STUDIES ON THE PHYSIOLOGY OF THE PARATHYROID GLANDS

V. Action of Parathyroid Extract on the Renal Threshold for Phosphorus

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The most striking end-result of the administration of the parathyroid hormone, and the one most important therapeutically, is the elevation of the serum calcium. The present paper is the fifth of a series (1) (2) (3) which have been largely concerned with the mechanism by which that result is achieved.

As previously emphasized, the four cardinal metabolic abnormalities which a lack of parathyroid hormone occasions are: 1. Fall of urinary phosphorus excretion. 2. Rise of serum inorganic phosphorus. 3. Fall of serum calcium. 4. Fall of urinary calcium excretion.

Similarly, the giving of parathyroid extract corrects these abnormalities, causing: 1. Rise of urinary phosphorus excretion. 2. Fall of serum inorganic phosphorus. 3. Rise of serum calcium. 4. Rise of urinary calcium excretion.

Many chemical investigations dealing with calcium and phosphorus metabolism have shown that the two substances are closely interrelated. It, therefore, seems probable that the parathyroid hormone effects one of the four changes mentioned above and that the other changes are sequelae. In previous experiments it appeared that after parathyroid extract administration the alteration in urinary calcium was very much delayed (1), whereas the increase in phosphorus excretion was immediate (1). This suggested the hypothesis that the phosphorus changes produced by the parathyroid hormone were primary and that the calcium changes followed them. In the earlier experiments, however, the analyses of blood serum, after injections of parathyroid extract, showed, as a rule, that by the time the serum phosphorus had fallen the serum calcium had already begun to rise. In the present experiments, which confirm the previous observations, the changes in blood and urine were examined more closely, with the result that some additional observations have been made.

EXPERIMENTS

Four nearly identical 8-hour experiments were performed on two patients suffering from postoperative hypoparathyroidism. Both were on the metabolism ward of the Osler Clinic. They were fasted and kept at rest for twelve hours before and during the whole time of the experiment. One hundred cc. of water was given each hour during the experiment. Hourly urine specimens were collected for three hours before and five hours after the injection of the parathormone. This was given intramuscularly and the site massaged for five minutes. Blood specimens were taken just before the extract was given and one-half, one, two, and either four or five hours afterwards. Precautions were taken to avoid venous stasis; the serum was separated after allowing one-half hour for clotting; the phosphorus filtrate was made at once. Serum calcium was estimated by the method of Kramer and Tisdall (4); inorganic phosphorus by that of Fiske and Subbarow (5).

The ultrafiltration experiments were carried on upon large samples of blood taken while fasting. Dry negative cotton in alcohol-ether was used as the substance for membranes. The technique and precautions described by Grollman (6) were followed.

It is perhaps useful to emphasize the method by which the filtrate was obtained for analysis. Ten cc. of serum was suspended in a collodion sac and enclosed in a glass chamber, which contained only a single small hole at the top. A pressure of 180 mm. Hg was applied. As soon as the membrane became damp on the outside, the moisture was removed by wiping with an ash-free filter-paper. As filtration proceeded, each 0.3 to 0.4 cc. coming through was separated and analyzed. A constant concentration was obtained usually in the third and fourth samples, samples one and two being slightly higher or lower in phosphate content. The constant value was thus obtained when less than one cubic centimeter had filtered. This minimizes one objection to ultrafiltration, namely the possible alteration in the filtrability of one ion by gross change in concentration of other ions.

OBSERVATIONS

In all experiments the parathormone injection was followed by a marked rise in urinary phosphorus excretion (Charts 1, 2). This was conspicuous in the first-hour specimen and even more marked in the subsequent specimens. There was a pronounced rise in the phosphorus concentration as well as in total amount.

There was a fall in serum inorganic phosphorus, apparent as early as one-half hour after the parathormone injection.

There was a rise in serum calcium; but, whereas the fall of serum inorganic phosphorus was immediate, the rise in serum calcium was delayed. In Experiments 1 and 2, the delay was slight, but in Experiments 3 and

¹ Parathyroid extract isolated by Collip. Prepared by Eli Lilly and Co.

4 there was no rise in serum calcium during five and four hours respectively after the parathormone injection. At the end of twenty-four hours after the injection the serum calcium had risen as usual.

Serum, subjected to ultrafiltration, showed that 97 to 100 per cent of the inorganic phosphorus was filtrable before parathormone was given (Table 2).

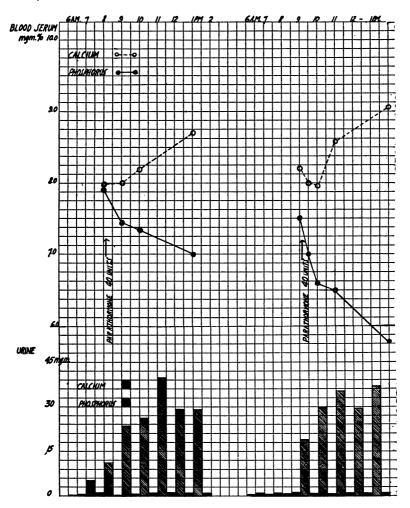


CHART 1. SERUM AND URINARY CALCIUM AND PHOSPHATE IN SUBJECT A.C.

DISCUSSION

In the present experiments, as in those previously reported, the injection of parathormone was followed by a rapid excretion of phosphorus in the urine. This we have observed repeatedly. Although there was sometimes a slight increase in fluid output (Experiments 2 and 4), there

was an enormous increase in phosphorus concentration in the urine, as well as in the total hourly phosphorus excretion.

The phosphorus diuresis was accompanied by a fall in serum inorganic phosphorus. It seemed desirable to obtain a rough figure for the total amount of phosphorus lost from the plasma in order to compare it with the amount of phosphorus found in the urine. These figures were obtained as follows: From the data of Chang and Harrop (7) for blood volumes, normal individuals with the surface areas of our subjects

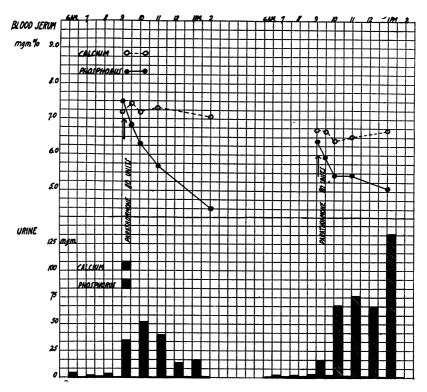


CHART 2. SERUM AND URINARY CALCIUM AND PHOSPHATE IN SUBJECT H.C.

would have blood volumes of approximately 2530 cc. and 3860 cc. respectively. Figures of 1800 cc. and 2500 cc. for the *plasma* volumes were taken as maximum figures, which would be well above any probable variation. The amount of phosphorus lost from the serum, assuming the maximum plasma volumes, was then calculated from the observed fall in serum phosphorus. In Table 1 it is seen that, even assuming the maximum plasma volumes, there is sufficient phosphorus in the urine, during the first hour after the injection of parathormone, to account for the decrease of phosphorus in the serum.

Experi- ment number	Subject	Surface area	Average blood volume per sq. m.†	Blood volume esti- mated from surface area	Maxi- mum probable plasma volume‡	Fall in serum inor- ganic phos- phorus 1st hour	Phosphorus lost assuming maximum plasma volume	Phos- phorus found in urine 1st hour after para- thormone
		sq. m.	cc.	cc.	cc.	mgm. per 100 cc.	mgm.	mgm.
1	A.C.	1.1	2300	2530	1800	0.45	8.1	11.8
2	A.C.	1.1	2300	2530	1800	1.00	18.0	18.7
3	H.C.	1.6	2300	3680	2500	1.3	32.5	33.6
4*	· H.C.	1.6	2300	3680	2500	1.0	25.0	83.9

TABLE 1
Comparison of serum phosphate and urinary phosphate excretion

- * First two hours taken, as first hour urine was collected few minutes early.
- † From Chang and Harrop (7).
- ‡ For maximum plasma volume approximate figures were chosen which would be well above any probable variations. Plasma volume × observed fall in inorganic phosphorus = mgm. phosphorus lost from plasma.

Subject	Sample	Inorganic phos- phorus in serum corrected for protein	Inorganic phos- phorus in filtrate	Filtrability	
		mgm. per 100 cc.	mgm. per 100 cc.	per cent	
A.C.	1	8.24	8.2	100	
	2*	8.05	7.9	98	
H.C.	1	7.66	7.5	97	
	2	6.9	6.8	98	

TABLE 2
Ultrafiltration

The behavior of the serum calcium shows an interesting contrast to that of the serum phosphorus. Whereas the change in the latter was immediately detected, the alteration in serum calcium level was delayed. In Experiments 1 and 2 the delay was slight, though definite, whereas in Experiments 3 and 4 the lag in calcium change was more than 5 and 4 hours respectively. In these experiments blood specimens taken 24 hours after the parathormone showed the usual rise in serum calcium. Such observations offer stronger evidence than we have before obtained for the hypothesis that the changes in phosphorus metabolism following parathyroid administration are primary and the alterations in calcium metabolism are secondary.

As an explanation of the phosphorus diuresis following the injection of parathormone, any hypothesis that the phosphorus is forced out of the serum in some way as an adjustment to a rising serum calcium is untenable in those instances in which the serum calcium did not rise for 4 hours.

^{*} One-half hour after parathormone.

One is again left with the hypothesis that the phosphorus changes occur as the first effect of the injection of parathormone.

To explain the outpouring of phosphorus in the urine in combination with a falling serum inorganic phosphorus, two possibilities suggest themselves. The first is that the hormone might convert a grossly nonfiltrable form of phosphorus into a filtrable state so that it would more readily pass the kidney. By using Grollman's technique, however, it was found (Table 2) that from 97 to 100 per cent of the inorganic phosphorus of the serum of these two subjects was readily filtrable before parathormone was given.

There remains then the hypothesis that parathyroid extract lowers the renal threshold for phosphorus, although the term renal threshold still wants an accurate definition. In this case the sequence of events leading to the eventual rise of serum calcium and the calcium diuresis would appear to be: (a) Lowering of renal threshold for phosphorus. (b) Rise of phosphorus excretion in urine. (c) Fall of serum inorganic phosphorus. (d) Rise of serum calcium in adjustment to (c). (e) Rise of urinary calcium excretion.

SUMMARY

- 1. In four experiments, as previously observed, the first effect of parathormone injection in two patients with hypoparathyroidism was an immediate outpouring of phosphorus in the urine and a fall of serum phosphorus.
- 2. By taking blood specimens at very short intervals it was found that the fall in serum phosphorus preceded the rise in serum calcium.
- 3. The hypothesis that the parathyroid hormone affects primarily the phosphorus metabolism is thereby strongly supported.
- 4. By direct ultrafiltration experiments the serum phosphorus was shown to be 97 to 100 per cent filtrable before parathormone was given.
- 5. To explain the initial phosphorus diuresis, one is left with the suggestion that parathormone lowers the renal threshold for phosphorus.

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