THE EARLY EFFECTS OF PARATHYROID HORMONE
ON THE BLOOD AND URINE

BY MILAN A. LOGAN

WITH THE TECHNICAL ASSISTANCE OF PATRICIA O'CONNOR

(From the Department of Biological Chemistry, Harvard Medical School,
and the Forsyth Dental Infirmary, Boston)

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Following the administration of the parathyroid hormone to young dogs, the urinary phosphate excretion increases, the blood inorganic phosphate usually decreases, and the plasma calcium increases (1–5). The increase of phosphate excretion in the urine occurs in advance of the maximum blood calcium increase. These experimental findings have been interpreted to indicate that the solution of bone is caused by depletion of blood and tissue inorganic phosphate resulting from increased excretion by the kidneys.

Histological changes in the bone have been observed very soon after administration of the hormone, indicating that stimulation of cellular activity in the tissue itself caused solution of the bone (6).

Previous experiments which included determinations of the blood levels of calcium and inorganic phosphate and also the urinary excretion of these substances have been carried out for 1 (1, 2) and 3 day periods (3–5, 7, 8). The results have clearly shown the influence of the hormone on calcium metabolism during extended experimental periods but the intimate details of the immediate changes have not been so well established. The effects of the hormone on the blood concentration of calcium and phosphate have been observed for shorter periods of time (9).

The hormone has also been administered to nephrectomized dogs (10). The results indicate that large doses produce no greater increase of blood calcium than that observed as a result of nephrectomy alone. The phosphate retention resulting from
nephrectomy increased the blood inorganic phosphate 80 per cent in 2 to 6 hours. (This increase of blood phosphate is greater than we have observed in the terminal stages resulting from the administration of fatal doses of the hormone.) As a result of the rapid accumulation of phosphate in the blood and tissues following nephrectomy, the solution of bone would be difficult to demonstrate. The results, therefore, would not appear to be conclusive evidence in support of the thesis that the action of the hormone is exclusively on the kidney.

The experiments reported here were designed to answer the following questions: (1) are the changes resulting from administration of the hormone entirely due to the increased excretion of phosphate by the kidneys, or (2) do the chemical changes indicate that the hormone also stimulates active solution of bone by the bone cells?

For that purpose, the urinary excretion and blood levels of calcium, magnesium, and phosphate were compared and the excretion of bases, chloride, and nitrogenous substances was examined at 1 hour intervals for 4 hours after administration of single, fairly large doses of parathyroid hormone to fasting young dogs. (Subsequent observations were made at longer intervals of time.) The time interval chosen is much shorter than has been previously employed and is near the shortest at which a definite response in both blood and urine can be observed.

The results indicate that the solution of the bone occurs almost immediately, because a definite rise of blood calcium occurs during the 1st hour. Increased excretion of phosphate by the kidneys is evident during the 1st hour in four of the experiments, and was accompanied by a decrease in the plasma inorganic phosphate. The increase of phosphate excretion in the 1st hour was, however, not more than twice the hourly fluctuation observed in normal fasting animals. That active solution of bone is also stimulated seems likely from the fact that the rise of blood calcium during the 1st hour was twice as great when the plasma phosphate decreased very little or not at all. This interpretation likewise appears to be favored by the reaction observed after 12 to 24 hours. At this time, the plasma inorganic phosphate is increased owing to retention by the kidneys, yet the blood calcium continues to remain above the normal level.
EXPERIMENTAL

Five young dogs were fasted 3 to 5 days. To each of three of them, the amount of parathyroid hormone shown on Figs. 1 to 3 was administered subcutaneously. To each of the other two, a similar dose was administered intravenously (Figs. 4 to 5). The dogs were catheterized each hour. The bladder was washed out with distilled water. The phosphate was determined in the washings and in the undiluted urine. The hourly volume

![Graph](https://example.com/graph.png)

**Fig. 1.** Calcium and inorganic phosphate concentration of the blood and excretion in the urine following subcutaneous administration (indicated by the arrow) of 6.6 units (U.S.P. XI) of parathyroid hormone.

of urine was calculated from the volume of undiluted urine obtained and the amount of phosphate in the washings. The dogs were allowed to rest in a metabolism cage following each catheterization.

Total nitrogen was determined by the Kjeldahl procedure (11), inorganic phosphate by the method of Fiske and Subbarow (12), and calcium by procedures previously described (13). Total base was determined by the procedure of Fiske (14).
Results

The results of the experiments are shown in Figs. 1 to 5. Before administration of the parathyroid hormone, the urinary phosphate excretion of the fasting young dogs was not constant from hour to hour. Analyses of specimens from the same animal on successive days indicated that it was not possible to predict at what time the phosphate excretion would be increasing or decreasing. Consequently, the parathyroid hormone was administered to different dogs when the excretion was falling and when it was rising.

In the 1st hour after the subcutaneous administration of the

![Graph showing calcium and inorganic phosphate concentration of the blood and excretion in the urine following subcutaneous administration.](http://www.jbc.org/)

Fig. 2. Calcium and inorganic phosphate concentration of the blood and excretion in the urine following subcutaneous administration (indicated by the arrow) of 6.7 units of parathyroid hormone.
hormone, the phosphate of the urine of the three dogs (Figs. 1 to 3) increased 2.3, 2.6, and 1.1 milliequivalents as compared with the previous hour. The inorganic phosphate of the plasma dropped in this time 0.17, 0.3, and 0.7 milliequivalent per liter respectively. In the 1st hour after the intravenous administration of a large amount of the hormone (34 units\(^1\) per kilo, Fig. 5),

\(^1\) The unit is defined by the United States Pharmacopoeia XI.
similar changes occurred. With a smaller dose intravenously (8.3 units per kilo, Fig. 4), increase of phosphate excretion and decrease of plasma inorganic phosphate did not occur until the 2nd hour.

The plasma calcium increased 0.3 milliequivalent per liter or more in all experiments during the 1st hour. Dog 4, in which no decrease of plasma phosphate occurred during the 1st hour, and Dog 1, in which the decrease was slight (0.17 milliequivalent per liter), showed the largest increase of plasma calcium (0.6

![Fig. 4](http://www.jbc.org/) Calcium and inorganic phosphate concentration of the blood and excretion in the urine following intravenous administration (indicated by the arrow) of 8.3 units of parathyroid hormone.

![Fig. 5](http://www.jbc.org/) Calcium and inorganic phosphate concentration of the blood and excretion in the urine following intravenous administration (indicated by the arrow) of 34.0 units of parathyroid hormone.

and 1 milliequivalent respectively). Urine calcium increased during the 1st hour in two experiments. Definite increases occurred later in all experiments.

The changes observed in the 2nd to the 4th hour indicated an extension of the changes observed in the 1st hour; namely, the phosphate and calcium excretion continued to increase, the plasma phosphate now decreased in all experiments, and the plasma calcium continued to increase. The increase of plasma phosphate, which occurred 18 to 24 hours after administration
of the hormone, is apparently due to retention by the kidneys, because, at that time, the excretion of nitrogen was decreased. In the case of Dog 3, the nitrogen excretion after 18 hours decreased to less than 10 per cent of the level which prevailed before the administration.

Relation of Phosphate to Nitrogen Excretion—It appears evident that the increased excretion of phosphate in the urine was not accompanied by an increase of nitrogen excretion such as occurs with increased catabolism of soft tissues. In Table I are given the 24 hour urinary excretions of phosphate and nitrogen by Dog 2. These results coincide with similar observations previously made during 3 day metabolism periods (5).

<table>
<thead>
<tr>
<th>Day of fast</th>
<th>Urine total N</th>
<th>Inorganic P</th>
<th>Ratio N:P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd</td>
<td>4820</td>
<td>374</td>
<td>12.9</td>
</tr>
<tr>
<td>4th</td>
<td>4584</td>
<td>402</td>
<td>9.3</td>
</tr>
<tr>
<td>5th*</td>
<td>4399</td>
<td>1080</td>
<td>4.1</td>
</tr>
<tr>
<td>6th</td>
<td>2212</td>
<td>255</td>
<td>8.6</td>
</tr>
<tr>
<td>7th</td>
<td>5250</td>
<td>438</td>
<td>12.0</td>
</tr>
</tbody>
</table>

* 6.7 units of parathyroid hormone per kilo were administered subcutaneously at the beginning of the 5th day of the fast.

The results of comparison of the N:P ratio of the urine for shorter periods are of less certain value. This is because the normal hourly phosphate excretion is variable, and because retention of nitrogen evidently occurred after 12 to 24 hours. Dog 3, which received the largest dose of hormone subcutaneously (34 units per kilo), showed no increase of urinary N excretion for 5 hours after administration, during which time the phosphate excretion had increased from 2.3 to 6.4 milliequivalents per hour. During the next 16 hours, the average nitrogen excretion was slightly lower, while the average phosphate excretion had increased to 9.8 milliequivalents per hour. Analysis of the urine for the succeeding hours indicated a retention of both nitrogen and phosphate. The nitrogen excretion of Dog 1 increased for
5 hours after administration of the hormone and then decreased to about half the level of the first period, while the phosphate excretion continued for 19 hours at a level well above the average hourly excretion expected from a dog of its size.

Results Not Given in Detail—Excretion of creatine and creatinine, magnesium, and ammonia, and the pH were determined but are not given in detail because they showed no unexpected changes. It was considered possible that increased phosphate excretion might involve creatine or creatinine. The hourly excretions of creatine and creatinine, as well as the hourly volumes of urine, were essentially constant until nitrogen excretion became markedly decreased. Following the administration of the parathyroid hormone, excretion of magnesium in the urine increased (Dogs 1, 2, and 3) as did also ammonia excretion (Dog 3). The pH of the urine dropped from 6.8 to 5.8 (Dog 3). Until marked decrease of nitrogen excretion occurred, these changes approximately paralleled the total base increase. The changes are such as would be expected to accompany the increased anion (phosphate) excretion. The increase in volume of the urine, together with the increase of base and chloride excretion and the decrease in nitrogen excretion which eventually occurred after a large dose of the hormone, is apparently due to kidney damage.

SUMMARY

The urinary phosphate excretion increases and the plasma inorganic phosphate usually decreases during the 1st hour after the administration of the parathyroid hormone. The results are interpreted to indicate that active excretion of phosphate by the kidney is one of the first effects of excess of the hormone. Because the blood calcium increased in the same time, whether or not the phosphate decreased, it is reasonable to suppose that active solution of bone also took place in the 1st hour.

BIBLIOGRAPHY

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