THE INFLUENCE OF BLOOD GLUCOSE ON THE RENAL CLEARANCE OF PHOSPHATE^{1, 2}

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Many factors have been shown to influence the level of inorganic phosphorus³ in the blood (1-5). Among these are glucose and insulin, each of which consistently decreases plasma phosphate (1, 3). Since it has been shown that phosphate excretion is dependent upon plasma phosphate (5), one would expect insulin or glucose to alter phosphate excretion in a predictable manner. However, reports on this point have been very conflicting; decreases (6), increases (1, 7) and no change (8, 9) in phosphate excretion following glucose or insulin have been described.

During the course of studies on the renal effects of glucagon (10, 11), a consistent relationship between blood glucose level and renal phosphate clearance was observed. The purpose of this paper is to define this relationship and to point out its physiologic implications.

METHODS

Studies were carried out in 40 hospitalized ambulatory male patients with no evidence of renal disease. All subjects were studied in the postabsorptive state (14 hour fast). Water was ingested before and during the experiments to assure adequate urine flows. Intravenous infusion of glucose, insulin,⁴ or buffered phosphate (pH 7.4) solutions was accomplished by a Bowman constant infusion pump. In two subjects glucose was administered orally as a 50 per cent solution. In two other subjects tolbutamide (Orinase®, sodium)⁵ was administered as a single intravenous injection over a five minute period. Standard renal clearance techniques were used with endogenous creatinine clearance as a measure of glomerular filtration rate. Phosphate clearance is

expressed as percentage of filtered load excreted, *i.e.*, phosphate clearance times 100 divided by creatinine clearance. All clearance data are corrected to 1.73 square meters of body surface area.

Urine was collected over 10 or 15 minute periods through a multiholed, indwelling catheter and complete collections were assured by multiple water and air wash-outs. Heparinized blood samples were obtained from the antecubital vein through an indwelling needle at the midpoint of each collection period. The samples were centrifuged immediately and plasma removed for analysis.

Creatinine determinations were made by the method of Bonsnes and Taussky (12). The Nelson-Somogyi method was used for blood glucose determinations (13). Urinary glucose was measured by the Benedict quantitative method (14). Phosphate was determined by the method of Fiske and Subbarow (15).

RESULTS

1. Effect of glucose on phosphate clearance

Eighteen subjects received glucose by vein or mouth. Blood sugar was elevated gradually in some, rapidly in others. In all subjects the effect on phosphate excretion was similar. One of these experiments is shown in Figure 1. Note the parallel relationship between blood sugar and phosphate clearance (expressed as percentage of filtered load excreted⁶). The pertinent data on all subjects are given in Table I. Creatinine clearance was not affected by glucose loading. In 16 of the 18 subjects there was a significant positive correlation (R_G)⁷ between blood sugar and phosphate

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³ Hereafter, inorganic phosphorous is referred to as phosphate.

⁴ Insulin free of glucagon (Lot T-3206) kindly supplied by Dr. W. R. Kirtley, of Eli Lilly and Co.

⁵ Kindly supplied by Dr. C. J. O'Donovan, the Upjohn Co.

⁶ The following abbreviations will be used in this report: C_P , renal clearance of phosphate; C_C , renal clearance of endogenous creatinine; P_P , plasma inorganic phosphate; R_G , correlation coefficient relating blood glucose and the percentage of filtered load of phosphate excreted; R_P , correlation coefficient relating plasma phosphate and the percentage of filtered load of phosphate excreted; p , the probability (indicative of significance level) associated with the correlation coefficients.

⁷ Since the experimental data indicated linearity between blood sugar and phosphate clearance in the majority of cases, the linear correlation coefficient was used as an index of the strength of relationship.

TABLE I
Effect of blood glucose on phosphate clearance

Subject	Glucose administration	Time*	Cc†	Pp‡	Cp/Cc§	Blood or plasma sugar	Rg	p¶	Rp	p¶
		min.	ml./min.	mg. %	%	mg. %				
C. M. 37 yrs. 63 Kg.	398 mg./min. I.V.	0	97	2.86	6.1	92	0.97	<0.001	0.01	>0.10
		20.2	91	3.10	8.7	106				
		40.8	96	3.02	13.3	145				
		61.8	96	2.79	14.6	167				
J. L. 54 yrs. 67 Kg.	440 mg./min. I.V.	0	93	3.31	9.8	85	0.96	<0.001	-0.66	0.02
		23.0	93	3.29	13.7	102				
		43.0	93	3.20	18.1	140				
		64.0	97	3.11	21.2	160				
		89.0	95	3.11	22.6	162				
		99.0	91	3.02	18.7	134				
A. T. 32 yrs. 62 Kg.	474 mg./min. I.V.	0	119	2.60	5.4	72	0.96	<0.001	-0.31	>0.10
		19.5	118	2.79	6.2	83				
		37.7	108	2.78	9.7	107				
		57.7	98	2.82	14.4	144				
		68.7	110	2.87	13.4	160				
J. M. 37 yrs. 80 Kg.	150 Gm. Oral	0	94	2.55	11.9	67	0.94	<0.001	-0.53	0.10
		20.1	98	2.63	16.0	81				
		40.2	92	2.64	29.2	129				
		60.1	76	2.39	32.6	142				
		79.9	89	2.27	30.9	130				
A. W. 31 yrs. 79 Kg.	908 mg./min. I.V.	0	115	3.58	20.7	87	0.82	<0.01	-0.42	>0.10
		20.5	113	3.48	25.3	105				
		40.0	101	3.25	37.2	162				
		60.9	103	3.29	34.3	192				
		79.1	95	4.14	32.4	210				
T. T. 32 yrs. 56 Kg.	475 mg./min. I.V.	0	107	2.92	9.0	70	0.81	<0.01	-0.42	>0.10
		19.2	123	2.89	10.8	93				
		39.7	123	2.73	13.0	128				
		59.6	123	2.75	14.3	138				
		80.2	114	2.75	11.3	122				
		89.5	124	2.71	6.7	64				
L. Q. 26 yrs. 64 Kg.	547 mg./min. I.V.	0	105	2.89	17.9	74	0.80	<0.001	-0.44	>0.10
		19.2	107	2.81	21.3	84				
		39.3	108	2.81	23.9	100				
		59.0	107	2.75	24.3	155				
		80.5	102	2.61	29.4	177				
		100.5	103	2.59	24.9	162				
		109.2	104	2.53	19.9	140				
A. J. 30 yrs. 69 Kg.	1,062 mg./min. I.V.	0	109	4.09	8.0	67	0.79	<0.01	-0.84	<0.001
		21.2	113	3.83	13.8	111				
		42.2	105	3.50	30.7	193				
		62.3	111	3.13	29.0	258				
		83.7	109	3.12	25.1	332				
		90.7	98	3.01	23.8	302				

* For the sake of brevity, control values are the mean of at least three 10 minute clearance periods, and all 20 minute periods are the mean values of two 10 minute periods.

† Cc, creatinine clearance.

‡ Pp, plasma phosphate.

§ Cp/Cc, per cent of filtered load of phosphate excreted.

|| Rg, correlation coefficient relating phosphate clearance and blood glucose; Rp, correlation coefficient relating phosphate clearance and plasma phosphate. Correlation coefficients are calculated from the 10 minute period values.

¶ p, significance level.

TABLE I—*Continued*

Subject	Glucose administration	Time*	Cc†	P _b ‡	C _P /C _c §	Blood or plasma sugar	R _G	p¶	R _P	p¶
		min.	ml./min.	mg. %	%	mg. %				
A. C. 29 yrs. 79 Kg.	878 mg./min. I.V.	0	114	2.91	8.6	62	0.93	<0.001	-0.72	0.02
		21.2	121	2.87	12.8	64				
		42.8	108	2.80	22.3	128				
		64.7	107	2.87	26.9	176				
		75.3	111	2.83	23.7	200				
M. A. 49 yrs. 79 Kg.	100 Gm. Oral	0	98	2.45	9.5	89	0.92	<0.001	-0.46	>0.10
		20.8	101	2.44	11.7	90				
		41.1	100	2.28	22.0	132				
		61.5	103	2.20	22.8	143				
		81.2	105	2.08	18.6	140				
M. P. 41 yrs. 67 Kg.	472 mg./min. I.V.	0	130	3.70	6.9	87	0.90	0.001	-0.80	0.02
		20.6	121	3.69	8.9	109				
		40.3	128	3.38	10.0	127				
		50.8	128	3.36	9.4	137				
R. G. 28 yrs. 82 Kg.	15 Gm. I.V.	0	132	3.26	11.9	100	0.89	<0.01	-0.50	>0.10
		28.1	148	3.10	18.0	163				
		56.9	121	3.31	11.1	112				
		71.2	138							
W. N. 26 yrs. 67 Kg.	694 mg./min. I.V.	0	121	3.15	13.5	69	0.85	<0.01	-0.71	0.02
		19.1	127	3.18	20.3	101				
		40.3	125	2.94	27.8	142				
		59.2	127	2.82	24.9	178				
		70.0	120	2.66	26.7	188				
K. Q. 51 yrs. 78 Kg.	477 mg./min. I.V.	0	128	2.76	6.6	69	0.75	<0.01	-0.52	0.08
		24.9	133	2.96	6.8	93				
		46.2	130	2.82	9.7	110				
		69.5	127	2.53	10.7	111				
		89.4	135	2.88	8.0	102				
		101.3	125	3.20	4.2	85				
C. R. 31 yrs. 86 Kg.	507 mg./min. I.V.	0	78	3.91	28.7	85	0.73	<0.01	-0.24	>0.10
		20.5	79	3.97	30.8	100				
		41.4	84	3.55	34.8	127				
		63.3	81	3.54	35.9	135				
		83.7	82	3.36	31.4	123				
		103.4	78	3.17	29.1	81				
C. C. 44 yrs. 82 Kg.	325 mg./min. I.V.	0	93	2.60	3.9	70	0.57	0.06	-0.70	0.015
		19.9	99	2.59	3.4	82				
		40.8	99	2.60	5.7	117				
		61.3	93	2.38	5.6	124				
		81.6	95	2.75	2.8	102				
J. L. 39 yrs. 64 Kg.	1,040 mg./min. I.V.	0	94	2.80	18.2	67	0.41	>0.10	-0.61	0.05
		17.6	104	2.42	30.8	138				
		39.4	81	2.26	39.7	229				
		58.8	79	2.08	34.6	315				
		78.5	71	2.14	28.4	382				
		88.3	61	1.89	28.8	409				
D. L. 23 yrs. 84 Kg.	942 mg./min. I.V.	0	126	2.60	7.1	74	0.24	>0.10	-0.49	>0.10
		19.7	128	2.54	9.1	93				
		40.4	125	2.48	11.6	146				
		60.8	114	2.34	11.1	175				
		79.7	121	2.37	9.0	196				
		100.1	119	2.52	6.9	167

FIG. 1. THE EFFECT OF BLOOD GLUCOSE ON PHOSPHATE CLEARANCE
During the infusion of glucose, phosphate clearance parallels blood glucose but only a slight decrease in plasma phosphate occurs.

clearance. In the remaining two subjects, significant positive correlations were maintained until a maximum level of phosphate clearance was reached (*vide infra*).

In contrast, there was a negative correlation (R_P)⁸ in all but one subject between plasma phosphate and phosphate clearance. This negative correlation was insignificant in 16 of the 18 experiments.

In eight subjects phosphate clearance reached a maximum level despite a progressive increase in blood sugar levels. This phenomenon was a consistent observation in the four subjects who manifested glycosuria. The maximum level of phosphate clearance bore no apparent relationship to blood glucose level and was extremely variable from patient to patient.

II. Effect of insulin and tolbutamide on phosphate clearance

Blood sugar was lowered in five subjects with insulin or tolbutamide (Orinase®, sodium). In no instance did symptoms or signs of hypogly-

cemia develop despite marked blood sugar depression. Creatinine clearances did not change significantly. Figure 2 shows the data from one of the experiments. The results of all these experi-

FIG. 2. THE EFFECT OF INSULIN ON PHOSPHATE CLEARANCE

During the infusion of insulin, phosphate clearance, blood sugar and plasma phosphate behave in a parallel manner.

⁸ Experimental data indicated linearity between plasma phosphate and phosphate clearance over the limited range studied. Hence, the linear correlation coefficient was employed.

TABLE II
*Effect of insulin and tolbutamide (Orinase®) on phosphate clearance **

Subject	Intravenous injections	Time	Cc	Pp	Cp/Cc	Blood or plasma sugar	R _G	p	R _P	p
		min.	ml./min.	mg. %	%	mg. %				
W. H. 64 yrs. 44 Kg.	Insulin 0.093 unit/min.	0 ↓ 20.0 39.7 59.6	89 103 95 98	3.19 2.93 2.45 2.17	10.5 10.7 3.3 0.8	88 78 56 57	0.91	<0.001	0.87	0.001
F. M. 46 yrs. 67 Kg.	Insulin 0.10 unit/min.	0 ↓ 20.2 40.9 60.0	113 120 124 123	3.08 3.09 2.81 2.74	10.0 9.9 6.3 2.3	87 84 70 52	0.99	<0.001	0.82	<0.01
L. S. 30 yrs. 67 Kg.	Insulin 0.096 unit/min.	0 ↓ 18.9 41.0 61.0	109 111 113 118	3.34 3.25 3.07 2.72	13.0 13.7 8.0 5.1	94 90 64 53	0.93	<0.001	0.94	<0.001
L. H. 30 yrs. 75 Kg.	Orinase® 1.5 Gm.	0 → 36.6 56.6 66.1	120 116 123 138	3.16 2.89 2.75 2.78	8.5 2.6 1.3 1.7	107 70 66 77	0.94	<0.001	0.95	<0.001
R. R. 22 yrs. 73 Kg.	Orinase® 2.0 Gm.	0 → 21.2 42.0 61.9	123 120 134 140	2.80 2.37 1.73 1.55	2.6 3.1 0.5 0.5	87 65 42 67	0.64	0.05	0.68	0.05
R. M. 21 yrs. 71 Kg.	Glucose Load, 8 Gm. Infusion, 336 mg./min. Insulin 0.29 unit/min.	0 ↓ 9.7 19.6 29.2 39.8 49.6 59.6 69.8	135 135 125 135 122 130 128 141	2.15 1.60 1.56 1.49 1.44 1.31 1.51 1.54	5.5 4.7 1.9 2.5 1.6 1.2 0.1 0.7	171 162 157 143 121 107 98 91	0.92	<0.001	0.68	0.015
T. C. 43 yrs. 89 Kg.	Glucose Load, 12 Gm. Infusion, 331 mg./min. Insulin 0.17 unit/min.	0 ↓ 9.6 19.6 29.0 39.4 49.0 59.4 69.4 79.4	99 110 122 116 126 134 126 126 127	2.44 2.20 2.17 2.09 2.00 1.92 1.70 1.58 1.52	22.1 20.5 17.0 16.4 11.7 8.0 4.5 3.0 2.2	165 151 147 140 135 131 128 119 118	0.96	<0.001	0.97	<0.001
K. W. 28 yrs. 63 Kg.	Glucose Load, 16 Gm. Infusion, 349 mg./min. Insulin 0.14 unit/min.	0 ↓ 10.8 21.1 31.9 42.3 51.7 62.2 72.3	105 88 116 105 110 106 113 109	3.43 3.11 2.97 2.99 2.94 2.86 2.83 2.90	17.3 24.3 23.2 22.9 20.5 20.8 18.7 16.7	90 186 186 186 176 167 137 131	0.91	<0.001	-0.03	>0.10

* For definitions, see Table I.

† Heavy vertical arrows refer to the insulin infusion period.

TABLE II—Continued

Subject	Intravenous injections	Time	C _G	P _P	C _P /C _G	Blood or plasma sugar	R _G	p	R _P	p
		min.	ml./min.	mg. %	%	mg. %				
G. B. 38 yrs. 61 Kg.	Glucose Load, 16 Gm. Infusion, 352 mg./min. Insulin 0.077 unit/min.	0 22.3 33.0 44.8 56.7 67.4 80.1 91.4 102.0 111.7	127 116 121 128 132 124 118 136 129 136	3.12 2.91 2.70 2.61 2.48 2.36 2.25 2.19 2.26 2.12	4.7 27.5 25.0 13.8 15.0 12.8 9.8 10.2 4.9 3.8	89 179 195 173 168 145 125 114 114 104	0.91	<0.001	0.01	>0.10
C. S. 35 yrs. 67 Kg.	Glucose Load, 8 Gm. Infusion, 185 mg./min. Insulin 0.24 unit/min.	0 11.2 21.7 30.7 41.7 51.0 62.0 72.4	94 96 96 93 94 98 96 98	3.38 3.43 3.14 3.29 2.93 2.90 2.92 2.82	13.6 21.8 19.7 16.1 16.4 15.2 14.3 14.6	81 105 113 113 127 116 109 101	0.43	>0.10	0.10	>0.10

ments are given in Table II. Note that in every case there was a simultaneous decrease in blood glucose, plasma phosphate and phosphate clearance following the control periods. Thus, there was a significant positive correlation between blood sugar and phosphate clearance as well as between plasma phosphate and phosphate clearance.

FIG. 3. THE EFFECT OF GLUCOSE AND INSULIN ON PHOSPHATE CLEARANCE

Phosphate clearance and blood glucose curves are remarkably parallel when blood glucose is lowered by insulin from hyperglycemic levels.

III. Effect of glucose and insulin on phosphate clearance

Five subjects were given glucose followed by insulin. Figure 3 shows the data from one experiment. The results from all these experiments are given in Table II. As in the experiments with glucose alone, phosphate clearance paralleled blood glucose, and significant positive correlations between blood sugar and phosphate clearance were present in four of the five subjects tested. In the remaining subject the correlation was positive but insignificant. Due to a continuous decrease in the plasma phosphate and an initial increase in phosphate clearance (resulting from the glucose load), correlations between plasma phosphate and phosphate clearance were poor. However, this correlation improved following insulin administration.

IV. Effect of phosphate on phosphate clearance

In nine subjects plasma phosphate was elevated by phosphate administration. These results are given in Table III. The correlation between plasma phosphate and phosphate clearance was excellent in all experiments. In two subjects (J. C. and J. P.) plasma phosphate was elevated gradually; in the remaining subjects, it was elevated rapidly. The results of the former experiments are shown in Figure 4. In the group of subjects

TABLE III
Effect of plasma phosphate on phosphate clearance *

Subject	PO ₄ inj., I.V.	Time	C _c	P _p	C _p /C _c	Blood or plasma sugar	R _p	p	R _g	p
		min.	ml./min.	mg. %	%	mg. %				
R. J. 58 yrs. 87 Kg.	221 mg. → 6.2 mg./min.	0	67	2.52	12.7	75	0.87	<0.001	0.81	<0.001
		21.9	75	4.20	61.3	82				
		40.7	79	4.72	54.9	84				
		66.9	76	5.17	51.2	84				
E. S. 36 yrs. 57 Kg.	221 mg. → 6.0 mg./min.	0	98	3.29	6.6	81	0.99	<0.001	0.76	0.02
		21.0	102	6.21	45.4	85				
		43.9	100	6.45	46.8	90				
		64.8	104	6.88	46.9	93				
R. L. 32 yrs. 61 Kg.	190 mg. → 5.2 mg./min.	0	135	3.33	14.1	90	0.86	<0.001	-0.41	>0.10
		19.6	133	4.88	24.1	85				
		40.6	143	5.23	21.2	80				
		62.6	133	5.47	22.8	91				
L. A. 37 yrs. 75 Kg.	158 mg. → 5.1 mg./min.	0	130	3.09	6.2	95	0.98	<0.001	-0.37	>0.10
		21.4	129	4.73	28.7	91				
		41.5	128	5.44	31.4	94				
		52.4	119	5.48	40.4	93				
L. O. 38 yrs. 81 Kg.	158 mg. → 5.8 mg./min.	0	117	2.84	4.3	92	0.99	<0.001	-0.18	>0.10
		21.0	119	4.51	28.8	91				
		44.8	122	4.95	31.3	93				
		55.9	122	5.22	34.3	92				
R. M. 30 yrs. 92 Kg.	158 mg. → 10.0 mg./min.	0	130	1.90	7.0	80	0.98	<0.001	0.21	>0.10
		21.2	134	3.74	34.3	79				
		42.1	138	4.20	46.6	79				
		51.8	143	4.83	47.4	88				
J. N. 24 yrs. 79 Kg.	285 mg. → 5.3 mg./min.	0	127	2.82	8.9	71	0.97	<0.001	0.29	>0.10
		20.2	129	5.59	42.6	70				
		41.8	126	5.56	38.4	76				
		60.7	144	5.67	38.7	80				
J. C. 59 yrs. 71 Kg.	0 mg. → 11.0 mg./min.	0	91	2.38	13.4	94	0.97	<0.001	0.65	0.05
		23.5	105	3.03	20.4	91				
		43.5	107	4.02	35.6	99				
		64.9	97	4.80	42.1	101				
		86.4	100	5.63	45.1	99				
		97.8	93	5.91	50.3	96				
J. P. 36 yrs. 72 Kg.	0 mg. → 10.8 mg./min.	0	102	3.11	8.4	83	0.99	<0.001	0.20	>0.10
		20.1	91	3.68	21.3	82				
		40.0	92	4.78	39.0	86				
		59.9	101	5.20	47.6	82				

* For definitions, see Table I.

in which a priming dose of phosphate was administered, the correlation coefficients were highly significant in all cases despite the excessively high phosphate clearance in the period following the priming dose.

In contrast, the correlation coefficients for blood sugar and phosphate clearance were variable in direction and significance. There were six positive correlations and three negative ones. Only one of the entire group was highly significant.

Creatinine clearances were unaffected by phosphate administration.

V. Effect of phosphate and insulin on phosphate clearance

The data on the three subjects who were given insulin and buffered phosphate solution simultaneously are shown in Table IV. Blood sugar fell in each case as expected. However, plasma phosphate showed a consistent rise rather than the fall which was regularly observed following insulin alone. In all cases the rise in plasma phosphate was accompanied by an increase in phosphate clearance despite the fall in blood glucose.

DISCUSSION

Blood glucose and phosphate clearance

The data show that phosphate clearance consistently parallels the blood glucose level whether it is elevated by glucose administration or depressed by hypoglycemic agents (Figure 5). Thus, the level of venous blood sugar exerts a

FIG. 4. THE EFFECT OF PLASMA PHOSPHATE ON PHOSPHATE CLEARANCE

Phosphate clearance is shown here as a function of plasma phosphate in two subjects who received a continuous infusion of buffered phosphate solution.

sensitive and potent influence on phosphate clearance. This influence appears to operate only up to a certain maximum level of phosphate clearance which varies considerably from patient to pa-

TABLE IV
*Effect of phosphate and insulin on phosphate clearance**

Subject	Phosphate and insulin infusion, I.V.	Time	Cc	Pp	Cp/Cc	Blood or plasma sugar
		min.	ml./min.	mg. %	%	mg. %
L. C. 27 yrs. 90.5 Kg.	Phosphate, 11.4 mg./min. Insulin, 0.11 unit/min.	9.1	118	3.06	7.0	93
		20.0	120	2.90	8.1	90
		30.0	116	3.06	8.6	92
		40.1	128	3.79	7.1	70
		49.9	123	3.84	11.3	62
		60.2	121	3.84	12.7	56
D. C. 32 yrs. 88.2 Kg.	Phosphate, 10.4 mg./min. Insulin, 0.13 unit/min.	10.4	130	2.74	13.3	89
		19.9	136	2.84	11.4	88
		30.9	135	2.95	11.3	87
		40.8	129	2.94	10.2	85
		50.4	131	3.10	17.1	83
		60.7	122	3.26	17.0	80
		74.9	127	3.39	16.0	75
		85.6	126	3.63	14.0	70
		96.4	132	3.92	12.6	68
P. V. 23 yrs. 65.5 Kg.	Phosphate, 11.0 mg./min. Insulin, 0.11 unit/min.	10.7	116	3.55	5.5	83
		20.6	118	3.63	5.3	85
		31.3	115	3.39	5.4	87
		42.1	112	3.87	6.8	87
		50.5	99	4.19	9.8	78
		60.4	126	4.52	9.1	67
		71.1	124	4.42	9.6	50
		83.0	122	4.42	9.1	39
		90.0	106	4.66	7.9	48

* For definitions, see Table I.

† Heavy vertical arrows refer to the insulin infusion period.

FIG. 5. THE RELATIONSHIP BETWEEN PHOSPHATE CLEARANCE AND BLOOD SUGAR

This graph exemplifies the dependence of phosphate clearance on blood glucose over a wide range of values of the latter.

tient. In all cases of glycosuria, phosphate clearance reached this maximum.

There are a number of reports in the literature which support the concept that phosphate excretion is a direct function of blood sugar level. Levitan (7) reported increased phosphate clearances in normal men following the administration of large amounts of glucose. Unfortunately, his experiments were complicated by the occurrence of glycosuria in all subjects. Reiser (1) also observed increased phosphate excretion in normal men following glucose administration. Pitts and Alexander (16) demonstrated that glucose decreased phosphate reabsorption in the dog when plasma phosphate levels were adequate to show a phosphate T_m (maximal rate of renal tubular reabsorption). They suggested that glucose and phosphate compete for reabsorption. The present data indicate a similar competition at normal or depressed plasma phosphate levels.

Not all previous work substantiates the concept that phosphate excretion is a direct function of blood sugar level. Levenson, Adams, Rosen, and Laskey Taylor (9) found no change in P^{32} excretion following a single injection of P^{32} when glucose or insulin was administered to normal men. Decreases in phosphate excretion following glucose have been reported in the dog by Sokhey

and Allan (6). Bachmann, Haldi, Ensor, and Wynn (8) observed no change in urinary inorganic phosphate in the two hour period following ingestion of 50 Gm. of glucose in normal men. These conflicting findings are probably due to the wide variability in experimental methods. It should be pointed out that all studies employing standard renal clearance techniques are in agreement with the present investigation.

Plasma phosphate and phosphate clearance

Several laboratories have shown in the dog and man that phosphate excretion was proportional to plasma phosphate over a wide range (16-18). The present experiments show that a direct relationship between plasma phosphate and phosphate clearance exists in man provided blood glucose level does not increase. A rise in blood sugar results in an increased phosphate clearance even though the plasma phosphate usually decreases; hence, a poor correlation between plasma phosphate and phosphate clearance. A fall in blood sugar from hyperglycemic levels is associated with a fair correlation between plasma phosphate and phosphate clearance, whereas a fall in blood sugar below normal fasting levels is associated with an excellent correlation. The simultaneous

TABLE V
Effect of blood glucose and plasma phosphate on phosphate clearance

		Blood glucose		
		High	Normal	Low
Plasma phosphate	High	Maximum increase*	Increase†	Increase
	Normal	Increase	No change	Decrease*
	Low	Increase	Decrease	Maximum decrease

* Predicted but not studied.

† Increase and decrease refer to the behavior of phosphate clearance.

depression of blood levels of glucose and phosphate results in a depression of phosphate clearance to nearly zero. This depression is prevented at low blood glucose levels if plasma phosphate is not allowed to decrease (Table V).

It would appear from the present experiments that the mechanism of fall in plasma phosphate following insulin differs from that following glucose. The small decrease in plasma phosphate after glucose administration could be explained by the observed increase in phosphate excretion. In contrast, the marked depression in plasma phosphate following insulin is associated with a striking decrease in phosphate excretion. This may be explained by increased phosphate uptake in the tissues or conversion of inorganic phosphate to other phosphate compounds (19-21).

SUMMARY AND CONCLUSIONS

Studies on the influence of blood sugar and phosphate levels on phosphate excretion by the kidney in 40 normal men have been presented. The data indicate that the concentrations of glucose and phosphate in the blood exert powerful, sensitive and independent influences on phosphate excretion by the kidney. At hyperglycemic levels, the influence of blood glucose predominates over that of plasma phosphate, whereas at hypoglycemic levels the influence of plasma phosphate takes precedence. It is concluded that this mechanism may play an important physiologic role in the minute to minute regulation of renal phosphate excretion in man and that other factors (such as insulin) may exert their influence via alteration of blood glucose or phosphate levels.

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