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## Effects of Serum Calcium Level and Parathyroid Extracts on Phosphate and Calcium Excretion in Hypoparathyroid Patients \*

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The known effects of parathyroid hormone on renal excretion of phosphate have tempted some investigators to ascribe a central role to the parathyroid glands in phosphate homeostasis. However, it has been shown that hypoparathyroid patients maintained on vitamin D are able to increase renal phosphate clearance in a manner similar to normal subjects when their oral phosphate intake is raised (1). The vitamin D used in therapy of this illness is generally believed to be directly responsible for increased renal clearance of phosphate, but such large doses of vitamin D cannot be given without affecting calcium metabolism. The possibility that the serum calcium level could affect phosphate homeostasis was explored by measuring the renal response to raising phosphate intake before and during prolonged calcium infusion in untreated hypoparathyroid patients. The experimental design also afforded an opportunity to measure directly the effect of parathyroid extracts on renal excretion of calcium in man.

### Methods

Six patients with untreated postsurgical hypoparathyroidism and one with untreated idiopathic hypoparathyroidism were studied. Of the six postsurgical patients four had been hypoparathyroid from 1 to 6 years. Two were only 1 week postoperative but have since been shown to have permanent hypoparathyroidism.

The patients received a standard diet containing 1,550

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mg of phosphorus throughout the study. Meals were given at 8:00 a.m., 12:00 noon, and 4:30 p.m. No other food was permitted, but tap water was allowed ad libitum. Ambulation and activity were the same each day. Urine was usually collected in two 12-hour periods daily from 8:00 a.m. to 8:00 p.m. and 8:00 p.m. to 8:00 a.m. Blood specimens were taken daily just before breakfast and dinner and, when necessary for monitoring the calcium infusion, before lunch, at bedtime, and during the night. After measurement of phosphate and calcium excretion on this diet the patients received an extra load of phosphate for 1 day. The extra phosphate load given was an additional 1,550 mg of phosphorus in the form of phosphate salts (775 mg as sodium basic phosphate and 775 mg as sodium acid phosphate). The salts were given in three doses with meals. Then a 72-hour calcium chloride infusion in 0.45% saline was given. The concentration of calcium chloride was adjusted to achieve and maintain as close to normal blood calcium level as possible. The amount varied from 20 to 75 mEq for a 12-hour period. The volume of infusate was 1 L every 12 hours. During the third day of calcium infusion an extra load of phosphate was again administered.

In four patients calcium infusion was carried into a fourth day, and hourly urine specimens were obtained. After 3 hours of control collections, parathyroid extract was given and urine collected for four more 1-hour periods. One patient received 200 U of parathyroid extract (PTE) <sup>1</sup> intravenously, another received 400 U of PTE subcutaneously, and two received 300 U of purified parathyroid polypeptide intravenously.<sup>2</sup> Serum and urine calcium were determined by the method of Loken, Teal, and Eisenberg (2), phosphate by the method of Tausky and Shorr (3), creatinine by the method of Folin and Wu (4). Sodium and potassium were determined on the Baird flame photometer with an internal lithium standard.

### Results

A representative protocol and data from one patient are shown in Table I and graphic representation of data from another patient in Figure 1.

<sup>1</sup> Commercial Lilly extract no. 4076-835756.

<sup>2</sup> Kindly supplied by Dr. Claude Arnaud and Dr. H. Rasmussen.

TABLE I  
Protocol and data for Patient 357914\*

Time hrs	Serum		Urine		
	Ca mEq/L	P mg/100 ml	Ca mEq/hr	C <sub>P</sub> ml/min	C <sub>Cr</sub> ml/min
0	3.4	5.2	0.03	3.2	68
Before any therapy					
After extra phosphate intake from 0 to 12 hrs					
24	3.0	5.6	0.03	3.3	77
After first 24 hrs of iv CaCl <sub>2</sub>					
48	5.6	5.6	0.82	11.8	76
After second 24 hrs of iv CaCl <sub>2</sub>					
72	4.9	4.4	0.90	13.0	80
After third 24 hours of iv CaCl <sub>2</sub> plus extra phosphate intake from 72 to 84 hrs					
96	5.1	4.4	1.30	26.6	92
Hourly collection from 96 to 103 hrs; iv CaCl <sub>2</sub> continued					
97			1.40	22.4	96
98			1.40	17.6	87
99	4.9	4.1	1.20	14.1	63
100			1.29	14.1	64
99:30, 400 U parathyroid extract subcutaneously					
101	5.3	4.2	1.00	34.8	63
102			0.59	36.3	73
103	5.4	4.0	0.58	40.5	65

\* C<sub>P</sub> = phosphate clearance; C<sub>Cr</sub> = creatinine clearance.

A) *Effects of calcium infusion* (Tables I, II; Figure 1). During the first 8 hours of calcium infusion, the change in serum phosphate was slight, amounting to +0.6, -0.1, -0.9, +0.4, and +0.2 mg per 100 ml. With prolonged calcium infusion that maintained the serum calcium at normal levels, the serum phosphate level dropped as the phosphate clearance increased. The serum phosphate fell to normal levels or close to it in all patients. The phosphate clearance rose steadily during the calcium infusion, climbing from the low levels usually associated with untreated hypoparathyroidism to within the normal range in all patients. Urinary calcium excretion rose from low values to rates far in excess of normal, even when serum calcium levels were normal or slightly below normal.

B) *Effects of phosphate loading before and during calcium infusion* (Table I; Figures 1, 2). Oral administration of the extra phosphate load before calcium infusion caused the two acute post-operative cases to develop severe tetany, and this phase of the study was abandoned in them. In the remaining five patients the extra phosphate load caused only slight increase in phosphate clearance. The fasting serum phosphate level

taken the next morning was higher (and the serum calcium level fell slightly) in four of the five patients so studied. When an identical phosphate load was given during the third day of calcium infusion, the clearance of phosphate increased markedly. The serum phosphate tended to decrease in spite of additional phosphate load.

C) *Effects of parathyroid extract* (Tables I, III; Figure 1). Administration of PTE to two patients and purified parathyroid polypeptide to two patients during maintenance of their serum

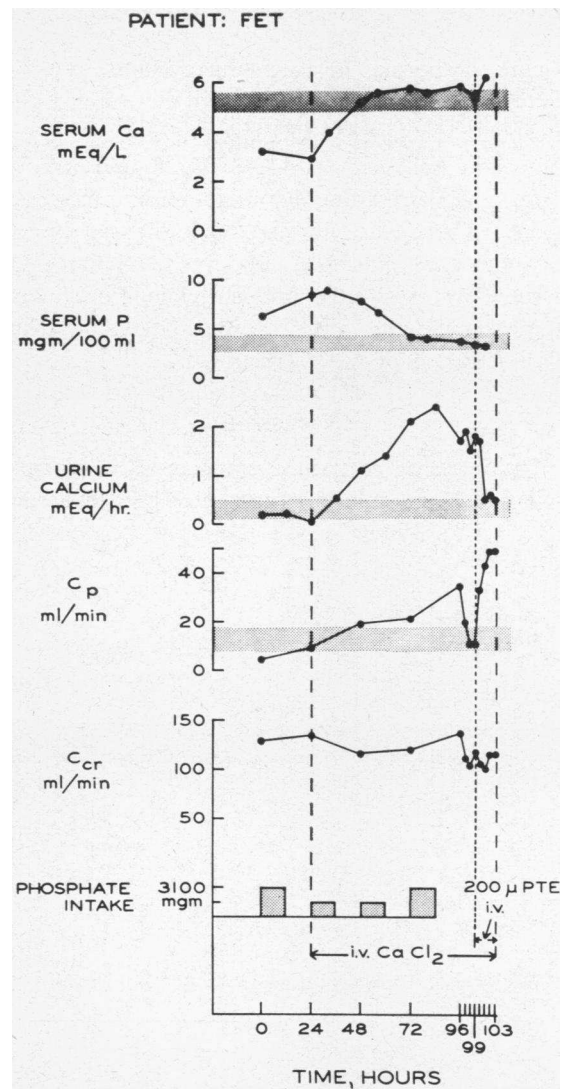


FIG. 1. GRAPHIC REPRESENTATIVE OF EFFECTS OF SERUM CALCIUM LEVEL AND PARATHYROID EXTRACT (PTE) ON PHOSPHATE AND CALCIUM EXCRETION IN PATIENT 308668. The horizontal gray bars represent the mean  $\pm$  2 SD for the normal subjects in this laboratory.

TABLE II  
Effects of calcium infusion on serum phosphate, phosphate clearance, and urinary calcium\*

Patient	Before any therapy					End of second day of calcium infusion				
	SCa	SP	UCa	CP	CCr	SCa	SP	UCa	CP	CCr
	mEq/L	mg/ 100 ml	mEq/hr	ml/min	ml/min	mEq/L	mg/ 100 ml	mEq/hr	ml/min	ml/min
308668	3.20	6.3	0.20	5.2	129	5.80	4.2	2.10	21.4	120
357914	3.40	5.2	0.03	3.2	68	4.90	4.4	0.90	13.0	80
236911	3.00	6.1	0.05	1.8	87	4.40	4.2	1.00	10.1	80
302542	3.80	4.2	0.07	1.5	91	5.20	4.1	1.60	16.0	113
360799	2.55	5.9	0.08	6.2	71	5.00	4.5	1.45	11.1	58
356654	3.30	5.6	0.20	3.0	75	4.60	4.5	1.10	15.9	78
382432	3.80	4.3	0.03	4.2	76	5.35	3.0	0.85	20.6	66

\* SCa = serum calcium level; SP = serum inorganic phosphate level; UCa = urinary calcium excretion.

calcium at normal levels by intravenous infusion of calcium chloride caused marked elevation of the phosphate clearance. The calcium content of the urine simultaneously fell to 44, 31, 30, and 50% of their values preceding administration of the extracts. There were no significant changes in endogenous creatinine clearance, and sodium and potassium excretion either did not change or tended to increase in the 4 hours immediately following administration of the extracts.

### Discussion

The response of normal subjects to a standard 4-hour calcium tolerance test is a rise in serum

phosphate and a fall in phosphate clearance. In untreated hypoparathyroid patients a rise in both serum phosphate and phosphate clearance is commonly observed (5-8). Lavender and Pullman (9) suggest that the difference in response between normal and hypoparathyroid subjects is accounted for by the level to which the blood calcium is raised. In normal subjects the serum calcium is raised higher, and the deleterious effect of hypercalcemia on glomerular filtration rate would lower phosphate excretion. With the moderate hypercalcemia achieved in the hypoparathyroid subjects the increased serum phosphate would account for the raised phosphate excretion. However, the data above demonstrate that when a normal calcium environment was provided for a longer time, the hypoparathyroid subjects increased phosphate clearance, even though the serum phosphate level fell and creatinine clearance did not significantly change. They also regained the ability to increase phosphate clearance further when phosphate intake was raised. This phosphuresis was accomplished without marked change in

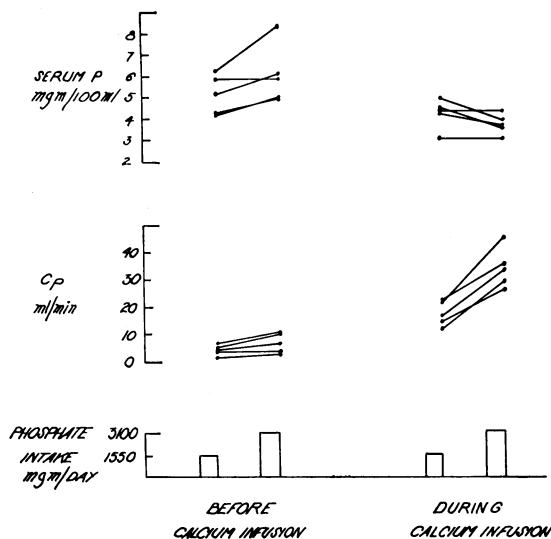


FIG. 2. EFFECTS OF INCREASING PHOSPHATE INTAKE ON SERUM PHOSPHATE LEVEL AND PHOSPHATE CLEARANCE DURING HYPOCALCEMIA (BEFORE CALCIUM INFUSION) AND WITH NORMAL CALCIUM LEVEL (DURING CALCIUM INFUSION).

TABLE III  
Effect of parathyroid extracts on urinary cation excretion

Extract	Calcium		Sodium		Potassium	
	C*	E*	C	E	C	D
200 U PTE iv	1.70	0.53†	12.8	24.1†	2.8	5.9†
400 U PTE subcutaneously	1.30	0.58†	12.9	16.2‡	6.4	6.7
300 U purified parathyroid hormone (PTH)	1.00	0.31†	15.8	16.0	4.4	6.6‡
300 U PTH	1.90	0.95†	6.3	6.5	3.0	5.3‡

\* C = mean of three 1-hour preinjection periods; E = mean of four 1-hour postinjection periods.  
† p < 0.001.  
‡ p < 0.01.

glomerular filtration rate and in spite of the reduced serum phosphate level. Presumably a decrease in tubular resorption of phosphate occurred.

It is clear that changes in phosphate excretion can be induced by dietary means in the absence of both parathyroid function and pharmacologic doses of vitamin D. The mechanism for this homeostatic response is obscure, but it does require a normal or near normal serum calcium level. The ability of vitamin D-treated hypoparathyroid patients to respond to oral phosphate loading would appear to be more directly related to the normal serum calcium level than to the vitamin D. These findings raise the possibility that parathyroid hormone and vitamin D induce phosphaturia by effects on calcium metabolism or on calcium transport in the renal tubular cells instead of by direct effects on renal tubular excretion of phosphate.

It has been reported that parathyroid hormone increases tubular reabsorption of calcium in the rat (10-12). Widrow and Levinsky (13) showed a similar effect of PTE in the dog but could not reproduce this effect with more purified hormone. There is not uniform agreement on the effect of parathyroid hormone on renal excretion of calcium in man. Gordan, Loken, Blum, and Teal (14) reported a decrease in percentage of tubular reabsorption of calcium in hyperparathyroid patients compared to normal subjects, and Horwith, Rich, Thompson, and Rasmussen (15) reported a slight increase in urinary calcium after administration of partially purified parathyroid hormone. Hiatt and Thompson (16) reported no change in urinary calcium after acute administration of PTE in hypoparathyroid patients even though glomerular filtration rate went up slightly after the extract was given. Kleeman and associates (17, 18) reported decreased "calcium clearance" in the presence of normal or increased amounts of parathyroid hormone when contrasted to low or normal amounts, respectively. In the reports by Kleeman and associates the "calcium clearance" was actually the ratio of calcium clearance to inulin clearance, and in many of their studies the serum calcium or glomerular filtration rate was changing rapidly. In those studies where these factors were relatively constant, they assumed that changes in parathyroid function were induced by altering the dietary calcium and phosphate of their subjects.

In the present study four patients whose serum calcium had been held at near steady state by slow intravenous administration of calcium chloride responded to administration of parathyroid extracts with a fall in urinary calcium content without a fall in creatinine clearance and without a fall in sodium excretion. Presumably, a rise in tubular reabsorption of calcium occurred. Evidence corroborating such an effect of parathyroid hormone on renal tubular resorption of calcium is provided by the uniform finding of hypercalciuria in all patients during calcium infusion, even though the serum calcium never quite reached normal level. In these patients the hypercalciuria could not be due to the gluconate ion (19, 20) or to excessive vitamin D (21). This observation supports the suggestion of Bernstein, Kleeman, and Maxwell (18) that the hypercalciuria seen in hypoparathyroid patients treated with vitamin D (21) is not due to a direct effect of vitamin D on tubular reabsorption of calcium but to elevation of the serum calcium towards normal in the absence of the parathyroid gland.

### Summary

Seven patients with untreated hypoparathyroidism were given prolonged calcium infusion. Calcium infusion alone over a period of 48 hours raised the phosphate clearance to normal and lowered the serum phosphate. Before calcium infusion, an oral phosphate load raised phosphate clearance only slightly. When an oral phosphate load was given during calcium infusion, the kidneys were able to excrete it in normal fashion. A mechanism for phosphate homeostasis that does not include the parathyroid glands exists. Since phosphaturia can be induced by maintenance of a normal serum calcium alone, the phosphaturic action of parathyroid hormone and vitamin D may be due to more basic action on calcium transport. Administration of parathyroid extracts to four patients while the calcium was maintained at a normal level by calcium infusion caused the urinary calcium to decrease significantly.

### Acknowledgment

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