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#### PHOSPHORUS EXCRETION IN RENAL FAILURE 1

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The kidney provides a sensitive mechanism which aids in the maintenance of phosphorus equilibrium despite varying intakes and alterations in metabolic demand. Under normal conditions a large proportion of the phosphorus which is filtered at the glomerulus is reabsorbed by the tubules which thereby effect regulation of the urinary phosphorus (1). Few studies have been performed on patients or animals to determine how phosphorus homeostasis is maintained as renal function is progressively decreased (2, 3). It is well known that the concentration of serum inorganic phosphorus increases and of calcium decreases as renal failure becomes more pronounced (4-6), and that anatomical changes occur in the parathyroid glands which suggest hyperfunction of these organs (7). parenteral administration of parathyroid hormone produces an increased phosphaturia, a decrease in the serum phosphorus, and an increase in the serum calcium, it is possible that the parathyroid hyperplasia represents a physiologic attempt to reverse these specific effects of renal failure (8). It seemed appropriate, therefore, to investigate the relationship of phosphate clearance to the general level of renal function and to test the response to exogenous parathyroid hormone at all gradations of renal impairment to determine whether a further response was possible or whether maximal effectiveness had been achieved by endogenous hormone activity.

#### MATERIALS AND METHODS

A series of twenty males between the ages of 25 and 60 years was selected. Their glomerular filtration rates as measured by inulin clearance varied from 142 to 1.5

ml. per minute, and covered the entire range of renal function from normal to advanced uremia. Those with reduced renal function had various diseases, chiefly chronic glomerulonephritis and chronic pyelonephritis. The patients with normal kidneys had been maintained on the regular hospital diet which provided 90 to 100 grams of protein and about 1.5 grams of phosphorus per day. Most of the patients with reduced renal function had ingested a diet in which the protein was restricted to about 40 grams and the phosphorus intake to approximately 0.75 grams per day.

Clearances were performed during the postabsorptive state and the glomerular filtration rate was measured by the use of inulin in all but four experiments in which the endogenous creatinine clearance was substituted. Three control periods of approximately 20 minutes each were obtained 30 minutes after the injection of the priming dose of inulin. Blood was drawn for the determination of serum inulin and phosphorus at the midpoint of each clearance period. During the fourth 20-minute period 500 units of parathyroid hormone 2 (Lilly) was given by slow intravenous injection. Three additional 20minute clearance periods were obtained following the administration of the hormone. A satisfactory rate of urine flow was maintained by the administration of 500 ml. of fluid in the inulin-sustaining solution and by the ingestion of about 200 ml. of water every hour. Completeness of urine collection was assured by two consecutive bladder irrigations with 20 ml. of distilled water followed by 20 ml. of air. The concentration of inulin in the plasma and urine was determined by the resorcinol method of Schreiner (9), creatinine by the method of Bonsnes and Taussky (10), and phosphorus by the method of Fiske and SubbaRow (11).

Glomerular filtration of phosphorus (GFP) was assumed to be the product of the serum inorganic phosporus concentration and the glomerular filtration rate, and has been expressed in milligrams of phosphorus filtered per minute. The filtered phosphorus which did not appear in the urine presumably was reabsorbed by the tubules (TRP). The TRP is thus the difference between the GFP and the urinary phosphorus (UP).

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<sup>&</sup>lt;sup>2</sup> The evening before the clearances were performed, 0.1 ml. of a 1:1000 dilution of parathyroid hormone was injected intradermally as a test for possible sensitivity. The few patients who showed positive skin reactions were excluded.

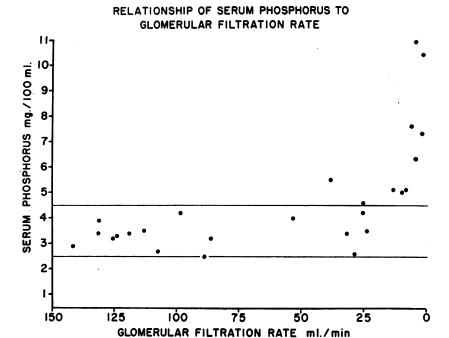


Fig. 1. The Relationship of the Serum Phosphorus to the Glomerular FILTRATION RATE

The open circles are derived from the data of Kleeman and Cooke (2).

TABLE I Renal excretion of phosphorus at varying levels of renal function \*

Patient	Age	Serum P mg./ml.	Urine vol. ml./min.	Urine P mg./min.	GFR ml./min.	GFP mg./min.	TRP mg./min.
R. N. L.	54	0.030	1.60	0.19	141	4.20	4.01
E. A. B.	43	0.033	1.07	0.31	129	4.20	3.89
E. L. S.	26	0.032	4.88	0.33	123†	3.86	3.54
G. T. H.	41	0.027	5.26	0.17	97.4	2.61	2.44
R. S.	51	0.043	2.87	0.47	86.7	3.72	3.25
T. K.	55	0.032	1.50	0.80	83.5	2.69	1.89
W. A. B.	66	0.024	3.29	0.41	89.0	2.15	1.74
J. G. G.	40	0.039	6.42	0.80	53.0	2.06	1.25
K. R.	33	0.058	2.36	0.64	38.1	2.19	1.55
S. T.	34	0.033	2.94	0.45	32.2	1.06	0.61
G. M. D.	26	0.025	3.01	0.45	27.6	0.70	0.25
I. R. D.	37	0.035	1.21	0.41	23.8	0.82	0.42
R. S.	41	0.043	0.85	0.48	23.6	1.02	0.54
E. S.	31	0.045	1.45	0.36	25.7†	1.16	0.80
G. O.	54	0.053	2.08	0.61	14.2	0.75	0.14
J. R. T.	56	0.048	2.47	0.28	9.0	0.43	0.15
C. E. D.	65	0.052	0.90	0.36	8.5	0.45	0.09
C. A.	53	0.077	2.40	0.52	6.3†	0.49	-0.031
R. C.	23	0.107	1.95	0.45	4.7	0.50	0.05
D. E. B.	54	0.104	0.30	0.15	1.5	0.16	0.01

<sup>\*</sup> UP—Urine phosphorus.
GFR—Glomerular filtration rate.
GFP—Glomerular filtrate phosphorus.
TRP—Tubularly reabsorbed phosphorus.
† Creatinine clearance.
† UP exceeded GFP by amount indicated.

#### RESULTS

The data are summarized in the tables and illustrated in two figures. With but one exception, the serum phosphorus remained within the normal range of 2.5 to 4.5 mg. per cent, until the filtration rate was reduced to 25 ml. per minute or below. At filtration rates of less than 15 ml. per minute, none of the serum phosphorus values were normal and they increased markedly as filtration was further reduced. These data have been plotted in Figure 1 which includes a few values (open circles) obtained by Kleeman and Cooke (2).

It is to be noted that there was some reabsorption of phosphorus except possibly in the final stages of renal insufficiency (Tables I and II). There were actually three observations in two uremic patients in which more phosphorus was excreted than was filtered, a circumstance which could occur only if there was some excretion of phosphorus by the tubules. We are inclined to minimize this possibility because in two of the three instances in which the excretion of phosphate exceeded the calculated amount filtered, the filtration rates are based on creatinine clearances. That PTH increased the excretion of urinary phosphorus was apparent in every subject down

to and including one with a filtration rate of 10.6 ml. per minute. Below this point UP so closely approximated GFP that the effect of the hormone was no longer evident. The decreasing response to PTH as renal function declines is visualized in Figure 2, where the ratios UP<sub>2</sub>: UP<sub>1</sub> (after and before PTH administration) are plotted against the GFR. Although there was some response to parathyroid hormone at all levels of function, it should be stressed that this became quite small even prior to gross impairment of glomerular filtration. Substantial increases in urinary phosphorus were observed in four patients whose filtration rates were above 100 ml. per minute, but there was only one instance in which as much as a twofold increase in UP occurred at a lower filtration rate. The absolute amount of phosphorus excreted following PTH was always small, and in only two subjects did it exceed 1.0 mg. per minute. Therefore, the high ratios of UP<sub>2</sub>: UP<sub>1</sub> were dependent upon a very low rate of phosphorus excretion during the control periods.

The factors participating in the production of phosphaturia were an increase in GFR, a decrease in TRP and a combination of these two. In patients with markedly impaired renal function both responses were greatly reduced or absent (Table

TABLE II

Renal excretion of phosphorus after parathyroid hormone administration \*

Patient	Serum P mg./ml.	Urine vol. ml./min.	Urine P mg./min.	GFR ml./min.	GFP mg./min.	TRP mg./min.
R. N. L.	0.029	8.40	0.95	142	4.08	3.13
E. A. B.	0.035	1.15	0.91	136	4.74	3.83
E. L. S.	0.031	7.60	0.83	128†	3.98	3.14
G. T. H.	0.027	4.49	0.69	118	3.18	2.49
R. S.	0.040	4.51	0.86	110.5	4.44	3.58
T. K.	0.032	3.85	1.03	89.8	2.87	1.84
W. A. B.	0.025	6.83	0.68	89.1	2.23	1.55
J. G. G.	0.040	4.31	1.10	54.4	2.18	1.08
K. R.	0.052	5.50	0.66	38.6	2.01	1.35
S. T.	0.034	3.87	0.57	31.7	1.08	0.51
G. M. D.	0.027	4.28	0.62	30.9	0.82	0.21
I. R. D.	0.035	2.30	0.52	24.6	0.85	0.33
R. S.	0.040	1.52	0.64	27.2	1.08	0.44
E. S.	0.046	2.10	0.71	25.6†	1.17	0.46
G. O.	0.049	1.93	0.51	13.1	0.65	0.14
J. R. T.	0.051	4.19	0.35	10.6	0.55	0.19
C. E. D.	0.050	0.88	0.31	7.9	0.40	0.08
C. A.	0.074	1.93	0.51	6.2†	0.44	-0.07‡
R. C.	0.110	1.48	0.36	4.0†	0.44	0.07
D. E. B.	0.103	0.45	0.17	1.4	0.15	-0.01‡

<sup>\*</sup> See Table I for explanation of abbreviations.

<sup>†</sup> Creatinine clearance. ‡ UP exceeded GFP by amount indicated.

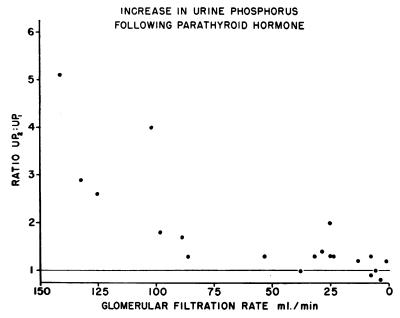


FIG. 2. THE RATIO OF THE RATE OF PHOSPHORUS EXCRETION AFTER PARATHYROID HORMONE ADMINISTRATION TO THE RATE BEFORE HORMONE ADMINISTRATION

III). Otherwise, with the exception of three cases whose clearances were above 85 ml. per minute and in whom an increase in GFR alone was responsible for the rise in urinary phosphorus, there was a measurable and apparently significant decrease in TRP.

TABLE III

Comparison of UP, GFR, and TRP before and after parathyroid hormone administration

Patient	UP2/UP1	GFR <sub>2</sub> GFR <sub>1</sub>	TRP <sub>2</sub> TRP <sub>1</sub>
R. N. L.	5.12	1.01	0.78
E. A. B.	2.89	1.05	0.99
E. L. S.	2.56	1.04	0.89
G. T. H.	3.97	1.21	1.02
R. S.	1.84	1.27	1.10
T. K.	1.28	1.08	0.97
W. A. B.	1.66	1.00	0.89
J. G. G.	1.35	1.03	0.86
K. R.	1.02	1.01	0.87
S. T.	1.27	0.99	0.84
G. M. D.	1.37	1.12	0.83
I. R. D.	1.25	1.08	0.79
R. S.	1.32	1.15	0.81
E. S.	2.00	1.00	0.58
G. O.	1.18	0.92	0.98
J. R. T.	1.25	1.18	1.30
C. E. D.	.87	0.93	0.95
C. A.	.98	0.98	
R. C.	.80	0.85	1.49
D. E. B.	1.10	0.93	

#### DISCUSSION

Ingestion of a normal diet containing 1500 mg. of phosphorus requires the urinary excretion of approximately 750 mg. of phosphorus daily in order to maintain metabolic balance. This is an average of 0.5 mg. per minute. At normal concentrations of serum inorganic phosphorus of 3.5 mg. per 100 ml., a minimum glomerular filtration rate of 14 ml. per minute is required to provide 0.5 mg. of filtered phosphorus. Apparently, the tubules continue to reabsorb filtered phosphorus despite inhibition by the administered PTH and the stress of renal failure. For this reason the GFP must be larger than 0.5 mg, per minute in order to maintain an average urinary phosphorus of 0.5 mg., and the serum phosphorus rises at filtration rates actually higher than 14 ml. more seriously ill patients, the tendency for the concentration of serum phosphorus to increase at filtration rates higher than that stipulated here, is, of course, partially offset by a reduction in the intake of phosphorus. This could, in some cases, have reduced the amount requiring excretion in the urine by as much as 50 per cent. Except for one example of an increase in serum phosphorus at a filtration rate of 38 ml., our information indicates that the critical point lies between 24 and 14 ml. From the data we have accumulated it seems reasonably certain that there is no significant excretion of phosphorus by the tubules and that increases in the concentration of serum phosphorus are required when filtration falls below a minimum set by the load imposed by the dietary intake. Thus, our observations support theoretical curves presented by Gamble (12) which relate the glomerular filtration rate and the required phosphate excretion to the concentration of serum inorganic phosphorus.

The assumption that at high concentrations of serum phosphorus all of the serum inorganic phosphorus is filterable, is supported by the observation that as the GFR decreases with renal disease, GFP and UP tend to become substantially identical. Should any significant amount of the phosphorus be nonfilterable, the true GFP would be less than the amount calculated and hence one would not expect identity between UP and GFP, unless the deficit was supplied by excretion of phosphate by the tubules. The reason for excluding this latter possibility has been commented upon in the presentation of the data. Handler and Cohn (13) have recently published information based upon isotopic studies which also support the concept of complete filterability of the serum inorganic phosphorus.

Although the cause of phosphaturia following the intravenous administration of PTH appears in our experience to be about equally divided between an increased glomerular filtration of phosphorus and a decreased reabsorption by the tubules, and thus tends to substantiate certain other investigations (14, 15), it is conceivable that this dual mechanism may not represent the physiological effects of the parathyroid glands on the kidneys. The increases observed in GFR may be an artefact since it has been found by Handler and Cohn (16) that the subcutaneous injection of parathyroid extract in the dog has little effect on renal hemodynamics yet is still capable of lowering the plasma inorganic phosphate concentration and producing phosphaturia.

If it may be assumed that the response to 500 units of PTH is maximal, then the ratio of increase in phosphorus excretion (UP<sub>2</sub>: UP<sub>1</sub>) depends upon the rate of excretion at the time of

PTH injection. No method for achieving minimal excretion was attempted, so the full range of response could not be determined. By performing the studies during the morning, when minimal excretion is expected (17-19), it was hoped that maximal increases, and, therefore, the largest ratios of increase, would be observed. the relatively normal individuals was there a very low pre-injection rate of excretion followed by a high rate after PTH. Thus, the normal kidney was capable of rapid changes in the rate of phosphorus excretion, a function which appeared to be lost early in renal failure. The response to PTH appears to depend upon both the integrity of this function of the kidney and a low rate of excretion during the period prior to injection. When renal function is grossly impaired, extra-renal mechanisms, notably fluctuations in the serum phosphorus level, affect regulation of phosphorus excretion.

Crawford, Osborne, Talbot, Terry, and Morrill (20) have found that in rats complete parathyroidectomy causes the TRP: GFP ratio to approach 1.0, while parathyroid hormone administration causes this ratio to approach zero. studies upon human subjects with presumably normal renal function showed changes in the anticipated direction after PTH administration, although not reaching the extreme values of the The present data demonstrate animal studies. changes in the same direction. However, as renal function decreases the TRP gradually decreases while the UP remains constant. In complete renal failure the TRP: GFP ratio approaches zero. It cannot be determined whether this is due to maximal physiologic activity of PTH or to a reduction in functioning tubular tissue to the point where no further reabsorption could be expected.

#### SUMMARY

- 1. The excretion of phosphorus was studied in 20 males whose renal function ranged from normal through various gradations of impairment including terminal uremia.
- 2. In an attempt to elucidate the mechanism of phosphorus excretion in the urine as kidney function became progressively worse, simultaneous measurements of inulin and phosphorus clearances

were performed before and after intravenous injection of 500 units of parathyroid hormone.

- 3. Glomerular filtration rates (GFR) varied from 142 to 1.5 ml. per minute. With but one exception, the serum phosphorus remained within the normal range of 2.5 to 4.5 mg. per cent until the GFR was reduced to about 25 ml. per minute. As GFR was further reduced the concentration of serum phosphorus increased markedly.
- 4. Phosphorus filtered at the glomerulus (GFP) was calculated as the product of the concentration of inorganic phosphorus in serum and the volume of glomerular filtrate. Phosphorus reabsorbed by the tubules (TRP) was assumed to be the difference between the filtered phosphorus and the urinary phosphorus (UP).
- 5. Evidence for TRP was found, except in terminal uremia, when GFP closely approximated UP, suggesting a quantitative transfer of phosphorus filtered at the glomeruli to the urine.
- 6. The administration of PTH caused an increase in UP which was apparently due both to an increase in GFR and a decrease in TRP. The responsiveness to PTH was lost in renal disease when the GFR was reduced below 10 ml. per minute. With further renal impairment it was impossible to determine whether there was a pre-existing maximum effect of endogenous PTH or whether the tubules failed to respond.

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