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Research Article

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Renal Bicarbonate Wasting during Phosphate Depletion

A POSSIBLE CAUSE OF ALTERED ACID-BASE HOMEOSTASIS IN HYPERPARATHYROIDISM

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ABSTRACT With hyperparathyroidism, serum bicarbonate (HCO_3^-) is low, urinary excretion of HCO_3^- is increased and the apparent T_m for HCO_3^- is reduced. These findings have been ascribed to a direct renal action of parathyroid hormone (PTH). Since hypophosphatemia and phosphate depletion may occur in hyperparathyroidism, it is possible that phosphate depletion could account for the abnormal renal HCO_3^- handling. To test this possibility, renal reabsorption of HCO_3^- was evaluated in dogs before and after phosphate depletion. Serum HCO_3^- was significantly lower in phosphate depleted dogs than in normal animals, and serum HCO_3^- was directly related to serum phosphorus. Both the threshold at which HCO_3^- appeared in the urine and the T_m for HCO_3^- were reduced during phosphate depletion. Intracellular pH of muscle was significantly higher in phosphate depleted dogs than in normals and the pH returned to normal after phosphate repletion. These data show that phosphate depleted dogs, which probably have physiological hypoparathyroidism, display abnormalities in both serum HCO_3^- and its renal handling which are similar to those seen in hyperparathyroidism, supporting the concept that the PTH-induced alterations in HCO_3^- homeostasis may be due to phosphate depletion. The latter could alter cell metabolism, resulting in reduced intracellular H^+ concentration, which may then impair H^+ secretion by the renal tubules and decrease their ability to reabsorb HCO_3^-. Consequently, T_m HCO_3^- and serum HCO_3^- fall.

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INTRODUCTION

Clinical and experimental observations indicate that there is a relation between the activity of the parathyroid glands, on the one hand, and acid-base homeostasis and renal handling of bicarbonate on the other. Thus, hyperchloremic acidosis has been noted occasionally in patients with primary hyperparathyroidism (1–3), and others have found impaired urinary acidification in response to an acid load in such patients (4–6). In addition, mild systemic acidosis, low levels of serum bicarbonate (HCO_3^-), excessive urinary loss of HCO_3^-, and impaired urinary acidification have been reported in patients with osteomalacia and secondary hyperparathyroidism (6–9). These abnormalities were usually reversed following treatment of the hyperparathyroidism (10). Furthermore, the levels of serum HCO_3^- are usually elevated both in patients with hypercalcemia which is not due to hyperactivity of the parathyroid glands and in patients with hypoparathyroidism (1, 11–14). Finally, Barzel (13, 14) found that patients with hypoparathyroidism had mild metabolic alkalosis. These observations led Muldowney et al. (10) to postulate that parathyroid hormone directly decreases the renal reabsorption of bicarbonate resulting in metabolic acidosis. Support for such a postulate is found in experimental observations that the acute administration of parathyroid extract (PTE)[1] produces a rise in urinary pH and an increase in urinary excretion of HCO_3^- (15–18). However, Kurtzman, Karlinsky, and Sager (19) found that the administration of PTE or dibutryl cyclic AMP, an analogue of the mediator of renal action of parathyroid hormone

[1] *Abbreviations used in this paper:* GFR, glomerular filtration rate; PTE, parathyroid extract; PTH, parathyroid hormone.

(PTH), caused only a transient and slight increase in HCO_3^- excretion and failed to reduce HCO_3^- reabsorption when evaluated during HCO_3^- loading.

It is possible that abnormalities of bicarbonate homeostasis in patients with hyperparathyroidism may be secondary to the metabolic consequences of the long-term action of excessive quantities of parathyroid hormone rather than being a direct result of the hormones action on the renal tubule. With sustained action of parathyroid hormone, phosphaturia and hypophosphatemia occur and phopshate depletion may develop. The present study was undertaken to evaluate whether phosphate depletion, per se, can affect renal bicarbonate handling and acid-base homeostasis.

METHODS

Experiments were carried out in 18 adult female mongrel dogs, weighing 13–22 kg. Phosphate depletion was produced in eight dogs by the feeding of a low phosphate diet and the administration of aluminum hydroxide gel (kindly supplied by Dr. Earl Lewis of the Wyeth Laboratories, Philadelphia, Pa.) as described previously from this laboratory (20). The diet was identical during control, depletion and repletion periods with regard to its content of sodium, potassium, calcium and magnesium; only the phosphate content was varied.

Experiments for measurement of maximum reabsorption rate for bicarbonate and determination of the renal threshold for bicarbonate were carried out in six animals during control and depletion periods as follows: Food was withheld for 16–18 h before each study but the animals were allowed free access to water. An oral water load, equal to 5% of body weight, was given by stomach tube at 8:00–8:30 a.m. on the day of the experiment. 45–60 min later, the dog was anesthetized with intravenous pentobarbital. A cuffed endotracheal tube was inserted, and respiration was maintained with a Harvard respirator (Harvard Apparatus Co., Millis, Mass.) adjusted to control P_{CO_2}. The animal's rectal temperature was measured and maintained stable with blankets and electric heating pads. After the intravenous injection of 500 mg of creatinine in an 8% solution, a creatinine sustaining solution was given at 2.0 ml/min. Another solution of 2.5% dextrose in water was administered at a rate adjusted so that the total amount of fluid infused was equal to urine flow. Urine was collected anaerobically under mineral oil from an indwelling catheter in the bladder, and blood samples were obtained anaerobically in syringes containing heparin from a catheter in the femoral artery. Manual pressure over the suprapubic area was utilized to empty the bladder at the end of each period. After a 45 min interval for equilibration, three control clearance periods of 7–20 min duration were obtained. Over the next 200 min, the serum level of bicarbonate (HCO_3^-) was elevated in a step-wise manner by increments of 2–5 meq/liter; this was carried out by the intravenous injection of 15–44 meq of $NaHCO_3$ as a priming bolus in a solution containing 880 meq/liter; after each priming dose, $NaHCO_3$ was added to the sustaining solution of creatinine in an amount to provide 60–240 meq/liter of HCO_3^-. This quantity of $NaHCO_3$ was calculated to maintain the elevation of serum HCO_3^- produced by the preceding priming injection. After 30 min of equilibration at each successively higher level of serum HCO_3^-, clearance periods of 5–10 min duration were obtained. Serum bicarbonate eventually reached levels of 27–43 meq/liter. During each experiment, an attempt was made to prevent wide variation in P_{CO_2} from the outset until the completion of

TABLE I

Effect of Phosphate Depletion on Serum Bicarbonate and Renal Handling of Bicarbonate

Dog no.	Diet	Duration of diet	C_{Cr}	S_P	P_{CO_2}		$S_{HCO_3^-}$		$T_m HCO_3^-$, $\frac{meq/min}{C_{Cr}} \times 100$	Total solids		S_K	
					C	T_m	C	T_m		C	T_m	C	T_m
		days	*ml/min*	*mg/100 ml*	*mm Hg*		*meq/liter*			%	%	*meq/liter*	
1	N	29	73.7	3.8	36	40	26.6	38.6	3.72	6.8	6.2	3.1	2.9
	L	95	65.2	1.3	36	41	23.0	36.3	2.91	7.0	6.9	3.2	3.0
2	N	27	50.0	2.9	39	39	27.1	34.3	3.32	7.0	6.7	3.4	2.5
	L	93	41.3	1.1	36	38	22.0	33.0	2.75	7.2	7.1	2.9	2.7
3	N	26	48.3	3.6	43	45	26.5	35.1	3.35	7.2	6.8	3.3	2.3
	L	66	39.8	0.4	36	46	22.4	42.6	3.04	6.9	6.5	3.1	2.5
4	N	25	84.9	4.4	38	48	23.3	40.0	3.49	6.8	6.7	2.8	3.1
	L	139	60.0	2.9	35	48	19.3	40.9	2.90	7.0	6.7	2.5	2.8
5	N	37	54.3	2.7	36	42	21.1	37.5	3.05	7.2	6.6	2.7	2.7
	L	40	57.4	0.6	33	37	20.1	35.1	2.29	7.2	6.9	2.9	2.9
6	N	21	91.1	3.0	37	38	22.5	33.2	2.70	7.7	7.8	2.7	2.7
	L	85	97.1	0.5	33	41	19.1	26.9	2.17	7.6	7.7	3.0	2.8
Mean	N		67.1	3.4	38	42	24.5	36.5	3.27	7.2	6.8	3.0	2.7
±SE			±7.6	±0.3	±1	±2	±1.0	±1.1	±0.14	±0.2	±0.2	±0.1	±0.1
	L		60.1	1.1	35	40	21.0	35.8	2.68	7.2	7.0	2.9	2.8
			±8.5	±0.4	±1	±3	±0.7	±2.3	±0.14	±0.1	±0.2	±0.1	±0.1
	P		NS	<0.001	0.05	NS	<0.02	NS	<0.02	NS	NS	NS	NS

Each data point represents the mean of three to five clearance periods. The values for P_{CO_2} and serum bicarbonate ($S_{HCO_3^-}$) are indicated during the control part of each experiment (C) and later when T_m was being measured. Other abbreviations: N, normal phosphate diet; L, phosphate depletion diet; C_{Cr}, exogenous creatinine clearance; S_P, serum phosphorus; $S_{HCO_3^-}$, serum bicarbonate; $T_m HCO_3^-$, maximum reabsorptive rate for bicarbonate; S_K, serum potassium.

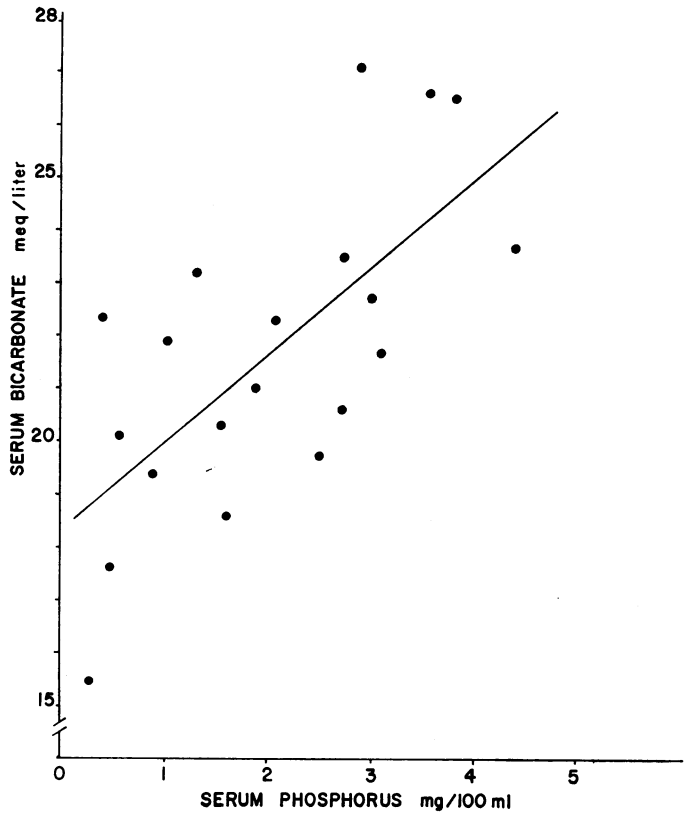

FIGURE 1 The relation between the levels of serum bicarbonate and phosphorus during the production of phosphate depletion.

the study; in most experiments, the changes were 8 mm Hg or less (Table I). During the latter part of the experiments when maximal rates of HCO_3^- reabsorption occurred, ventilation was closely regulated so that the P_{CO_2} was similar in the same animal during both the control and phosphate depleted state; the variation was 5 mm Hg in one dog and 3 mm or less in the others (Table I). Also, the volume of fluid and quantity of sodium given to each animal was similar in experiments carried out during the control and phosphate depleted states.

Intracellular pH was measured in seven additional dogs receiving a normal diet of Purina dog chow, and in eight dogs during phosphate depletion (including all six described above); in four of the latter group, the measurements of intracellular pH of muscle were repeated 64–87 days after phosphate repletion. The method for measuring intracellular pH was similar to that reported by Waddell and Butler (21) and Adler, Roy, and Relman (22) utilizing [^{14}C]DMO (55-dimethyl-2,4-oxazolidinedione) and non-labeled DMO as a carrier. Extracellular space was measured by $^{35}SO_4$, and $^{35}SO_4$ activity was separated from ^{14}C activity by precipitation of $^{35}SO_4$ with barium chloride as described previously from our laboratory (23). Both isotopes were obtained from the New England Nuclear Corp., Boston, Mass.

The analytical methods for creatinine, phosphate, sodium, and potassium are reported elsewhere (24). Total solids in plasma were measured by refractometry (Goldberg Refractometer, American Optimal Corp., Buffalo, N. Y.). The pH and P_{CO_2} in arterial blood and urine were measured utilizing a blood microsystem acid-base analyzer (model BMS 3-PHM 71; Radiometer, Copenhagen). The concentrations of bicarbonate in plasma and urine were calculated from the Henderson-Hasselbach equation utilizing the following factors: Solubility coefficients for CO_2 in plasma and urine of 0.0301 and 0.0309, respectively; a pK of 6.10 for plasma, and a pK for urine calculated from its ionic strength according to the formula, $pKa = 6.33 - 0.5\sqrt{Na^+ + K^+}$, with the concentrations of Na and K given in equivalents per liter (25); corrections were not made for Donnan factors.

RESULTS

The animals appeared healthy and maintained or even gained body weight during the period of phosphate depletion. The effect of phosphate depletion on serum HCO_3^- and the renal handling of this ion are shown in Table I and Figs. 1, 2, and 3. With the development of phosphate depletion, serum HCO_3^- levels fell in each animal, and the mean value of 21.0±0.7 (SE) meq/liter noted in the phosphate depleted animals was significantly lower than that observed before phosphate depletion (24.5±1.0 meq/liter), $P < 0.02$. Furthermore, there was a direct correlation between the serum concentrations of HCO_3^- and phosphorus with $y = 1.64\ x + 18.30$, $r = 0.68$, $P < 0.001$ (Fig. 1).

Fig. 2 depicts the quantity of HCO_3^- appearing in the urine with increasing concentrations of serum HCO_3^- in experiments before and after phosphate depletion. These data were obtained before and during the early periods of infusion of $NaHCO_3^-$ prior to the achievement of the apparent maximal rate for HCO_3^- reabsorption. These thresholds for HCO_3^- were lower in each animal during phosphate depletion than in control studies. As filtered HCO_3^- was raised, its reabsorption increased gradually and then stabilized, reaching an apparent T_m level. This maximal rate of HCO_3^- reabsorption was lower in each dog during phosphate depletion than in control studies, with mean values of 2.68±0.14 and 3.27± 0.14 meq/min per 100 ml GFR ($P < 0.02$), respectively. The relation between HCO_3^- reabsorption and its filtered load for all clearance periods during all experiments with bicarbonate infusion is shown in Fig. 3. At comparable filtered loads of HCO_3^- (above 2.3 meq/min per 100 ml GFR), the reabsorption of HCO_3^- was lower during phosphate depletion than in control studies.

The intracellular pH in the phosphate depleted animals was higher than values obtained in seven normal dogs (Table II, Fig. 4), with a mean value of intracellular pH of 7.02 (95±7 nmol/liter H^+) in the phosphate depleted animals compared with 6.86 (136±4 nmol/liter H^+) in normal dogs, $P < 0.01$. After phosphate repletion, intracellular pH returned to 6.84 (146±9 nmol/liter H^+), a mean value not different from normal but significantly different from the value during phosphate depletion, $P < 0.01$.

DISCUSSION

The results of the present study demonstrate that phosphate depletion is associated with a fall in serum bicarbonate and a reduction in both the threshold at which bicarbonate appears in the urine and the apparent maximal tubular reabsorptive capacity for bicarbonate. These data indicate that phosphate depletion per se can cause abnormalities in bicarbonate homeostasis which are similar to those described in humans with primary (1–6) or secondary (6–9) hyperparathyroidism. There is indirect evidence to indicate that the activity of the parathyroid glands is inhibited during phosphate depletion. Thus, rats show hypoplasia of the parathyroid glands

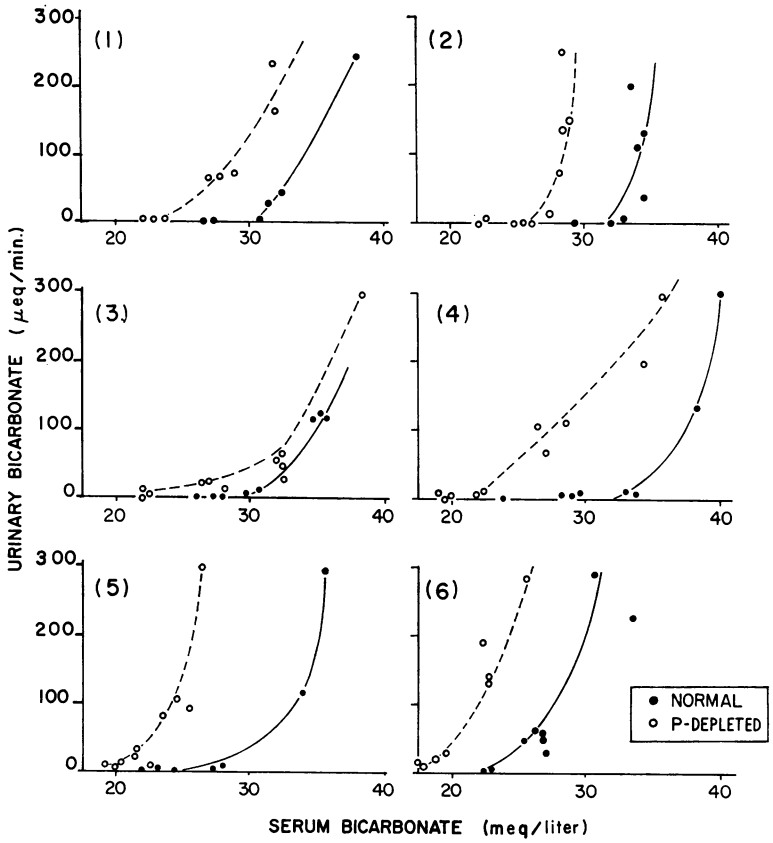

FIGURE 2 The relation between the amount of bicarbonate appearing in the urine as serum bicarbonate was elevated by bicarbonate infusion in experiments before (●) and after (○) phosphate depletion. The lines were drawn by visual approximation.

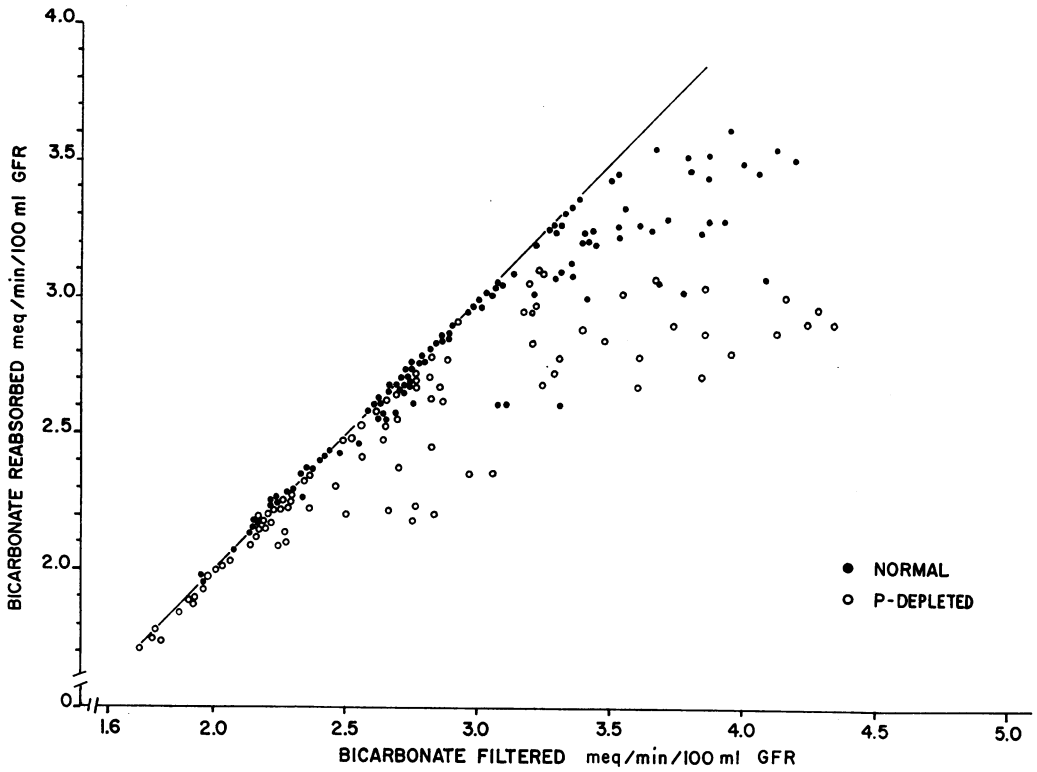

FIGURE 3 The relationship between the quantity of bicarbonate reabsorbed and that filtered for all clearance periods during all experiments with bicarbonate infusion both before (●) and after (○) phosphate depletion.

during phosphate depletion (26); also serum calcium levels remain normal or slightly elevated after removal of the parathyroid glands in phosphate depleted rats (26, 27) and dogs (20, 28), indicating that serum calcium was maintained at normal levels in the absence of parathyroid hormone in the phosphate depleted state. Moreover, an increase in blood calcium to normal has been observed in humans with hypoparathyroidism during phosphate depletion (28). Such inhibition of the parathyroid glands during phospate depletion is probably caused by transient or persistent elevation of serum calcium, a feature noted in rats and dogs during phosphate depletion (24, 25). It is, therefore, reasonable to conclude that the abnormalities of bicarbonate homeostasis observed in the present study, are associated with reduced rather than increased activity of the parathyroid glands despite the lack of measurement of parathyroid hormone in the blood of these animals; hence, the alterations in bicarbonate regulation are probably related to phosphate depletion per se.

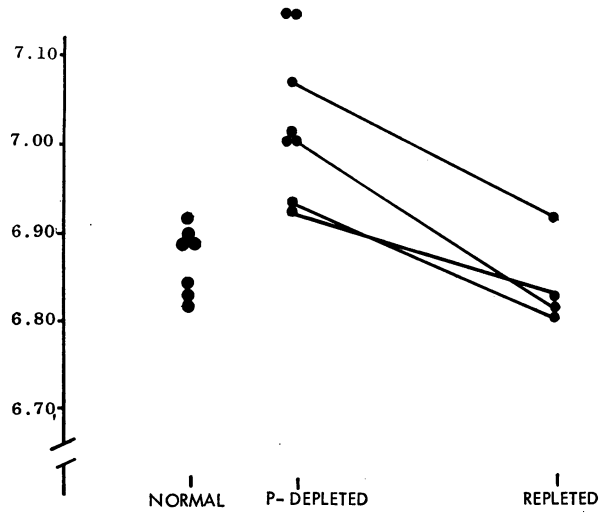

FIGURE 4 The effect of phosphate depletion and repletion on intracellular pH. The lines connect values obtained in the same animal.

It has been suggested that parathyroid hormone can cause an immediate and direct inhibition of the tubular reabsorption of bicarbonate. Nordin (17) gave PTE to humans and Helman, Au, and Bartter (18) to dogs and man. They found an immediate increase in urinary pH and an increase in HCO_3^- excretion after the intravenous injection of the extract. However, these changes could have resulted from alterations in filtered load of HCO_3^- secondary to an augmented glomerular filtration rate

TABLE II

Effect of Phosphate Depletion on Intracellular pH

Dog no.	Diet	Duration of diet	S_P	pHe	pHi	P_{CO_2}
		days	*mg. 100 ml*			*mm Hg*
Normal dogs						
A	PC		5.1	7.37	6.84	34
B	PC		4.4	7.36	6.83	34
C	PC		4.3	7.37	6.89	35
D	PC		3.9	7.34	6.88	34
E	PC		3.3	7.32	6.82	40
F	PC		4.4	7.33	6.92	38
G	PC		2.7	7.40	6.88	35
Phosphate depleted dogs						
1	L	93	0.5	7.36	7.15	36
2	L	86	1.9	7.38	7.07	36
	N	64	3.4	7.43	6.92	31
3	L	78	0.9	7.41	7.00	35
	N	75	4.8	7.39	6.81	33
4	L	119	0.2	7.40	7.00	34
5	L	33	0.9	7.32	6.93	38
	N	75	5.2	7.33	6.82	37
6	L	65	0.5	7.39	6.93	30
	N	87	4.6	7.35	6.80	41
7	L	48	0.6	7.45	7.15	35
8	L	63	0.3	7.21	7.01	39

Abbreviations: PC, Purina Dog Chow (Ralston Purina Co., St. Louis, Mo.); L, phosphate depletion diet; N, normal phosphate (repletion) diet; S_P, serum phosphorus level; pHe, blood pH; pHi, intracellular pH. Phosphate depleted dogs are designated by the same numbers as in Table I.

(GFR) or be due to spontaneous diurnal variations in HCO_3^- excretion. Kleeman and Cooke (16) found an inconsistent effect of PTE on HCO_3^- excretion, and Muldowney et al. (6, 10) studied the effect of PTE infusion in four subjects and reported data suggesting that an increase in HCO_3^- excretion could occur independent of changes in GFR or diurnal variations in HCO_3^- excretion. However, it may be more appropriate to study the effect of PTE during HCO_3^- loading in order to critically evaluate a possible role of the hormone in reducing renal reabsorption of HCO_3^-. Under such circumstances, Kurtzman, Karlinsky, and Sager (19) found no effect of either PTE or dibutryl cyclic AMP on tubular reabsorption of HCO_3^-.

It is well established that parathyroid hormone causes phosphaturia due to decreased renal tubular reabsorption of phosphate, leading to a reduction in serum phosphorus (28, 29), and phosphate depletion may ensue. These observations and the results of the present study suggest that the alterations in HCO_3^- homeostasis noted in patients with hyperparathyroidism may be largely mediated by phosphate depletion rather than by a direct action of parathyroid hormone on the renal handling of HCO_3^-.

The precise mechanisms responsible for altered HCO_3^- reabsorption in phosphate depletion have not been delineated. The reduced tubular reabsorption of HCO_3^- cannot be accounted for by factors known to affect its renal handling such as changes in serum potassium, alterations in P_{CO_2} (30), or variations in the degree of expansion of extracellular fluid volume (31, 32) since these parameters were either similar or carefully controlled during studies carried out in the control and phosphate depleted states. The present observation of an elevated intracellular pH during phosphate depletion may provide an explanation for the reduced tubular reabsorption of HCO_3^-. Since tubular reabsorption of HCO_3^- is dependent on secretion of hydrogen ion (H^+) by the tubular cell (30), a decrease in intracellular concentration of H^+ would be expected to impair its secretion and, hence, reduce HCO_3^- reabsorption. The mechanisms responsible for the increase in intracellular pH during phosphate depletion remain unknown.

The results of the present study may permit construction of the following sequence of events whereby phosphate depletion affects HCO_3^- homeostasis: Through some as yet undefined mechanism, phosphate depletion causes a decrease in intracellular H^+ concentration. This intracellular alkalosis may impair tubular H^+ secretion and HCO_3^- reabsorption. Increased urinary losses of HCO_3^- lead to a fall in serum HCO_3^- and mild acidosis.

Phosphate depletion has been reported to cause alterations in the renal tubular transport of other actively transported substances: Thus, there is decreased tubular reabsorption of calcium and magnesium (20), and, under certain circumstances, of sodium as well (33). Moreover, the maximal reabsorptive capacity for glucose is also reduced during phosphate depletion (unpublished observations). It is possible that the reduced reabsorption of HCO_3^- represents another manifestation of altered renal tubular transport mechanisms caused by phosphate depletion.

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