INVESTIGATIONS IN TETANY. *

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Research on experimental and clinical tetany in recent years has to a large extent been dominated by the view that tetany occurs when the calcium ion concentration falls below a certain threshold on account of a change in the reaction of the blood towards the alkaline side. In support of this theory use has been made, amongst other things, of the equation given by Rona and Takahashi (18)

\[
\frac{[\text{Ca}^{++}] \cdot [\text{HCO}_3^-]}{[\text{H}^+]} = K
\]

which is valid for saturated watery solutions of calcium bicarbonate.

As will be seen from the equation a shift of the reaction in an alkaline direction causes a fall in the calcium ion concentration, and a shift in an acid direction, a rise.

This alkalosis theory has had further support from the fact that acid treatment, as for example the administration of CaCl₂ and NH₄Cl, in addition to making the blood temporarily more acid, also causes the total calcium in the serum to rise and the clinical symptoms to disappear.

Quite recently an extensive investigation by Turpin (24) in France has appeared, which on the whole gives clinical support to these more hypothetical theories, since he finds a more alkaline pH and a greater alkali reserve in tetany than in normal persons.

* The determinations of the pH and BHCO₃ and the calculations of the [Ca+++] were carried out by Paul Drucker. The calcium and phosphorus analyses were done by Frans Faber.

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Turpin, however, compares the values found by himself in tetany with normal values obtained elsewhere for adults without, as far as one can see, having himself determined the normal values, at any rate of the pH, with his own technique and for children. Moreover, in his material of 50 cases there are only four where determinations were made on the same child during tetany and after its disappearance. On these grounds it does not seem to us that these experiments can rightly be taken as confirmation of the alkalosis theory, especially as only two of the cases show more marked alkaline values during the disease than after it.

In order to throw more light on this theory we have determined simultaneously the actual pH of the blood, its alkali reserve, total calcium, and acid-soluble P and the calcium ion concentration calculated with the Rona-Takahashi equation in twenty small children with tetany, while the disease was manifest and also after it was cured. Further, we have made determinations during the course of the disease, during CaCl₂, NH₄Cl, and calcium lactate treatment, during bicarbonate and phosphate administration, and lastly during and after light treatment.

Technique.

The pH determinations were made by the method described by Cullen (2) with Hawkins’ (10) modification using the technique recently described by Drucker and Cullen (3). The determinations of the alkali reserve were done by Van Slyke’s (25) titration method, the total calcium determinations by Tisdall’s (23) modification of Kramer and Tisdall’s method, and the P determinations by Tisdall’s (22) method. The blood samples were all taken by heel puncture after about 8 hours fasting. The diet consisted of milk foods and oatmeal gruel five times and twice daily respectively. All the determinations were duplicated apart from the P determinations and some of the bicarbonate determinations.

I. Reaction of Blood in Tetany and Relation between This, Total Calcium, and [Ca++]

The first problem we set ourselves was: Do we find so great a displacement of the reaction of the blood in the alkaline direction in manifest tetany, that in virtue of the decreased calcium ion
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concentration we can explain the occurrence of tetany? Our results lend no support to this because we find no signs of alkalosis when compared with a number of normal children or when compared with the reaction of the blood in the same child after it was cured.

As will be seen from Table I, the pH values are the same in manifest tetany and under normal conditions. The same practically applies to the alkali reserve of the blood; in fact, this is slightly less in tetany than after the disease is cured.

If we observe what happens to the calcium ion concentration calculated by the Rona-Takahashi equation during and after

TABLE I.

<table>
<thead>
<tr>
<th>pH</th>
<th>BHECO₃</th>
<th>[Ca²⁺] (calculated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tetany</td>
<td>After tetany</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>vol. percent</td>
<td>vol. percent</td>
</tr>
<tr>
<td>7.31</td>
<td>7.29</td>
<td>-0.02</td>
</tr>
<tr>
<td>7.42</td>
<td>7.37</td>
<td>-0.05</td>
</tr>
<tr>
<td>7.45</td>
<td>7.39</td>
<td>-0.06</td>
</tr>
<tr>
<td>7.39</td>
<td>7.39</td>
<td>0</td>
</tr>
<tr>
<td>7.37</td>
<td>7.39</td>
<td>+0.02</td>
</tr>
<tr>
<td>7.46</td>
<td>7.43</td>
<td>-0.03</td>
</tr>
<tr>
<td>7.37</td>
<td>7.43</td>
<td>+0.06</td>
</tr>
<tr>
<td>7.43</td>
<td>7.42</td>
<td>-0.01</td>
</tr>
<tr>
<td>7.36</td>
<td>7.40</td>
<td>+0.04</td>
</tr>
<tr>
<td>7.50</td>
<td>7.45</td>
<td>-0.05</td>
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<td>7.38</td>
<td>7.37</td>
<td>-0.01</td>
</tr>
<tr>
<td>7.40</td>
<td>7.40</td>
<td>0</td>
</tr>
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<td>7.30</td>
<td>7.42</td>
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<td>7.40</td>
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</tr>
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<td>7.40</td>
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</tr>
<tr>
<td>7.39</td>
<td>7.42</td>
<td>+0.03</td>
</tr>
<tr>
<td>7.47</td>
<td>7.41</td>
<td>-0.06</td>
</tr>
<tr>
<td>7.38</td>
<td>7.41</td>
<td>+0.03</td>
</tr>
<tr>
<td>7.41</td>
<td>7.32</td>
<td>-0.09</td>
</tr>
<tr>
<td>7.35</td>
<td>7.39</td>
<td>+0.04</td>
</tr>
<tr>
<td>Average. 7.40</td>
<td>7.40</td>
<td>+0.002</td>
</tr>
</tbody>
</table>

*(7.41)* (46.9)* (2.6)*

*Average from thirty-five normal children.*
tetany, we find that the calcium ion concentration is rather greater during manifest tetany than after it is cured, which was only to be expected from the values found for the alkali reserve. This

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

**Chart I.** Chart I shows the action of ammonium chloride and calcium chloride. It will be seen that ammonium chloride affects the reaction of the blood—both the actual (pH 7.04) and the potential—to a considerably greater extent than calcium chloride, whereas calcium chloride produces a far greater rise in the total calcium with a corresponding fall in the acid-soluble phosphorus. The high values of the calculated calcium ion concentrations are also noteworthy, especially after the ammonium chloride treatment (16.0) as compared with the value found for the total calcium (9.1). Lastly it will be observed how the light treatment makes all the values tend towards the normal value.
difference is, however, so slight that even on the assumption that the Rona-Takahashi equation applies to tetany (which we shall return to presently) no real significance can be attributed to it.

**CHART II.** Chart II, like Charts I and V, shows that calcium chloride is capable of raising the total calcium to a considerably greater extent than ammonium chloride in spite of the latter's stronger acidosis effect. Further, the action of calcium lactate will be seen, and the favorable and permanent action of light treatment during which the total calcium rises to normal while the clinical symptoms disappear, and finally the sharp rise in the total calcium after the administration of calcium chloride will be observed, *in spite of the unaltered blood reaction*, which is also the case after the administration of calcium lactate, although to a lesser degree.

**Explanation of Symbols in Charts.**

Chlor. calc., dried calcium chloride.

Chlor. amm., ammonium chloride.

Lact. calc., calcium lactate.

P.F., primary sodium phosphate NaH₂PO₄.

S.F., secondary sodium phosphate Na₂HPO₄.

Bicarb. natr., sodium bicarbonate.

1 denotes general radiation with quartz lamp.

1 X 4 denotes 1 gm. four times daily.

+ denotes the severity of the tetany.

0 denotes no clinically demonstrable tetany.
The value 2.8 mg. per cent moreover agrees well with the normal values found by other authors, as for example Bigwood (1).

If we now compare these calculated calcium ion concentrations which are, practically speaking, normal with the total calcium values also found during and after tetany, which in all cases of manifest tetany are far below the normal, we must conclude, always with the proviso that the Rona-Takahashi equation applies to tetany, that if hypocalcemia is synonymous with tetany then tetany must be due to too low values of the undissociated part of the calcium in the blood.

As mentioned, the change in the reaction of the blood will be accompanied by an alteration in the calcium ion concentration according to the Rona-Takahashi equation.

The second problem we set ourselves was: What is the extent of the change in the calculated calcium ion concentration of the blood that we can produce, and what agreement do we find between these calculated values and those obtained by direct determinations of the total calcium; and finally is the Rona-Takahashi equation applicable to tetany?

To elucidate these points we have devised the following provisional experiments in children with tetany, with oral administration of CaCl₂ and NH₄Cl, both of which, as is known, are able to change the reaction of the blood. The experiments extended over 2 to 4 days with the administration of 1.0 gm. four times daily in a 10 per cent solution, the last dose being given 1 hour before the blood sample was taken.

With regard to the calculated calcium ion concentration (Charts I and V), we find high values during the acid treatment, in fact in a few cases values (16.0 mg. per cent) which even considerably exceed the total amount of calcium found by direct determination, a result which shows that the blood under these conditions cannot be saturated with calcium, as the total quantity in such a case would be at least equal to or, more correctly, greater than the concentration of the ionized calcium.

The Rona-Takahashi equation which, as stated, only applies to saturated solutions, cannot, therefore, be used to determine the ionized calcium in tetany when the blood is rendered acid.

That it cannot be employed in tetany with a normal blood reaction either, follows from later experiments which show that
the blood again is not saturated with calcium under these conditions.

If we next look at the curves of the pH and alkali reserve values (Charts I, II, and V) the acidosis effect of CaCl₂ and NH₄Cl (7.04) will be clearly seen. Further, it will be observed how the total calcium rises with an acid reaction and falls again when the reaction becomes more alkaline. But there is another fact of interest which reappears in all our experiments; namely, that the total calcium always rises higher with the CaCl₂ administration than with the NH₄Cl, in spite of the reaction being the same or even more acid after the dose of NH₄Cl.

We think that this justifies the same conclusion that we arrived at previously by another method, that the blood is not saturated with calcium when it is made acid in tetany, as it would otherwise take up equal amounts of calcium for the same shift in the reaction and with more acid reactions even larger amounts.
That the blood cannot be saturated with calcium in tetany at the normal reaction of the blood either is shown by two experiments (see Chart II) with the administration of CaCl₂ and calcium lactate, where a considerable rise in the total calcium occurs in spite of no change in the reaction of the blood.

The higher values for the total calcium with the administration of CaCl₂ further show that the therapeutic action of CaCl₂, as was to be expected, is to be regarded as a combination of an acid and calcium effect and one which we do not find in the more weakly acting calcium lactate.

In accordance with this calcium chloride must, therefore, be regarded as the most rational symptomatic remedy in tetany.

We have tried the oral administration of sodium bicarbonate in only two cases of latent tetany, and found a displacement of the reaction of the blood in an alkaline direction attended by a slight
fall in the total calcium, but a rise in the amount of P. Only in one case did we observe an increase in the electrical hypersensitivity, but otherwise no aggravation of the clinical condition in spite of a marked fall in the [Ca++] (see Chart IV) (compare Tezner (20)).

II. Relation between Total Calcium and Acid-Soluble Phosphorus during Acid Treatment.

If we consider the relation between the total calcium and the acid-soluble P during the acid treatment (Chart I) we observe, as earlier authors (11) have done, that a rise in the amount of calcium is accompanied by a fall in the amount of P and vice versa, which may be assumed to depend upon the fact that the organism in its efforts to preserve its reaction reacts upon the acidosis produced by these substances partly by excreting large
quantities of P in the urine chiefly in the form of primary phosphates.

In the case of the CaCl₂ treatment there is probably the additional factor that insoluble Ca₅(PO₄)₂ is formed in the intestine.

III. Experiments with the Administration of NaH₂PO₄ and Na₂HPO₄.

In the experiments with the administration of primary and secondary sodium phosphate (Chart III) by mouth we find, also in agreement with other authors (12, 14), a clinical aggravation of latent tetany with a simultaneous rise in the acid-soluble P and a fall in the total calcium. The reaction of the blood on the other hand is not markedly affected; the small changes we observed occurred both in an acid and alkaline direction, so that again in these experiments we have been unable to find any relation between the severity of the tetany and the reaction of the blood.

Light Treatment.

All our cases were treated by general radiation with a quartz lamp for a total of 15 to 45 minutes, and in agreement with other authors we obtained a permanent cure (Charts II and V) which was manifested in the blood by the normal total calcium value, while the reaction of the blood, as previously mentioned, was practically unchanged.

As already stated, we found the calculated calcium ion concentration after the cure of the tetany by light treatment about the same as the normal values given by other authors, which in conjunction with the normal values of the total calcium (values which, as is known, are only appreciably exceeded temporarily) might indicate that the blood must now be nearly saturated with calcium.

The antagonistic relation between P and Ca with the acid and phosphate treatment does not occur with the light treatment, since with the latter the low P value also rises.

RÉSUMÉ.

1. Tetania infantilis cannot be explained by an "alkalosis" of the blood since neither are the pH values more alkaline nor the
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alkali reserve greater when the tetany is manifest than when it is cured. The theory that hypocalcemia, and hence tetany, is due to a change in the blood reaction in an alkaline direction cannot, therefore, be substantiated.

2. The Rona-Takahashi equation, which was evolved for saturated aqueous solutions in vitro, cannot be applied to blood plasma in vivo in tetany.

3. The blood in tetania infantilis is not saturated with calcium.

4. Treatment with CaCl₂ must be regarded as a combined acid and calcium therapy.

5. Investigations by other workers into the effect of the administration of acid and phosphates on the reciprocal relation between the calcium and phosphates of the blood, as well as on the clinical symptoms, are confirmed.

6. In two cases of latent tetany the disease could not be made manifest by the oral administration of moderate doses of sodium bicarbonate in spite of the shift in the reaction of the blood in an alkaline direction.

7. After general radiation with the quartz lamp the blood must be considered to be practically saturated with calcium.

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