

# RENAL REABSORPTION OF PHOSPHATE IN NORMAL HUMAN SUBJECTS AND IN PATIENTS WITH PARATHYROID DISEASE

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(Submitted for publication August 30, 1956; accepted December 13, 1956)

A number of studies in the dog and in man (1-6) have demonstrated a maximal renal tubular reabsorptive capacity for phosphate (TmP<sup>3</sup>). However, some investigators have denied that the reabsorption of phosphate conforms to Tm characteristics (7-9). These workers have suggested that phosphate reabsorption is conditioned by the rate of phosphate filtration such that a fairly constant proportion of the filtered phosphate is reabsorbed. In view of the conflicting evidence and the relative paucity of phosphate titration studies on man, experiments were performed in order to obtain information on the mechanism of phosphate reabsorption, the constancy of reabsorption in any one individual, and its variability in a group of subjects. The data were required for subsequent investigations designed to evaluate the influence of several factors on renal phosphate transport. The studies were performed on normal individuals and in patients with parathyroid disease.

It was found that in any given experiment a TmP was demonstrable. However, the variability in TmP seen in most of our normal subjects between consecutive periods of a single experiment and between experiments generally exceeded the variability reported for glucose Tm and for PAH Tm. Furthermore, the range of values for TmP within a group of normal individuals is so large that an average value has little meaning. Fluctuations in TmP in our subjects could not be con-

sistently correlated with the level of calcium or phosphate in the diet.

## METHODS

**Subjects.** Studies were carried out on ten normal subjects, three patients with post-thyroidectomy hypoparathyroidism, and one individual with hyperparathyroidism. The normal individuals included five male and three female volunteers aged 20 to 27 years, one 17-year-old male (C. H.) convalescing from a hip injury, but ambulatory during most of the studies, and a 26-year-old female (W. H.) hospitalized with a diagnosis of hypoparathyroidism, but found to have normal parathyroid function. The hypoparathyroid patients, a 37-year-old male and two females, aged 42 and 52, had not been treated previously with any medication other than calcium salts. The manifestations of hypoparathyroidism were severe in the male and mild in the females. The hyperparathyroid subject, a 72-year-old male, was subsequently cured by the removal of a parathyroid adenoma.

All subjects were hospitalized on a metabolism ward, and during many of the studies they received constant diets of calculated calcium and phosphate content. There were no restrictions on the patients' activities.

**Design of experiments.** Studies were begun about 9 a.m. with the patient fasted for 12 to 16 hours. One-half hour prior to the start of each study the subject ingested a liter of water and thereafter drank 200 ml. of wa-

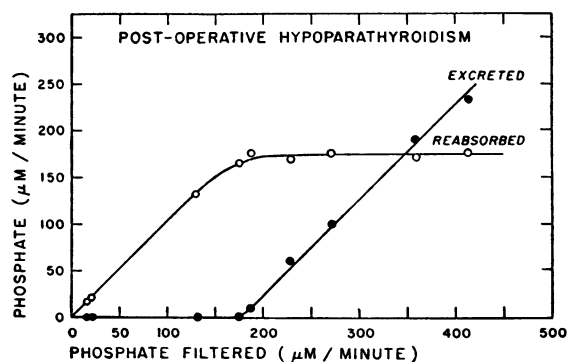


FIG. 1. THE QUANTITIES OF PHOSPHATE FILTERED, EXCRETED, AND REABSORBED DURING INTRAVENOUS PHOSPHATE LOADING IN A HYPOPARATHYROID SUBJECT

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<sup>3</sup> The following abbreviations will be used in this paper: P, inorganic phosphate;  $C_{in}$ , inulin clearance; GFR, glomerular filtration rate; RPF, effective renal plasma flow; Tm, maximal rate of renal tubular reabsorption; Ca, calcium; K, potassium; PAH, para-amino hippurate.

TABLE I

*Effect of elevation of plasma inorganic phosphate on the quantity of phosphate filtered, excreted, and reabsorbed \**

Total concurrent time min.	Urine flow ml./min.	C <sub>Ia</sub> ml./min.	C <sub>PAH</sub> ml./min.	Plasma P μM/ml.	Urine P μM/ml.	Phosphate			P reab. P filt.
						Filtered μM/min.	Excreted μM/min.	Reabsorbed μM/min.	
35-39	Prime containing inulin and PAH given								
39	Infusion I containing inulin and PAH begun at 3.2 ml. per min.								
90-101	11.2	127	525	0.91	0.02	116	0.2	116	1.00
101-116	11.3	130	541	0.93	0.02	121	0.2	121	1.00
118	Infusion II begun; sodium phosphate at 0.55 mM per min. plus inulin and PAH								
148-180	4.28	133	526	1.95	17.5	260	75	185	0.71
180-214	2.92	134	504	2.82	48.0	378	135	243	0.64
214-241	7.39	142	560	3.25	29.2	461	216	245	0.53
241-267	5.70	138	509	3.49	44.5	481	254	227	0.47

\* Patient C. H., normal male subject, age 17.

ter every 20 to 30 minutes to maintain a water diuresis. Female subjects were catheterized with a six-hole rubber catheter which remained in place throughout the experiment. In the early studies the male subjects were also catheterized. However, it was found that these individuals were able to void on command; hence, catheterization was not performed in later experiments. After a sample of venous blood and one of urine were obtained for determination of inulinoid blank, a priming dose of inulin and PAH calculated to provide plasma levels of 20 and 2 mg. per cent, respectively, was given over a period of 3 to 5 minutes. Constant infusion of these substances dissolved in physiological saline solution was maintained by a pump. Thirty to sixty minutes after the sustaining infusion was begun, timed urine collection periods were started. The period varied in duration from 20 to 40 minutes, and at the midpoint of each, blood was drawn from an antecubital vein into a heparinized syringe, immediately centrifuged, and the plasma separated. To close each period urine was collected by spontaneous voiding or through the catheter followed by irrigation with 20 to 60 ml. of distilled water and about 30 ml. of air.

After two to four periods the infusion was changed to one containing buffered sodium phosphate, pH 7.40, in addition to inulin and PAH. A sufficient volume of a 0.5 M phosphate solution was incorporated in the infusion to provide for the delivery of 0.4 to 0.8 mM P per minute. Such an infusion was continued for sixty minutes before urine collections were again begun. This period was sufficient to allow elevation of the plasma P to the desired levels and to assure a relatively slowly increasing plasma P concentration during the collection periods. Studies were carried out for two to four periods at the elevated plasma P levels. In some experiments there followed a third infusion designed to elevate further the plasma P.

**Dietary intake.** The low, intermediate and high calcium diets contained 130, 800, and 1500 mg., respectively, daily. A low P intake was achieved by the administration of a diet containing 600 mg. of P daily, and, in sev-

eral studies by administering, in addition, 35 ml. of aluminum carbonate gel, one hour after each meal and at bedtime. The intermediate P diet contained 1,200 mg., and the high P diets 1800 to 3,000 mg. P. In several experiments variations in Ca or P intake without changes in other dietary constituents were studied by the administration of a constant low Ca-low P diet supplemented at meal time with calcium lactate or 10 per cent phosphoric acid. The patient was placed on a given dietary regimen at least three days, and often more than a week prior to the renal function studies.

**Chemical methods.** Inulin was determined in plasma and urine by the method of Schreiner (10), PAH by the method of Smith, Finkelstein, Aliminoso, Crawford, and Graber (11), inorganic P by the method of Fiske and Subbarow (12). Plasma Ca was determined by the method of Clark and Collip (13), and urine Ca by the method of Shohl and Pedley (14). Plasma K was determined on a flame photometer utilizing an internal standard.

**Calculations.** The clearances of inulin and PAH were taken as measures of GFR and RPF, respectively. Filtered P was calculated as the product of the inulin clearance and the plasma P. Excreted phosphate was calculated as the product of urine P concentration and urine flow. The difference between filtered and excreted P was considered to be the reabsorbed P.

## RESULTS

In thirteen studies on four normal and one hypoparathyroid subjects P reabsorption was determined at endogenous plasma P levels and following stepwise elevations of the plasma P. In all instances a maximal rate of phosphate reabsorption was reached, and further elevation of plasma P resulted in no further increase in the rate of reabsorption. This result is shown for one normal subject in Table I. Following two

TABLE II  
*Variation of TmP in nine normals and three hypoparathyroid subjects*

Subject	Date	Diet		GFR ml./min.	TmP μM/min.	TmP/GFR μM/ml.	Standard deviation of TmP μM/min.	Coefficient of variation %
		Ca mg./day	P mg./day					
Normal males								
C. H.								
2.00 M**	3-25-54	1,500	1,800	147	199	1.35	25.4	11.5
	4-6-54	130	600(B)†	142	222	1.56		
	11-4-54	130	3,000	148	186	1.26		
	11-10-54	1,570	600(B)	138	238	1.72		
	12-22-54	130	600	146	219	1.50		
	3-14-54	1,500	600	149	256	1.72		
	Mean			145	220	1.52		
W. R.								
1.76 M‡	8-12-54	2,000	2,800	114	122	1.07	25.6	27.6
	3-24-55	800	1,200	112	75	0.67		
	4-4-55	130	600(B)	103	81	0.79		
	Mean			110	93	0.84		
D. F.								
1.94 M‡	1-3-55	610	1,015	115	102	0.89	11.3	12.9
	2-7-55	610	1,015	99	73	0.74		
	Mean			107	88	0.81		
J. N.								
1.91 M‡	6-10-54		900(B)	109	179	1.64	2.7	1.5
	6-22-54	High	High	121	175	1.45		
	Mean			115	177	1.54		
M. L.								
2.10 M‡	12-14-54	High	High	151	159	1.05		
L. B.								
1.91 M‡	11-17-54	High	High	138	125	0.90		
Normal females								
R. H.								
1.78 M‡	1-17-55	130	600	115	137	1.19	14.3	12.4
	2-3-55	1,500	600	112	105	0.94		
	3-3-55	130	1,600	118	120	1.02		
	3-28-55	130	3,000	145	101	0.70		
	4-14-55	2,200	3,000	138	111	1.24		
	Mean			126	115	0.91		
E. E.								
1.82 M‡	5-25-55	130	600(B)	142	185	1.30	9.2	4.8
	6-15-55	1,500	1,800	131	198	1.51		
	Mean			136	191	1.40		
E. P.								
1.77 M‡	3-21-55	Medium	Medium	96	108	1.15		
Hypo-parathyroid								
A. W.								
65 kg.	8-25-54	4,400	1,200	96	158	1.65	11.7	7.1
	9-14-54	2,200	600(B)	88	163	1.85		
	10-20-54	3,300	600	84	172	2.04		
	1-10-55	130	600	95	179	1.88		
	2-21-55	2,200	700	110	149	1.35		
	Mean			95	164	1.75		
L. D.								
B. C.	3-9-55	Inconstant		76	102	1.34		
	2-9-55	2,000	600	73	98	1.34		

\* Surface area.

† (B) = Basaljel.

periods at endogenous plasma P levels, buffered sodium phosphate was administered, and the plasma P and, hence, the filtered P rose. The

initial increase in filtered P noted in periods three and four (148 to 180 minutes, and 180 to 214 minutes) resulted in a rise in both reabsorbed and

excreted P. However, with the further elevation of plasma and filtered P, noted in periods five and six, no increase in reabsorbed P resulted, indicating that a maximal rate of reabsorption had been reached. This relationship between filtered and reabsorbed P is shown in Figure 1, which presents a similar study in a hypoparathyroid subject (A. W.). The constancy of P reabsorption at elevated plasma P levels resulted in a reduction in the ratio of filtered P/reabsorbed P with further increases in the filtered load. This was a consistent finding and is shown for one experiment in the last column of Table I. In both of these studies endogenous urinary P excretion was reduced by the prior administration of a low P diet and aluminum carbonate gel. The Tm phenomenon was also noted in patients not given aluminum carbonate gel.

Repeated determinations of TmP in the same individual over a period of weeks or months indicated considerable variability in most subjects. The mean values of TmP on different days for five normal subjects (C. H., W. R., D. F., J. N., R. H.) and one hypoparathyroid individual (A. W.) are shown in Table II. The standard deviation of the mean and the coefficient of variation are included as indices of the variability. The TmP values listed in Table II were obtained at different dietary levels of Ca and P. The relationship of dietary Ca and P to TmP was investigated. In two normal individuals, C. H. and R. H., intensive studies of the effect of changes in dietary Ca and P on TmP were made, and less complete studies were carried out on four other normal and one hypoparathyroid (A.W.) subjects. Analysis of the results indicated that variations of TmP from one period to another on a given day were about as great as the variations on different dietary regimens in all but two subjects (C. H. and E. P.). Since C. H. was one of the two subjects in whom an extensive study of the effects of changes in dietary Ca and P was made, these results are considered worthy of mention. The highest TmP values were obtained when the patient was on a high Ca-low P intake, (11-10-54, 3-14-55) and the next highest when on a low Ca-low P diet (4-6-54). These results are shown in Table II.

It is of interest that the individuals who showed the greatest variation in TmP between experiments also showed the largest fluctuations within

TABLE III

*Variations of TmP with relative constancy of  $C_{in}$  and  $C_{PAH}$  in two experiments on a normal subject \**

Date	Total concurrent time min.	$C_{in}$ ml./min.	$C_{PAH}$ ml./min.	TmP $\mu M$ /min.
3-24-55	105-141	110	670	61
	141-171	111	652	74
	171-188	114	636	89
4-4-55	128-158	102	522	104
	158-182	101	566	95
	182-214	104	556	44

\* W. R., 22-year-old normal male.

a given experiment. That this does not appear to be due to technically poorer experiments or to overall fluctuations in renal function in these individuals is suggested by the fact that the inulin and PAH clearances did not reveal large changes from period to period. This is illustrated in two experiments on W. R., a normal subject (Table III). It can be seen that although the clearances of inulin and PAH were fairly constant, there is considerable fluctuation in TmP. These results are in contrast to the small variations in TmP in a given experiment noted in some of the other normal subjects. The data suggest that physiological variations in TmP of considerable magnitude may occur over short time intervals.

No consistent change in TmP was noted to occur in the course of an experiment. Although most of the experiments lasted from two to five hours, in two experiments on two normal subjects phosphate was infused for fourteen and eighteen hours. No appreciable change in TmP was noted during, or at the end of this period of time.

Plasma calcium was usually reduced when phosphate was infused, and the degree of reduction appeared to be correlated with the magnitude of the increase in plasma P. In the normal individuals the plasma Ca never fell below 8 mg. per cent, and at no time was tetany produced. In two of the hypoparathyroid individuals mild tetany did result during P infusions.

Although the plasma K was often lowered immediately after a P infusion was begun, there was little change thereafter, and no correlation could be made between changes in plasma K and variations of TmP.

The variability of TmP among the normal indi-

viduals cannot be accounted for by differences in body size (Table II). Calculations of TmP per unit of surface area did not appreciably alter the wide range of values for TmP. The average TmP for the three hypoparathyroid subjects falls within the broad range of values found for the normals (Table II). Insufficient data were obtained to determine whether the variability of TmP on repeated determinations was significantly different than in normal individuals. A single study on one hyperparathyroid subject revealed a mean TmP of  $26 \mu\text{M}$  per min., a figure distinctly lower than that seen in the normal subjects.

No consistent relationship between GFR and TmP was noted (Table II). The variability of the ratio TmP/GFR is greater than that found for glucose (TmG/GFR) by Smith and his co-workers (15). They found that in normal individuals the coefficient of variation for TmG/GFR was 15 per cent. The coefficient of variation for TmP/GFR in the normal subjects included in Table II is 30 per cent.

#### DISCUSSION

Our data are in accord with the observations in the dog (1-5) and in man (6) which indicate that there is a maximal rate of phosphate reabsorption by the renal tubules. These results are in contrast to those obtained by Smith, Ollayos, and Winkler (7), Eggleton and Shuster (8), and Crawford, Gribetz, and Talbot (9), who found increased P reabsorption with increased filtered P without any apparent Tm. Furthermore, our results do not indicate that P reabsorption is conditioned by GFR at elevated plasma P levels such that a constant fraction of filtered P is reabsorbed. Were this conditioning to exist, the ratio, P reabsorbed/GFR, would remain constant. The data in Table II indicate that this ratio is quite variable.

It is apparent that there is a considerable variability in TmP in a given individual and between individuals. For the most part this variability remains unexplained. The attempt to correlate TmP with the dietary level of Ca and P in our studies has been inconclusive. A correlation between the level of phosphate in the diet and phosphate reabsorption has been demonstrated in rats (16), dogs (17) and newborn infants (18). A high level of P intake was associated with a reduction in P reabsorption. Our failure

to demonstrate a clear-cut effect on TmP with an elevated P intake may be related to the fact that the amount of dietary P per kg. of body weight was lower than that achieved in rats (16) and in infants (18). That factors other than diet influence phosphate reabsorption is known. Roberts and Pitts showed that the administration of cortisone to dogs consistently reduced TmP (19). A reduction in TmP with prolonged P infusions has been shown by Michie (20) and by Hogben and Bollman (2). The latter workers showed in studies on dogs that this reduction was usually accompanied by a decrease in plasma K, and that addition of K to the infusion reversed the drop in Tm. In the occasional instance in our studies where TmP fell during an experiment there was no associated decrease in plasma K. Our experiments were usually short in comparison with those of Hogben and Bollman, and it is possible that we might have seen reductions in TmP and plasma K if the experiments had been prolonged. However, in two experiments on two normal subjects in which prolonged P infusions were given no decrease in TmP was noted. Clearly, our data do not reveal the cause of fluctuations in TmP. Elucidation of these factors will require further experimentation.

The range of values for TmP in this group of normal subjects makes the use of any average figure of little value and indicates the necessity of using the subject as his own control in any study designed to evaluate factors influencing TmP. Furthermore, the uncontrolled and unexplained "spontaneous fluctuations" in TmP make it apparent that small changes in TmP cannot be accepted as significant without critical analysis of control studies.

Certain considerations of the mechanism of phosphate reabsorption are pertinent to an evaluation of our data. The reabsorption of phosphate, like that of glucose, shows a limited maximal transfer rate. However, differences exist in the transfer characteristics of these two substances. Whereas the maximal rate of glucose transport is quite constant in any one individual and between individuals (when differences in body surface area are taken into consideration), the maximal rate of phosphate reabsorption is more variable. What is the significance of this fact? The maximal rate of glucose reabsorption is considerably

greater than is required for total reabsorption even with physiological variations in load. Thus, the kidney serves to conserve the body stores of glucose and is not normally an important regulator of plasma concentration. On the other hand, the  $T_m$  for phosphate is only slightly greater, and in some instances no greater, than reabsorption at endogenous plasma levels. Hence, relatively small changes in  $T_m$  would be expected to affect the plasma concentration of phosphate, whereas this would not be true for glucose. It may be postulated that the considerable variability of  $T_mP$  is due to factors which act upon the phosphate transport mechanism to alter reabsorption of phosphate, thus providing an important mechanism for the regulation of plasma phosphate concentration. Our studies and those of others have indicated that a parathyroid hormone is one factor of importance in the regulation of phosphate transport in the renal tubule (4, 21-23).

A consideration of maximal reabsorptive and secretory rates in the renal tubules led Shannon to a general kinetic analysis for  $T_m$  substances (24). Similar kinetic considerations apply to any enzyme-catalyzed reaction where the reaction rate reaches a maximum value with increasing substrate concentration (plasma concentration) because of enzyme saturation. The maximal rate of renal tubular transport of any substance ( $T_m$ ) may be visualized as that rate which is observed when the enzyme system(s) involved is saturated with regard to substrate. Since factors (*e.g.*, parathyroid hormone) other than substrate concentration may influence the activity of the enzyme system it is not surprising to find that variations in  $T_m$  values occur. It seems likely that an explanation of the variability of  $T_mP$  will require an understanding of the mechanisms by which substances exert their effects on the enzymes involved in phosphate transport.

#### SUMMARY AND CONCLUSIONS

1. A maximal renal tubular rate of reabsorption of phosphate ( $T_mP$ ) has been demonstrated in normal and hypoparathyroid subjects.

2. In man considerable variability in  $T_mP$  often occurs within a given experiment and also between experiments. This variability remains unexplained.

3. Dietary variations in calcium and phosphorus

produced no consistent changes in  $T_mP$ . Data in one subject suggested that  $T_mP$  is greatest when the dietary level of P is low, and least when dietary P is high.

4. Comparison of  $T_mP$  between normal individuals indicated a wide range of values.

5. The values for  $T_mP$  in hypoparathyroid subjects fell within the broad range of normal. The  $T_mP$  in one hyperparathyroid subject fell below the normal range.

6. Because of the variability of  $T_mP$  in a given individual and between individuals each subject must serve as his own control in any study designed to determine the influence of an experimental regimen on phosphate reabsorption.

7. The possible significance of the variability of  $T_mP$  is discussed in relation to current concepts of transport mechanisms.

#### ACKNOWLEDGMENTS

We wish to express our gratitude to Misses Mary Margaret Brown and Doris Graves for their technical assistance.

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### ANNOUNCEMENT OF MEETING

The 49th Annual Meeting of the American Society for Clinical Investigation will be held in Atlantic City, New Jersey, on Monday, May 6, 1957, with headquarters at the Chalfonte-Haddon Hall. The scientific session will begin at 9 A.M. at the Steel Pier Theater.