metabolism per sq. m. per hr., 56.8 cals.; 23.6 per cent above normal.

On May 22 a second study was made. Meanwhile the general condition of the patient had improved and his respirations were quieter. The respirations were studied as before, but the rate and volume at the end of each minute were noted separately. Arterial puncture was performed during the run. The site of puncture had been anesthetized in advance, the artery was rapidly and easily entered, and the subject said that he experienced no
TABLE VIII.
Total Acid-Base Equilibrium of the Plasma of a Patient with Prolonged Overventilation.
Case 28976.

<table>
<thead>
<tr>
<th>Date</th>
<th>Oxygen capacity</th>
<th>Cell volume</th>
<th>Plasma</th>
<th>CO₂ content of separated plasma at CO₂ tension of:</th>
<th>Blood non-protein nitrogen.</th>
<th>Nature and treatment of blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2)</td>
<td>(4)</td>
<td>(5)</td>
<td>(6)</td>
<td>(7)</td>
</tr>
<tr>
<td>May</td>
<td>18.6%</td>
<td>30.5%</td>
<td>7.59%</td>
<td>21.2%</td>
<td>414</td>
<td>3.1</td>
</tr>
<tr>
<td>15</td>
<td>15.5%</td>
<td>40.7%</td>
<td>7.08%</td>
<td>42.2%</td>
<td>403</td>
<td>4.0</td>
</tr>
<tr>
<td>“ 22</td>
<td>16.9%</td>
<td>37.7%</td>
<td>6.89%</td>
<td>46.9%</td>
<td>392</td>
<td>4.2</td>
</tr>
</tbody>
</table>

In this and all succeeding tables, after the protein value in Column 4 indicates that serum instead of plasma was employed for analysis.
† Saturated at 20 mm. CO₂ tension.
Acid-Base Equilibrium. IV

pain at all. There was no objective evidence that he noticed the puncture. The respirations during the experiment were comparatively quiet and only slightly irregular. At times the left hand assumed a position that suggested carpopedal spasm, but could be voluntarily or passively relaxed. None of the other limbs was similarly affected and application of a bandage after the arterial puncture did not elicit any spasms. The results of the respiratory experiment appear in Table VI and the blood analysis in Table VIII.

This time the respirations were probably in general under the normal control (respiratory quotient 0.83). The metabolism was normal for one of his age and size. The rate and the minute volume were, however, still greater than normal. In view of these facts and the absence of any clear evidences of tetany or alkalosis it seemed justifiable to see what effect alkaline therapy would have on the symptoms. Accordingly 2 gm. of sodium bicarbonate were given on May 25, 5 gm. on May 26, 10 gm. on the 27th, 15 gm. on the 28th, and 5 gm. at 7 a.m. on the 29th. A third respiratory study was made at 8.30 a.m. May 29, 90 minutes after the last dose of bicarbonate.

The night following the second examination the patient got into a fist fight with another patient on the wards. The next day the respirations, which had been subsiding, returned to their former character. The administration of bicarbonate had no apparent effect on the respirations. Before the run he was overventilating wildly. After the mask was applied the breathing quieted down with surprising rapidity, with long periods of complete apnea. The quiet breathing continued throughout the 1st minute of the test. At the end of that time arterial puncture was begun. For some reason this proved difficult and painful, necessitating two punctures, and blood was not actually obtained until the 6th, 7th, and 8th minutes. The pain and difficulty is reflected in the respiratory record in Table VII. Overventilation was not, however, striking.

In spite of the abnormally large minute volume and the high respiratory rate, the low respiratory quotient suggests hypo- rather than hyperventilation, and the period of observation probably represented compensation for previous overventilation.

It is evident from the history and the respiratory studies that the patient was overventilating markedly for considerable periods; nevertheless he presented no symptoms of tetany nor any disposition to develop signs of tetany. Davies, Haldane, and Kennaway (9) and others found that alkalosis usually resulted in ketonuria. The urine in this case was examined repeatedly, but no acetone or diacetic acid was ever detected. It seemed possible if not probable, that the effect of hyperventilation was, in this case, compensated so that alkalosis did not develop. The blood studies were made to determine the nature of the compensatory mechanism.
At the time of the first examination total base and total acid were both within normal limits. Bicarbonate was extremely low, only 21.2 volumes per cent of total CO₂. Protein was somewhat high, phosphate and undetermined acids were normal. Chloride was considerably elevated and had evidently replaced the bicarbonate deficiency. pH was not determined, but can be estimated very roughly from the respiratory study.

If it is assumed that the dead space is 150 cc. and that the expiratory air beyond this comes from the alveoli and is approximately at the same tension as the arterial blood, one can calculate the arterial CO₂ tension from the CO₂ of the expired air and the effective minute volume, by the following formula:

$$\frac{100 \text{ CO}_2}{V - 150 \text{ R}} = A$$

in which CO₂ represents carbon dioxide consumed per minute; V the total volume of air expired per minute; R the number of respirations per minute; and A the per cent of CO₂ in the alveolar air. A (B - w) = alveolar or arterial CO₂ tension, where B is the barometer reading under standard conditions and w the water vapor tension at body temperature.

The arterial CO₂ tension calculated by these equations from the first respiratory run, in this case would be

$$\frac{100 \times 1.85}{18,500 - (30.4 \times 150)} (764.5 - 49.4) = 17.5 \text{ mm}.$$  

The pH of the serum, using the Henderson-Hasselbalch equation with a pKₐ of 6.10, would be 7.32. The validity of these calculations is open to serious question in this experiment not only because of the uncertainty of the dead space volume, but also because the arterial puncture and the respiratory run were not made simultaneously. The values obtained do, however, probably give an idea of the order of magnitude of the arterial tension, even though they have no absolute value. If this is granted it is obvious that hyperventilation in this case did not result in alkalosis, but was compensated by a reduction of bicarbonate and a proportionate rise of chloride.

At the time of the second experiment, as has been already pointed out, the condition of the patient had improved considerably, and during the run there was no evidence of over-
ventilation. Examination of the blood this time revealed an increase of CO₂ to almost twice its original value. Total base and total acid had both increased somewhat; protein and chloride had fallen. This time pH was determined gasometrically by the technique described above and equation 1.

In the experiment under discussion the separated serum, saturated at 20 mm., contained 38.8 volumes per cent of CO₂, and at 60 mm., contained 48.3 volumes per cent of CO₂. The CO₂ tension of the blood in the body was, therefore, 30.3 mm. and the pH 7.37, an entirely normal figure. Calculated from the respiratory study the alveolar CO₂ tension proved, from equation 2, to be 30 mm. This illustrates the value of this method of approximating the CO₂ tension when respiration is normal. It has been employed by Krogh and Lindhard, Pearce, and by one of the authors in another connection (5).

In the third experiment the administration of bicarbonate had resulted in elevating the serum CO₂ somewhat further, again at the expense of the chlorides. The pH was again determined gasometrically. In this case serum CO₂ at 30 mm. was 43.3 volumes per cent, and at 60 mm. 51.7 volumes per cent. The CO₂ tension of the blood as drawn, calculated from these points by means of equation 1, was 32.8 mm., giving a pH of 7.38. From the respiratory study the CO₂ tension by equation 2 came out 28.8 mm.

For the disagreement in the last case between the arterial CO₂ tension calculated by the two methods a partial explanation may be found in the irregularity of the breathing during the experiment. The spirometer gas on which the calculations were based was the product of the whole 10 minutes, while the blood was obtained during 3 of these minutes only. The effective ventilation was not, however, especially small during these minutes. It is more probable that during hyperventilation, especially when the respiratory rate is unduly increased, the air is less effectively mixed than usual. This would have the same effect as an enlargement of the dead space of the lungs and would invalidate calculations of the alveolar CO₂ from expired air by a formula that involved the use of an assumed dead space value.

It is clear from the gasometric pH determinations that the pH of the blood during the second two experiments was normal.
About the first there must be more uncertainty. It is, however, highly unlikely that the patient had any alkalosis at this time. The errors in calculations derived from the expired air would all tend to minimize the CO₂ tension and, therefore, to exaggerate the pH. Furthermore, with the observed serum CO₂ content the arterial tension would have had to be as low as 14 mm. to give a pH of 7.4 and at the extreme low level of 11.4 mm. to raise the pH to 7.5.

It is reasonably certain that in this case definite overventilation occurred at frequent intervals, sometimes persisting for long periods, without the appearance of tetany and it seems to be more than a simple coincidence that the overventilation did not produce alkalosis. The overventilation did, however, result in a reduction of the CO₂ tension. There was, at the same time, a replacement of bicarbonate by chloride, which compensated for the reduction of CO₂ and was primarily effective in preventing alkalosis. Whether any significance is attached to the alterations of total base one cannot say. The base did, however, vary in the same direction as bicarbonate and reduction of base may have played its part in preventing the development of alkalosis.

It is impossible to say from the blood studies alone whether high chloride or low bicarbonate represents the primary disturbance; but the clinical condition favors the latter interpretation of the data. The disease from which the patient suffered affected the central nervous system. Apparently the respiratory mechanism had escaped from the normal control and responded wildly to extraneous stimuli. The heart and the vasomotor system showed a similar tendency. Apparently the response to intrinsic stimuli was comparatively normal because, when he was asleep, pulse and respirations lost their unusual character. Evidence of such a dissociation is also seen in the first experiment. During the second run, when he went to sleep, the ventilation quieted down and, indeed, frequent periods of apnea developed. Even under these conditions, however, there was an abruptness and violence in the periodic respiration that is not usually observed in normal subjects after overventilation.

If it is assumed that overventilation was the primary cause of the changes in the blood electrolytes, it follows that the chloride response must have taken place with extraordinary rapidity.
If the bicarbonate reduction were effected by means of the respiratory mechanism alone, alkalosis could hardly have failed to ensue unless chlorides increased almost as rapidly as CO₂ diminished. At the time of the third experiment a freshly voided specimen of urine was examined and found to be distinctly alkaline (it contained no acetone). Apparently the kidneys played their part in compensation, probably by excreting bicarbonate, even though the pH of the serum was not high. The administration of extra bicarbonate placed an additional load on the mechanism, but did not succeed in overcoming the defenses of the organism and producing alkalosis.

In any event it is obvious that the organism can and does mobilize chloride for the maintenance of neutrality in response to changes of bicarbonate. The response to overventilation in this case is quite different from that of JP. This may be due to the difference in duration and intensity of the excessive breathing. From measurements in unpublished experiments it has been found that the effective minute volume of JP during voluntary hyperventilation far exceeds that of the patient under discussion.

The first reaction to extremely rapid and short hyperventilation may consist in a reduction of free CO₂ and chlorides. If the hyperventilation could have been prolonged at this excessive rate it is possible that chloride would have increased. As it was, organic acid increased, perhaps as a result of tetany. When overventilation is carried on more slowly for a long period, chloride may respond so completely that no alkalosis develops and organic acid does not appear. The resulting picture, when judged from the standpoint of the blood alone, is indistinguishable from that of a compensated chloride acidosis. There may be a slight recession of total base to aid in the adjustment. The end-result is conservative in preventing disturbances in the reaction of the blood which would inevitably result in frequent or continuous tetanic convulsions.

Vomiting and Gastric Tetany, a Study of Two Cases.

About the same time there was admitted to the medical service a patient with vomiting, mild hyperventilation, and fully developed tetanic symptoms.
Case 18406.—American, female, age 43, admitted to the hospital June 2, 1925. 2 years earlier her first pregnancy had been terminated during the 8th month because of a toxemia. At that time she was vomiting and complained of pain in the back and the epigastrium, frequent severe headaches, loss of vision, and slight swelling of the lower extremities. Her systolic pressure was over 200, diastolic about 140; she had a well developed optic neuritis and retinitis, slight puffiness of the face and lower extremities, and moderate exophthalmos. The urine contained considerable albumin and occasional granular casts. The blood non-protein nitrogen was 26 mg. per cent; phenolsulfonephthalein excretion 30 per cent in 2 hours. Blood Wassermann was negative. She gave a history of dyspnea on exertion antedating the onset of pregnancy. The child died immediately after delivery, but the patient improved rapidly. The symptoms ceased, the systolic blood pressure gradually fell to 150 and the diastolic to 100; the optic neuritis receded; and the phenolsulfonephthalein excretion rose to 60 per cent. The blood non-protein nitrogen at the time she left the hospital was 29 mg. per cent.

The patient returned from time to time after this for observation. On each occasion she complained of occasional headaches, nausea, and slight swelling of the feet. The blood pressure gradually rose again to its original high level; the systolic pressure was 180 mm. in July, 1923; 240 in March, 1924; 248 in June; 250 in July; and 240 in September. The diastolic pressure at the last observation was 140 mm. At this time, September, 1924, she again complained of blurring of vision. In the early part of May, 1925, the headaches became more severe, she developed morning sickness, vomiting frequently, and noticed that her urine was becoming scanty. The vomiting gradually increased in frequency and severity until for a few days before she entered the hospital she was unable to retain anything at all. During this period she became somewhat drowsy. At times she had attacks of breathlessness during which she developed spasms of her hands and feet. The night before admission she had a more severe attack than usual in which the spasms became so marked that she was unable to move.

When brought into the hospital she had another of these attacks in which she was seen by the members of the staff. The picture presented was quite typical of tetany with striking carpopedal spasm and a positive Chvostek's sign. On examination she appeared flushed and, at times, somewhat cyanotic. Her breathing was irregular. Sometimes she pumped rather violently; at other times the respirations subsided and became quite slow and shallow. These changes were evidently referable in part, at least, to psychic factors because the overventilation occurred especially when she was disturbed or examined. During the periods of hyperventilation she usually developed tetanic spasms of the extremities. The eyes were proptoturant, with all the signs of exophthalmos. There was striking edema of both optic nerve heads. The systolic blood pressure was 230; diastolic 135. The heart was somewhat enlarged. There was no edema of the extremities. She appeared dehydrated and complained of thirst, but was too nauseated to take anything by mouth. The urine contained a trace of albumin and
a few hyaline casts. Blood count 4.7 million red blood cells; 11,500 leucocytes with 78 per cent of polymorphonuclear neutrophils. The blood non-protein nitrogen was 36 mg. per cent.

Blood was withdrawn from an artery shortly after the patient entered the hospital. A little before and a little after the arterial puncture she had attacks of overventilation and tetany, but while the blood was being withdrawn the respirations were little increased and she had no spasms. She was immediately given a hypodermoclysis of 1500 cc. of normal saline solution. She was ordered carbohydrate fluids and salt by mouth, but little was given during the first 24 hours because of the persistent nausea and severe headache. The hyperventilation and tetanic seizures ceased, however, soon after the administration of the saline and by the next morning the headache and nausea had also disappeared. Owing to an error salt was not added to the diet for the first few days. After the 2nd day she was given a high carbohydrate diet with 50 gm. of protein, and on June 9 this was increased to 60 gm. The basal metabolism was determined June 5 and proved to be quite normal. The expiratory minute volume at this time was 5000 cc., the respiratory rate 21.7 per minute, and the expired air contained 2.87 per cent of CO₂. The second blood examination was made the morning of June 9, before breakfast. She was then entirely free from symptoms of all kinds. She was discharged June 13. Her systolic blood pressure was 190, diastolic 130. The results of metabolism studies and blood examinations appear in Tables IX and X. Impression: Essential hypertension (malignant); vomiting; overventilation tetany.

The first blood contained the normal amount of bicarbonate, but less than the usual amount of chloride. The total base was also somewhat low. After recovery almost every element was altered.

In the first place the serum proteins had diminished. This would seem to indicate that the blood had taken up water. However, oxygen capacity, which should also be affected by such a change, remained unaltered. The reason for this discrepancy is found in the cell volume values. Apparently the cells shrunk during the improvement. If hemoglobin be considered a measure of the water content of whole blood, one can say that the hydration of the blood has not changed. The relative volume of the plasma in the second observation is, however, greater than that of the first as 100 – 35.9 : 100 – 40.6 or 64.1 : 59.4. These figures are almost the exact reciprocals of the serum protein values 5.96 and 6.35. The agreement is almost too good to be the result of coincidence. It seems more likely that the serum has really gained water at the expense of the cells. Be this as it may, it is
### TABLE IX.

**Total Acid-Base Equilibrium of the Plasma of Three Patients with Tetany.**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Date</th>
<th>Oxygen capacity (vols. per cent)</th>
<th>Cell volume (vols. per cent)</th>
<th>Protein (per cent)</th>
<th>CO₂ (mg. per 100 cc.)</th>
<th>Ω₂ (mg. per 100 cc.)</th>
<th>Total acid (mm)</th>
<th>Total base (mm)</th>
<th>Organics acid (mg. per 100 cc.)</th>
<th>Blood non-protein nitrogen (mg. per 100 cc.)</th>
<th>Nature and treatment of illness</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>18406</td>
<td>June 2, 1925</td>
<td>15.3</td>
<td>40.6</td>
<td>6.35</td>
<td>60.9</td>
<td>337</td>
<td>2.7</td>
<td>133.3</td>
<td>145.1</td>
<td>11.8</td>
<td>36</td>
<td>A. cont.</td>
</tr>
<tr>
<td>22459</td>
<td>Aug. 13, 1923</td>
<td>15.3</td>
<td>35.9</td>
<td>5.96</td>
<td>61.4</td>
<td>352</td>
<td>3.5</td>
<td>137.4</td>
<td>158.1</td>
<td>20.7</td>
<td>23</td>
<td>&quot;</td>
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<tr>
<td>35417</td>
<td>Dec. 15, 1924</td>
<td>7.09</td>
<td>64.0</td>
<td>3.8</td>
<td>318</td>
<td>124.7</td>
<td>200.6</td>
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</table>

Remarks:
TABLE X.

*General Metabolism Data of Subject 18406.*

<table>
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<tr>
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<tr>
<td>June</td>
<td>cc.</td>
<td>cc.</td>
<td>cc.</td>
<td>gm.</td>
<td>gm.</td>
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<td>2</td>
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<tr>
<td>3</td>
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<td>-2.9</td>
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<td>950</td>
<td>1,300</td>
<td>1.2</td>
<td>0.6</td>
<td>0.6</td>
<td>1,020</td>
<td>7.5</td>
<td>4.2</td>
<td>3.3</td>
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<td>1,740</td>
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<td>1.1</td>
<td>0.3</td>
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<tr>
<td>6</td>
<td>3,800</td>
<td>1,270</td>
<td>2,530</td>
<td>3.2</td>
<td>1.0</td>
<td>2.2</td>
<td>1,020</td>
<td>7.5</td>
<td>8.6</td>
<td>-1.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3,600</td>
<td>1,370</td>
<td>2,230</td>
<td>7.5</td>
<td>3.2</td>
<td>4.3</td>
<td>1,720</td>
<td>10.2</td>
<td>7.3</td>
<td>2.9</td>
<td></td>
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</tr>
<tr>
<td>8</td>
<td>3,800</td>
<td>2,090</td>
<td>1,110</td>
<td>10.9</td>
<td>92.0</td>
<td>10.1</td>
<td>2,560</td>
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<td>10.1</td>
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<tr>
<td>9</td>
<td>1,700</td>
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<td>14.0</td>
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<td>2,030</td>
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<tr>
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<td>2,220</td>
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<td>14.8</td>
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<td>9.9</td>
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<td></td>
<td>2,400</td>
<td>9.4</td>
<td>7.0</td>
<td>2.4</td>
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<tr>
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<td>1,570</td>
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<td>6.2</td>
<td></td>
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<td>2,400</td>
<td>9.4</td>
<td>7.0</td>
<td>2.4</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Remarks:
- 1500 cc. saline hypodermoclysis and orange juice by mouth.
- Allowed unlimited salt in diet and given additional 10 gm. in capsule form.
at least certain that the cells at the time of the first observation contained more water for each unit of hemoglobin than they did after recovery. Furthermore, the relative water content of the cells was high in relation to normal standards. According to the method employed in this work the average value of the ratio, oxygen capacity : cell volume in defibrinated blood of normal individuals is about 0.42. In the first blood specimen in this case it was only 0.38; in the second it had returned to normal, 0.43. For this peculiar tendency of the cells to become relatively or absolutely excessively hydrated in conditions in which the organism as a whole appears to be dehydrated no explanation offers itself. It has, however, been frequently encountered by us and will be referred to in other connections. Gamble and Ross (11) have recently shown that the serum protein concentration increases after pyloric obstruction and interpret this as an indication that the serum has lost water. As long as discussion is limited to serum such a conclusion is probably warranted, but it cannot be assumed from the same data that the blood as a whole has become dehydrated.

Gamble and Ross (11) in the same paper have pointed out that pyloric obstruction leads to a depletion of the chloride and, to a lesser degree, of the sodium of the plasma. Our findings are quite in keeping with theirs. The deficiency, according to them, may be ascribed to an excessive loss of these elements in the vomitus. Haden and Orr (13), on the other hand, do not believe that the loss of chloride in the vomitus plays an important part in determining the low level of blood chloride. Although the case under discussion is not one of pyloric obstruction, the vomiting had been so persistent that the condition is more or less comparable to that produced by pyloric obstruction. The changes in the serum are also quite typical except for the fact that bicarbonate is normal. The patient, unfortunately for the investigators, ceased to vomit almost as soon as she entered the ward, so that the chloride and base lost in the vomitus could not be estimated. The scanty metabolism data given in Table X, however, show that she retained both fluid and salt in large quantities during recovery. This may be considered as presumptive evidence that she had

3 In oxalated blood it is about 0.46.
suffered an excessive loss of the same elements during the preceding period.

If the defense of the body against the alkalosis of overventilation lies in the replacement of carbonic acid by chloride, the cause of tetany in this case is not hard to find. With chlorides depleted by vomiting compensation could not be effected. In consequence overventilation of a grade that reduced bicarbonate only to the normal level resulted in the development of true tetanic spasms. It is unfortunate that pH was not determined. It is more than probable that it would have been found to be abnormally high.

The blood non-protein nitrogen is usually found to be elevated in cases of organic obstruction of the gastrointestinal tract (23, 7, 14). This elevation has been ascribed by Haden and Orr (14) and others to a toxic destruction of protein. In this case the non-protein nitrogen was not abnormally high, but it was lower at the time of the second blood examination. Study of the nitrogen balance reveals no evidence of abnormal nitrogen catabolism. The excretion of nitrogen did increase strikingly, however, as soon as diuresis was established.

The low phosphate encountered in the first studies of this and the preceding patient are interesting in relation to the results of the anoxemia experiments. It may be that reduction of serum phosphate regularly follows overventilation.

Case 22459 presents a similar condition. In this instance vomiting occurred as a complication of typhoid fever. The chloride reduction is even more marked than that of the preceding case and bicarbonate is also lower. With the chloride defense so seriously compromised it is easy to understand why alkalosis and tetany developed under the influence of moderate overventilation and without any elevation of bicarbonate.

Case 22459.—Danish, female, age 31, admitted to the hospital August 8, 1923, in the 2nd week of typhoid fever, which had occurred in the 2nd month of pregnancy and precipitated a miscarriage. On August 11 she developed a mild diarrhea and at the same time began to vomit frequently. 2 days later carpopedal spasm was observed. For 24 hours previous to this her respirations had been rapid, at times rising above 40. It was during these periods of dyspnea that signs of tetany appeared. There seemed to be a distinct psychic factor involved, because the dyspnea increased when she was examined or knew that she was observed. The blood was examined on
August 13. At this time the temperature was about 103°F, pulse 110, respiration about 30 per minute. Vomiting ceased the next day, but she proved difficult to feed, the diarrhea persisted, and tetanic symptoms recurred at intervals for some days longer. After a protracted and complicated illness she was discharged from the hospital, cured, in the middle of September. The results of the blood examination appear in Table IX.

Case 35417.—American, female, age 32, married, admitted to the hospital, December 13, 1924. For 3 years she had had attacks of needle-like pains, beginning in the left hand, gradually travelling up the arm and spreading to the trunk and the other limbs. These gradually increased in severity. With the pains came a sense of numbness. In August, 1924, she had a seizure of muscular rigidity that suggested tetany, during which she became unconscious. She had two milder attacks subsequently. She appeared well developed and nourished. Temperature was normal; the pulse 80 to the minute with a rather striking sinus arrhythmia; the systolic blood pressure was 104, diastolic 75. The palms of her hands were dripping with perspiration and her pupils were abnormally dilated. Otherwise the physical examination and special examinations including blood Wassermann test, urinalysis, blood count, gastrointestinal x-rays, x-ray examination of the skull, gastric test meal, and basal metabolism, proved negative. Blood was examined before breakfast on December 15. She had no symptoms at the time. Impression: Tetany.

The results of the blood examination appear in Table IX.

Case 35417 presents an entirely different blood picture associated with definite tetanic symptoms. The patient was admitted to the private pavilion under the care of an outside physician and it was impossible to make a complete study or to repeat the examination of the blood. The striking thing in this case is the high level of total base. Bicarbonate is high, but does not exceed the extreme normal limits. In this instance it seems likely that the excessive amount of base in the serum rendered the patient more susceptible to alkalosis and tetany. Serum calcium was quite normal.

DISCUSSION.

In certain respects these experiments throw some light on the probable nature of the differences between arterial and venous blood shown in Paper III (22). When the venous blood from a local part of the body is altered under the influence of extraneous conditions, this alteration can only come about if the arterial blood is changed as it passes through the part. Although arterial blood was not taken, the preliminary venous blood, es-
especially after the arm had been immersed in hot water, was more nearly like normal arterial blood than was the second specimen, taken after stasis or exercise, and the difference between the two must be qualitatively similar to the difference between arterial and venous blood. Studying the blood before and after a given disturbance is equivalent to magnifying the change that occurs between arterial and venous blood during this disturbance, because no alteration of the constitution of the blood can take place except by abstraction or addition of material in the tissues.

The types of change that can occur are quite various and depend, as we suggested in the preceding paper (22), on the nature of the provoking disturbance. In the stasis experiment the water and chlorides of the blood changed; in tetany chlorides fell; in exercise base rose. Each one of these changes affected the carbon dioxide absorption curve of both blood and serum in a different manner. The nature of these effects is shown in Table XI. One cannot assume that because any one of the constituents of blood is unchanged the reaction of the blood to carbon dioxide will remain unaltered.

The rapidity with which chloride and base respond to disturbances in the other electrolytes is striking. In this response chloride must play a part quite analogous to that which it plays in the transfer of electrolytes across the cell membrane. Any
diminution of chlorides without a corresponding loss of base liberates base to combine with carbonic or other acids and, therefore, tends to prevent excessive acidity and to promote a state of alkalosis. *Vice versa* the passage of Cl from the tissues to the blood has the opposite effect. Presumably the Cl is released or taken up by base in the tissues and this base, like that of the blood cells is, therefore, rendered available for the maintenance of the reaction of the plasma and the general exchange of electrolytes throughout the body.

The objection may be raised that the data thus far presented do not prove that Cl actually passed into the tissues and not merely into the blood cells. The answer to this objection is given in Table XII which shows the whole blood Cl before and after stasis, exercise, and tetany. Column 1 gives the chloride concentration observed, Column 2 the actual amount of chloride per unit of original blood. The succeeding 4 columns give similar data for plasma and cell chlorides. The methods of calculation are similar to those applied to the analysis of arterial and venous blood in the preceding paper of this series (22). The direction of the changes in concentration and total amount of chloride in the blood reflect the similar changes encountered in the plasma. Although the two differ in magnitude they are always the same in direction.

**TABLE XII.**

*Changes in the Chlorides of the Blood and Their Distribution under Various Conditions.*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Date</th>
<th>Blood.</th>
<th>Plasma.</th>
<th>Cells.</th>
</tr>
</thead>
<tbody>
<tr>
<td>JP</td>
<td>1924</td>
<td>mg. per 100 cc.</td>
<td>mm</td>
<td>mg. per 100 cc.</td>
</tr>
<tr>
<td>Mar. 11</td>
<td></td>
<td>274</td>
<td>77.3</td>
<td>370</td>
</tr>
<tr>
<td>Apr. 3</td>
<td></td>
<td>260</td>
<td>60.7</td>
<td>349</td>
</tr>
<tr>
<td>&quot; 10</td>
<td></td>
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<td>82.2</td>
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<tr>
<td>&quot; 16</td>
<td></td>
<td>283</td>
<td>81.6</td>
<td>355</td>
</tr>
</tbody>
</table>

* Millimols of Cl in the plasma, cells, or whole of a liter of blood.
In the past observers, confining their studies largely to carbon dioxide and oxygen changes and the hydrogen ion concentration, have obtained an unbalanced view of the purpose and effect of the acid-base mechanism. A certain group has insisted that the hydrogen ion concentration of the blood played the dominant role in determining the automatism of the respiratory mechanism, others have ascribed the same function to carbonic acid. Neither group has been able to maintain its theory in the face of the growing body of experimental data. In oxygen-want, for example, dyspnea is found associated with a reduced bicarbonate and an elevated pH (3). The alkalosis that follows the administration of bicarbonate is not attended by a cessation of respiration. Even the most ardent exponents of the theory that pH regulates respiration have been forced to admit that this chemical control is frequently replaced by some other stimulus.

Y. Henderson (15) in a reaction against the restricted viewpoint of the chemists has called attention to the fact that the true function of respiration is to supply the tissues with adequate oxygen and to relieve them of sufficient carbon dioxide to carry on their normal functions and has suggested that the maintenance of a constant blood pH may be only an incidental result. From this point of view he argues that respiration is dependent on a combination of two factors, the alkali and the oxygen tension of the blood. The argument is most ingeniously developed and seems to explain many of the phenomena of respiration for which the pH theory failed to account, and especially the dyspnea of oxygen-want. The chief criticism against Y. Henderson’s hypothesis depends on the fact that he used the terms alkali and bicarbonate as if they were synonymous. To be sure, he did qualify this by adding the adjective “available” in some connections; but from his discussion it is not at all clear that he appreciated the restrictive significance of the term “available alkali.” This term, like the term “alkaline reserve,” is of doubtful value. At best it applies only to the discussion of test-tube experiments. It is quite evident that all the alkali in the cells and in the plasma is available for the neutralization of acid and that the tissues contain a further store which forms a highly mobile “alkaline reserve.”

Y. Henderson discredits the idea that the acidosis of diabetes
and the symptoms that ensue are due to the abstraction of base from bicarbonate by the ketone acids. The latter, he believes, enter the blood as neutral salts, already combined with base. At this point he is not entirely clear, but gives the impression that the blood base increases without any direct association with bicarbonate changes.

A highly mobile, fluctuating blood alkali such as Henderson postulates would result in frequent and extreme variations in the osmotic pressure of the serum. The latter must be in large part determined by the concentration of electrolytes. This is defined by the sum of the cations and anions. As blood is practically neutral and all the important organic elements, especially the protein, behave as anions, total base may be used as a measure of the fraction of the total osmotic pressure which is contributed by electrolytes.

All determinations of the osmotic pressure of serum have shown that it is comparatively constant even under the most diverse conditions of health and disease. Gamble and his associates (10) have, furthermore, shown that the total base of serum is maintained at a very uniform level by the action of the kidneys and the tissues. They have also shown that chloride can be made to replace bicarbonate. They have not, however, attempted to demonstrate the reverse of this process. In consequence they have concluded that bicarbonate holds a "mendicant position," giving way to every other acid that enters the blood. Bicarbonate is no more mendicant than chloride, and may remain constant or increase while the latter diminishes. It has been demonstrated that chloride may be forced to replace bicarbonate when the latter is depleted. Finally, the exercise experiment showed that base itself may be compelled to depart from its fixed and even course under the proper stimulus.

Current theories that postulate a greater constancy for one element or function of the blood than for another cannot survive the results of such experiments as these, and there is no good evidence that any element is especially favored at the expense of another. Undoubtedly any alteration of equilibrium relations will invoke a compensatory reaction that will tend to minimize the effect of that disturbance. This is true in any chemical or physical system. In a system as complex as that of the blood,
especially when it is in the body in contact with the still more complex tissues, alteration of even a single component must initiate a train of reactions that affects not another single component, but almost every constituent of the blood, and the influence of which will extend far into the tissues.

In the rearrangement and adjustment which ensues each one of these components will yield somewhat and each will resist until an equilibrium is again restored under conditions as near as possible to the normal state. A short or trivial disturbance must necessarily initiate one set of reactions; a more prolonged or drastic disturbance will elicit a different response. The effect of any condition will depend on the nature, intensity, and duration of the disturbance it provokes; but this effect will seem to have a conservative tendency.

There is no reason for confining the term equilibrium to electrolytes nor the term components to recognizable individual constituents of the blood or tissues. The processes of metabolism that occur in the tissues are almost certainly reactions in a state of equilibrium and the process of respiration itself must be included as a component of the system. In this respect a biological system differs from a test-tube experiment. If such a conception is admitted it is impossible to entertain the idea that respiration can respond to pH only, without reference to the metabolic needs of the body, or that osmotic pressure will yield to no other function of the blood. The disturbance of metabolism that would result from such an unbalanced reaction would, in itself, inevitably initiate further reactions that would again have a conservative effect. Biological automatism is an undeniable fact. It is quite as obvious that there must be an interaction between all the various parts of the whole automatic organism. One can, then, consider the reactions that occur in response to a given disturbance as tending towards the maintenance of the normal bodily functions as a whole without accepting a vitalistic philosophy.

In the stasis experiments the most striking phenomenon is the loss of water from the blood to the tissues. Estimations based on the cell volume and oxygen capacity figures alone in the experiments of March 11 and April 18 show that this loss was borne almost entirely by the plasma and amounted to 30 per cent of the
volume of the plasma. The reaction is quite like the loss of water to the blood cells after the addition of CO₂; but in this case the blood cells are left unchanged and the tissues gain all the fluid. Furthermore the reaction is not simply a response to CO₂ because it does not occur in either of the exercise studies or after combined exercise and stasis, although both CO₂ and pH are quite as much or more altered in these experiments. The occurrence of serum dehydration in oxygen-want experiments leads one to wonder whether anoxemia may not also be the factor that determines the transfer of water in stasis. This loss of water may represent an effort to dilute the waste products of metabolism which have accumulated in the tissues because they are deprived of their normal means of egress from the body. The metabolism may itself be compromised and rendered abnormal by lack of oxygen and the accumulation of these products. The transfer is probably a result of increased capillary pressure possibly aided by elevation of the osmotic pressure in the tissues due to the accumulation of catabolites. One result of the fluid exchange may be to permit a larger proportion of the carbon dioxide load to be carried by the more highly buffered tissue cells.

Concerning the value of the diminution of chloride there can be little doubt. In the first place by rendering its base available for combination with these acids it lessens the pH alteration that would occur if bicarbonate alone carried the CO₂ and acid load. Furthermore the blood is enabled to carry more CO₂ at a lower tension. The latter point must be of prime importance in permitting metabolism to continue in a comparatively normal manner. With all opportunities for carbon dioxide to escape cut off, no set of reactions could well be conceived to meet the situation with less ultimate disturbance of the original equilibrium conditions and the metabolic processes of the tissues.

In exercise the blood water was not seriously altered and the distribution of fluid between the two phases of the blood was not affected in any characteristic manner. The main problems to be met in exercise are, first the elimination of the excessive amount of carbon dioxide produced by the heightened metabolism, and second the neutralization of lactic acid. The provision of an adequate oxygen supply is secondary during short periods of exercise, at least. Neglecting for a moment the pulmonary
ventilation, which is probably not seriously affected by such limited local exercise as that of the present experiments, the delivery of carbon dioxide from the blood will be facilitated as the CO₂ tension of the blood increases. By sparing chloride and forcing bicarbonate to bear a larger part of the burden the CO₂ tension is elevated and the pH falls. This fall is not, however, great enough to carry the whole of the added acid. The remainder is sustained by the abstraction of base from the tissues and not from chloride.

When tetany is rapidly induced by overventilation bicarbonate gives up little of its base, although by doing so the change of reaction that is generally considered to be the cause of the tetanic symptoms would be diminished or prevented. Foreign organic acids which should aid in promoting such compensation do appear, but are entirely taken up by base provided by chloride. It is worthy of note that in overventilation the removal of CO₂ far exceeds the demands of metabolism. If base were ceded to Cl by bicarbonate the reduction of CO₂ tension and elevation of pH would be minimized. The very fact that the CO₂ tension remained relatively high would result in the loss of an excessive amount of CO₂. Direct loss of base to the tissues would have the same effect and would, furthermore, lower the osmotic pressure of the blood.

The effect of oxygen-want on the blood electrolytes is quite as variable as is its effect on respiration and the results of the three experiments of this series indicate that there is some relation between the two sets of phenomena. This is further borne out by the study of Case 28976, with postencephalitic hyperventilation. Apparently, if hyperpnea of moderate degree due to causes other than excessive CO₂ production continues for a long enough period, Cl is yielded by the tissues to replace the base freed by bicarbonate, thus preventing the development of serious alkalosis and forestalling tetany. Just why a similar reaction should not occur after short, violent overventilation is not clear. Time alone cannot be the determining factor. Chloride can respond in the reverse direction, at least, with surprising rapidity, as the stasis and voluntary hyperpnea experiments indicate. Some may object that the reduction of chlorides in response to hyperpnea is not a general reaction but one peculiar to the subject JP.
This is possible, but hardly probable. Furthermore it is the same subject who presented the reverse change in response to the hyperpnea of oxygen-want. At any rate it has been demonstrated by these observations that the organism is capable of compensating for reductions of bicarbonate by substituting chloride, and that this reduction diminishes the pH change that would otherwise result. No generalizations about the effect of low oxygen tensions are warranted on the basis of these observations. The more gradual or prolonged production of anoxemia may initiate an entirely different set of compensatory reactions. On the other hand this work compels reconsideration of the theory advanced by Y. Henderson and now rather generally accepted, that the reduction of bicarbonate at high altitudes is followed by withdrawal of base from the blood. As far as we know the level of serum chloride at high altitudes has not yet been investigated. On theoretical grounds an increase of chloride is more probable than a reduction of total base, because the latter would entail an alteration of total electrolyte concentration and osmotic pressure. Koehler and his associates (16) have recently shown that, although the primary reaction to low oxygen pressure is the production of an overventilation alkalosis, acidosis supervenes if oxygen deprivation is carried to an extreme degree or greatly prolonged. The degree of oxygen reduction required to induce such an acidosis varied greatly in different animals. The experiments on JP, June 18, and HAB, June 26 (see Table IV), perhaps offer a clue to these variations in reaction. The alkalosis may well be simply the response to hyperpnea and not directly related to oxygen-want. The acidosis, which develops only in extreme stages may be the direct result of anoxemia. Koehler et al. (16) recognize the probable importance of organic acids in the production of this acidosis and further suggest that phosphates play a part. The latter suggestion is not borne out by our experiments in which serum phosphate fell.

The fact that both in exercise and in oxygen want the added load of organic acid was borne by base derived from the tissues leads one to wonder whether this does not represent the usual reaction to the rapid accession of organic acid.

The last cases show that severe vomiting, due to conditions other than obstruction of the gastrointestinal tract, may reduce
the chlorides and base of serum and that under these conditions, when the chloride defense is weakened, even moderate hyperpnea quickly leads to tetany.

SUMMARY AND CONCLUSIONS.

Prolonged venous obstruction leads to the transfer of water from the blood to the tissues and a concentration of the proteins. Base combined with bicarbonate is unavailable for the neutralization of this excess acid because the usual escape of CO₂ through the lungs is prevented by the presence of the tourniquet. Under these circumstances plasma chloride diminishes, yielding its base to protein and carbonic acid.

In brief, vigorous exercise considerable lactic acid and an excess of carbonic acid are formed, and the pH of the serum falls. Chloride remains unchanged. Bicarbonate cedes some base to the organic acid, but the major portion of the latter is neutralized by base yielded from the tissues.

If overventilation is produced as rapidly as possible, symptoms of tetany appear when the pH has risen by not more than 0.2. Although the total CO₂ of the serum falls, the carbon dioxide capacity remains unaltered. Organic acid, probably partly ketone acids, but mostly lactic acid, is considerably increased. The total base remains unchanged and the base required for the neutralization of the foreign acids is largely derived from the chlorides, which are diminished.

The reaction of the electrolytes to oxygen-want varies according to the respiratory response. If moderate overventilation develops and continues for a long time bicarbonate falls. The HCO₃⁻ is replaced partly by an increase in the concentration of serum protein, but chiefly by Cl withdrawn from the tissues. If extreme anoxemia is produced organic acid rises and is neutralized by base derived from the tissues.

A postencephalitic case presenting overventilation without tetanic symptoms compensated for an extreme reduction of CO₂ by an equivalent increase of chloride. On three occasions chloride and bicarbonate were found to have changed, always in reciprocal directions.

A malignant hypertension case and one with typhoid fever by vomiting depleted the chlorides of the serum. Under these cir-
cumstances tetany followed mild overventilation. The loss of Cl appears to diminish the ability of the organism to prevent tetany by readjusting the acid-base balance after loss of H₂CO₃.

It is suggested that all these reactions are conservative in nature. Any given disturbance of electrolyte equilibrium will evoke a train of reactions and changes in all the other electrolytes. These reactions always tend to restore equilibrium. The response is not directed towards the maintenance of the concentration of any single constituent or group of constituents, but will be manifested to a greater or less degree in one or the other according as it may best serve to restore the equilibrium and maintain the functional automatism of the whole organism.

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