THE RELATION OF SERUM PHOSPHATES TO PARATHYROID TETANY*

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As early as 1911 Greenwald (1) showed that one of the first detectable results of the removal of the parathyroid glands was a decreased excretion of phosphorus in the urine. In 1913 he (2) extended these studies to show that the effect was on phosphorus directly and not on sodium or potassium. Some years later Greenwald (3) again drew attention to these findings. However, little emphasis was given to phosphorus in its relation to the function of the parathyroid glands until the work of Albright, Bauer, Ropes, and Aub. In 1929 they (4) presented evidence to indicate that the primary action of the parathyroid hormone is on renal excretion of phosphorus. In a later publication Albright and Ellsworth (5) expressed the belief that the whole effect of the parathyroid secretion on the calcium and phosphorus levels of the blood could be explained on the basis of a variation in the ability of the kidney to excrete phosphorus. They believe that in hypoparathyroidism there is a retention of phosphate which forces the concentration of calcium down. The reverse is true during hyperparathyroidism, in which there is a loss of phosphorus with a subsequent solution of calcium phosphate from the skeleton. Albright, Bauer, Claflin, and Cockrill (6) are of the opinion that there is a definite renal threshold for phosphorus; in hypoparathyroidism the threshold is raised and in hyperparathyroidism it is lowered. This idea has been further developed by Ellsworth (7).

* A report concerning this work was presented before the Thirtieth meeting of the American Society of Biological Chemists at Washington, March 25-28, 1936 (Proc. Am. Soc. Biol. Chem., 8, liv (1936); J. Biol. Chem., 114 (1936)).
About 2 years ago the present author (8) showed that if young rats were parathyroidectomized and then placed on a high calcium-low phosphorus rachitogenic ration, the animals did not show the low serum calcium and high phosphorus characteristic of parathyroid deficiency. Instead, the blood picture was that typical of rachitic rats; that is, low blood phosphorus and normal or slightly elevated calcium. If, however, the calcium was omitted from this diet, the rats invariably went into parathyroid tetany and showed a low serum calcium and high phosphorus within a day or two after removal of the glands. The most plausible interpretation of this difference is that the high calcium intake on the one diet was sufficient to prevent the development of the hypocalcemia necessary for the onset of tetany; whereas, on the other diet the supply of calcium was inadequate to maintain a concentration of serum calcium above the tetany level. In view of the work concerning the effect of phosphorus on the development of parathyroid tetany, it is possible that the results were not due directly to the difference in calcium intake but indirectly to decreased availability of the phosphorus of the high calcium diet consequent to the formation of insoluble calcium phosphate. It may well be that the formation of an insoluble phosphate in the intestinal tract prevented the absorption and subsequent accumulation of phosphorus in the blood, with the result that the calcium remained high. If the high calcium of the diet on which tetany did not develop functioned primarily by decreasing the availability of phosphorus, it should be possible to obtain similar results with diets low in calcium but in which the availability of the phosphorus was decreased by the addition of some metal other than calcium which forms an insoluble phosphate. The results of such experiments are reported at the present time. Deobald and Elvehjem (9) have recently shown that the feeding of either aluminum or iron salts, in rather large quantities, produces a condition of phosphorus want, presumably by the formation of insoluble phosphates of these elements in the intestinal tract. In view of these observations we have used basic aluminum acetate in most of the work. A few results were also obtained with aluminum sulfate.

EXPERIMENTAL

Three diets with varying degrees of calcium deficiency were employed in these studies. In the first few experiments young rats
were fed the dry portion of the Steenbock (10) stock diet from which the 0.5 per cent calcium carbonate had been omitted and to which was added 4 per cent aluminum acetate (Diet 1). If this diet is given without the aluminum acetate, parathyroidectomized rats will regularly develop tetany with a low serum calcium and high phosphorus within 24 to 48 hours. In the present experiments the diet containing aluminum was fed for 2 to 3 weeks before the removal of the glands, during which time the animals developed rachitic symptoms. The parathyroid glands were then removed, but only those animals from which both the glands were definitely identified in the manner previously described (11) were included in the experimental results. Following parathyroidectomy the animals were killed at varying intervals, and the sera were analyzed for calcium by the method of Clark and Collip (12) and for phosphorus on the calcium-free filtrate by the method of Gunther and Greenberg (13). It was necessary to pool the blood of two or more animals to obtain sufficient serum for these analyses. In Table I are shown the results of two such experiments. In the first experiment (Rats 1 to 8) two control animals (Rats 1 and 2, sacrificed shortly before the parathyroids were removed from the others) had a serum calcium content of 11.5 and a phosphorus content of 2.7 mg. per cent. As seen from Table I, the removal of the parathyroid glands had no effect on the blood calcium or phosphorus at 2 and 4 day intervals.

In another experiment on this same diet (Rats 9 to 16, Table I)

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>No. of days after parathyroidectomy</th>
<th>Serum Calcium (mg. per 100 cc.)</th>
<th>Phosphorus (mg. per 100 cc.)</th>
<th>Rat No.</th>
<th>No. of days after parathyroidectomy</th>
<th>Serum Calcium (mg. per 100 cc.)</th>
<th>Phosphorus (mg. per 100 cc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 2</td>
<td>Control</td>
<td>11.5</td>
<td>2.7</td>
<td>9, 10</td>
<td>Control</td>
<td>13.6</td>
<td>2.9</td>
</tr>
<tr>
<td>3, 4</td>
<td>2</td>
<td>11.2</td>
<td>2.3</td>
<td>11, 12</td>
<td>1</td>
<td>12.8</td>
<td>2.9</td>
</tr>
<tr>
<td>5, 6</td>
<td>2</td>
<td>11.8</td>
<td>2.5</td>
<td>13, 14</td>
<td>7</td>
<td>13.0</td>
<td>3.9</td>
</tr>
<tr>
<td>7, 8</td>
<td>4</td>
<td>11.9</td>
<td>2.8</td>
<td>15</td>
<td>13</td>
<td>12.0</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>13</td>
<td>11.2</td>
<td>3.0</td>
</tr>
</tbody>
</table>
the animals were sacrificed at intervals of 1, 7, and 13 days, with no appreciable change in the calcium and phosphorus levels of the blood. This particular group of animals had a rather high concentration of calcium in the serum. We have observed this occasionally at other times when the aluminum is given with a diet in which the calcium is either ample or only moderately deficient. None of these animals was ever observed showing any signs of tetany.

In the next experiment a diet still lower in calcium was used. A number of young rats were fed the aluminum-containing diet described above (Diet 1) for a period of 2 weeks. About 48 hours before removal of the parathyroids the animals were transferred to the Steenbock-Black (14) rachitogenic ration from which the calcium carbonate was omitted and to which was added 4 per cent of aluminum acetate (Diet 2). This diet contained only from 0.03 per cent to 0.04 per cent calcium. When fed without the aluminum acetate to parathyroidectomized rats, it invariably produced marked tetany, within a day or so after removal of the glands, with the usual high blood phosphorus and low calcium.

The results of this experiment are summarized in Table II. Consideration of the last group of three animals being omitted for the present, it is seen that the aluminum salt not only prevented a rise in phosphorus, but there appears to have been an actual decrease during the 11 day period following the removal of the glands. This occurred in spite of the initial low phosphorus.

**Table II**

*Effect of Basic Aluminum Acetate on Parathyroidectomized Rats Receiving a Diet Decidedly Deficient in Calcium (Diet 2)*

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>No. of days after parathyroidectomy</th>
<th>Serum</th>
<th>Rat No.</th>
<th>No. of days after parathyroidectomy</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Calcium</td>
<td>Phosphorus</td>
<td></td>
<td>Calcium</td>
</tr>
<tr>
<td>17, 18</td>
<td>Control</td>
<td>11.8</td>
<td>2.6</td>
<td>27, 28</td>
<td>4</td>
</tr>
<tr>
<td>19, 20</td>
<td>1</td>
<td>10.4</td>
<td>2.7</td>
<td>29, 30</td>
<td>7</td>
</tr>
<tr>
<td>21, 22</td>
<td>1</td>
<td>9.3</td>
<td>Lost</td>
<td>31, 32</td>
<td>11</td>
</tr>
<tr>
<td>23, 24</td>
<td>2</td>
<td>9.3</td>
<td>2.1</td>
<td>33, 34, 35</td>
<td>9</td>
</tr>
<tr>
<td>25, 26</td>
<td>2</td>
<td>9.1</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To the Steenbock-Black (14) rachitogenic ration from which the calcium carbonate was omitted and to which was added 4 per cent of aluminum acetate (Diet 2). This diet contained only from 0.03 per cent to 0.04 per cent calcium. When fed without the aluminum acetate to parathyroidectomized rats, it invariably produced marked tetany, within a day or so after removal of the glands, with the usual high blood phosphorus and low calcium.
There was also a definite fall in calcium but not to the level which usually results in tetany. It cannot be stated at the present time whether this drop was due entirely to the low intake of calcium or to a deficiency of parathyroid function. However, it is evident that it was not caused by a rise in phosphate.

It so happened that three of the animals of this group (Rats 33, 34, and 35, Table II) were in tetany on the 9th day following the operation. Food consumption records showed that these animals had been eating considerably less than average, and during the 24 hours previous to the onset of the tetany they had consumed practically no food. They were losing weight rapidly. As indicated in Table II, the blood phosphorus was very high and the calcium low. It appears that the inorganic phosphorus which was liberated as the result of excessive endogenous metabolism accumulated in the blood stream and forced the calcium down with the onset of tetany. Three other animals of this series died at varying intervals following the removal of the parathyroids. As they all died during the night, no tetany was observed, but it was probably experienced shortly before death.

In another series of experiments, the results of which are shown in Table III, rats were treated the same as above but were transferred to a synthetic diet (Diet 3) practically free from calcium. This diet was also low in phosphorus and contained 4 per cent of the aluminum acetate. It was the same as the low calcium diet previously described (15) except that the phosphates of the salt mixture were omitted and cod liver oil was substituted for the

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**Table III**

*Effect of Basic Aluminum Acetate on Parathyroidectomized Rats Receiving a Diet Containing Only Traces of Calcium (Diet 3)*

<table>
<thead>
<tr>
<th>Rat No.</th>
<th>No. of days after parathyroidectomy</th>
<th>Serum</th>
<th>Rat No.</th>
<th>No. of days after parathyroidectomy</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Calcium</td>
<td>Phosphorus</td>
<td></td>
<td>Calcium</td>
</tr>
<tr>
<td>36, 37</td>
<td>Control</td>
<td>11.5</td>
<td>4.0</td>
<td>41, 42</td>
<td>11.1</td>
</tr>
<tr>
<td>38, 39</td>
<td>1</td>
<td>9.8</td>
<td>5.7</td>
<td>43, 44</td>
<td>11.2</td>
</tr>
<tr>
<td>40</td>
<td>2</td>
<td>11.7</td>
<td>4.5</td>
<td>45, 46</td>
<td>11.2</td>
</tr>
</tbody>
</table>

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carotene solution. The amount of calcium in this diet was less
than 0.005 per cent. Although the intake of calcium on this
diet was negligible, the calcium of the serum remained high and
the phosphorus low. Despite the lower amount of calcium in the
food both the calcium and phosphorus of the serum of the animals
on Diet 3 were slightly higher than in the serum of the animals on
Diet 2. No explanation for these somewhat paradoxical results is
at present available.

Several adult rats also were fed Diet 3 for a few days, after
which the parathyroids were removed. Another small group of
adult rats was given a diet which was the same except that the
aluminum acetate was replaced by an equal amount of crystalline
aluminum sulfate. Parathyroidectomies likewise were performed
a few days after the beginning of the feeding of this diet. In
both these cases the calcium of the serum remained high and
the phosphorus low. One adult female on the diet containing alumi-
num acetate gave birth to eight young 2 days after the parathyroid
glands were removed. Seven of the young were still alive on the
18th day after parturition. They were all very small (average
weight 10 gm.) and weak, but were covered with hair, had their
eyes open, and could walk. They were considerably deformed.
By the 23rd day after birth they had all died. In the absence of
the parathyroid glands, with only a trace of calcium in the diet
and most of the phosphorus not available, this female rat had been
able to call upon its own body stores in sufficient amount to main-
tain itself and also keep a litter of young alive for 3 weeks. At the
end of this time both the calcium and phosphorus of the serum of
the mother rat were within normal limits. Owing to the fact that
the food consumption of this animal had decreased considerably
during the last 48 hours before it was sacrificed, the serum phos-
phorus was probably higher than it would have been otherwise.

In order to study further the influence of food consumption on
the development of tetany under these conditions, the following ex-
periment was carried out. A group of young rats was placed on
Diet 1 and after a period of 2 weeks the parathyroids were re-
moved. At the same time these animals were deprived of food.
Without exception every animal was in violent tetany on the morn-
ing following the ablation of the glands. The blood calcium was
low and the phosphorus was high. As these animals were some-
what rachitic, it was to be expected that they would develop tetany when deprived of food. However, the severity of the tetany and the regularity with which it appeared were much more marked in the animals from which the parathyroids had been removed than in a similar group which was only fasted.

Experiments were also conducted in which the aluminum acetate was omitted from the diet at the time of the removal of the glands. All of these animals developed tetany within 24 hours following the loss of the parathyroids. As in the fasting experiments, the simple omission of the aluminum acetate from the diet produced tetany in some of the animals. Here again, however, the frequency and severity of the tetany were considerably increased by removal of the parathyroids.

**DISCUSSION**

These data apparently are in accord with the theory of Albright and Ellsworth (5). However, it is difficult to believe that a simple decrease in the inorganic phosphorus of the blood can produce the marked degree of hypercalcemia which follows the administration of large doses of parathyroid extract. A very low concentration of phosphorus in the blood is often encountered with a normal or even a low level of calcium. When young rats, for instance, are put on a high calcium-low phosphorus rachitogenic diet the inorganic phosphorus of the blood is low, while the calcium is either normal or only slightly raised. This is the case in spite of the large amount of calcium in the food. A similar blood picture is observed in rickets produced by adding to the diet some metal other than calcium which forms an insoluble phosphate. As previously stated, during the latter type of rickets in rats the blood calcium may be a little above normal, but the rise is not more than 1 or 2 mg. per 100 cc. of serum. This is much less than the corresponding drop in phosphorus; consequently there is a fall in the calcium X phosphorus product. Under similar conditions in the dog (16) there is no appreciable rise in the calcium of the serum. It might be pointed out, however, that as these animals were young and frequently rachitic, the stores of calcium in the bones might have been insufficient to compensate for the decrease in phosphorus. However, we have been able to produce a very low serum phosphorus in adult rats by adding aluminum sulfate to an adequate diet without any rise in serum calcium.
As further evidence in favor of the phosphorus excretion theory Shelling (17) has shown that a high intake of phosphorus predisposes to tetany in parathyroidectomized rats. Tweedy, Templeton, and McJunkin (18) have recently reported that deletion of kidney function protects the dog from overdosage effects of parathyroid extract, and have concluded that the mobilization of calcium stores of the body into the blood by parathyroid hormone is dependent on kidney function. In contrast to this, Collip, Pugsley, Selye, and Thomson (19) claim that the characteristic effect of parathyroid extract on the bones of the rat is obtainable after bilateral nephrectomy. Ellsworth and Futcher (20) also were able to produce a marked hypercalcemia by administering parathyroid extract to dogs from which the kidneys had been removed. Goadby and Stacey (21) found that large doses of parathyroid extract did not produce the usual diuresis in patients with kidney disease, but there was a definite rise in serum calcium. They conclude that the hormone acts on the excretion of phosphorus and also to liberate calcium. From the data available at the present time this appears to be a logical view.

SUMMARY

The addition of 4 per cent of basic aluminum acetate to diets low in calcium protected rats from the symptoms which usually follow the removal of the parathyroid glands. The calcium of the serum remained high and the phosphorus low. This was found to be the case on a diet which did not contain over 0.005 per cent of calcium. If for any reason the animals did not eat after the loss of parathyroid function, serum phosphorus increased, the calcium fell, and tetany followed. Apparently, if the phosphorus of the blood can be kept low, the calcium remains above the tetany level, even though there is a pronounced deficiency of calcium in the diet. If, however, there is a source of available phosphorus either from the diet or from excessive endogenous metabolism resulting from fasting, the blood phosphorus rises, the calcium falls, and tetany appears.

The relation of these observations to the phosphorus excretion theory of parathyroid function has been discussed.

BIBLIOGRAPHY

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