JCI The Journal of Clinical Investigation

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J Clin Invest. 1957;36(4):557-565. https://doi.org/10.1172/JCI103454.

Research Article

THE EFFECTS OF PARATHYROID EXTRACT ON RENAL FUNCTION IN MAN

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

The evidence that parathyroid extract acts directly on bone appears conclusive (1–3). Whether the extract exerts an effect on the kidney, however, has not been so convincingly answered. It has long been known that an increase in urinary phosphate follows the administration of parathyroid extract (4, 5), but the mechanism of the phosphaturia has not been clearly elucidated.

Although the osteoclastic action of parathyroid hormone could effect an increase in urinary inorganic phosphate, it could not simultaneously produce the hypophosphatemia observed in patients with hyperparathyroidism. Inhibition by the hormone of the renal mechanism for conserving phosphate, on the other hand, would account for both a rise in urinary and a fall in plasma phosphate.

Our studies demonstrate that a depression of the maximal renal tubular reabsorptive capacity for phosphate follows the administration of parathyroid extract, although in normal subjects prolonged treatment is required before such an effect is demonstrable.

SUBJECTS AND METHODS

Forty studies were carried out in nine of the normal subjects, the three patients with post-thyroidectomy hypoparathyroidism and the hyperparathyroid male described in the previous paper (6). The experimental procedures have been outlined (6).[3] All of the experiments were performed with the patients in the post-absorptive state.

Four lots of commercial (Eli Lilly & Company) parathyroid extract were used. Each lot was shown to be effective as demonstrated by a rise in serum Ca in at least one subject. Dosage is expressed in U.S.P. units, as assayed by the manufacturer. When given intravenously the hormone was usually administered over a period of 4 to 8 minutes. For the more prolonged studies it was given subcutaneously at 6 to 12 hourly intervals, except where otherwise indicated.

To study the effects of PTH on TmP, buffered sodium phosphate, pH 7.40, was infused until conditions of renal tubular saturation were assured. Simultaneous with the intravenous administration of PTH a sustaining infusion was begun containing, in addition to inulin and PAH, an amount of sodium phosphate calculated to maintain as constant as possible the elevated plasma P level. Thus, observations of the influence of PTH on TmP were permitted without the possible interference of rapidly changing plasma levels.

RESULTS

Acute effects of intravenous parathyroid extract at endogenous levels of plasma P

A rise in urinary phosphate occurred immediately following the intravenous administration of 200 to 1,000 units of PTH both to normal (Figure 1) and to hypoparathyroid (Figure 2) subjects. A typical study in a normal subject is outlined in Table I, while data from studies in three normal subjects are summarized in Table II. In two of the normal individuals, C. H., and J. N., the rise in urinary P occurred as a result of an increase in filtered P, which in turn, was caused by an increase in GFR. Phosphate reabsorption was increased in one subject and unchanged in the other. In the third normal individual, E. E., the increase in excreted P could be accounted for by a decrease in tubular reabsorption of P (Table II). No change in serum calcium was observed during the 2 to 4 hours following the administration of PTH. Flushing frequently followed the intravenous administration of PTH, and transient headache was an occasional complaint. A mild and brief tachycardia often occurred, but no changes in temperature or blood pressure were observed. There was

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[3] The following abbreviations will be employed: GFR, glomerular filtration rate; RPF, effective renal plasma flow; C_{In}, inulin clearance; C_{PAH}, para-amino-hippurate clearance; Tm, maximal renal tubular transport rate; PTH, parathyroid extract; Ca, calcium; P, inorganic phosphate.

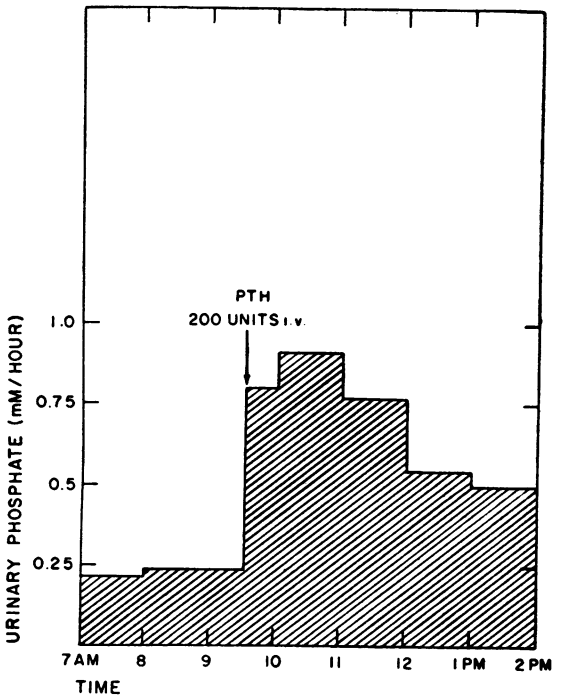

FIG. 1. URINARY PHOSPHATE EXCRETION BEFORE AND FOLLOWING THE INTRAVENOUS ADMINISTRATION OF 200 UNITS OF PARATHYROID EXTRACT TO R. H., A 24-YEAR-OLD NORMAL FEMALE

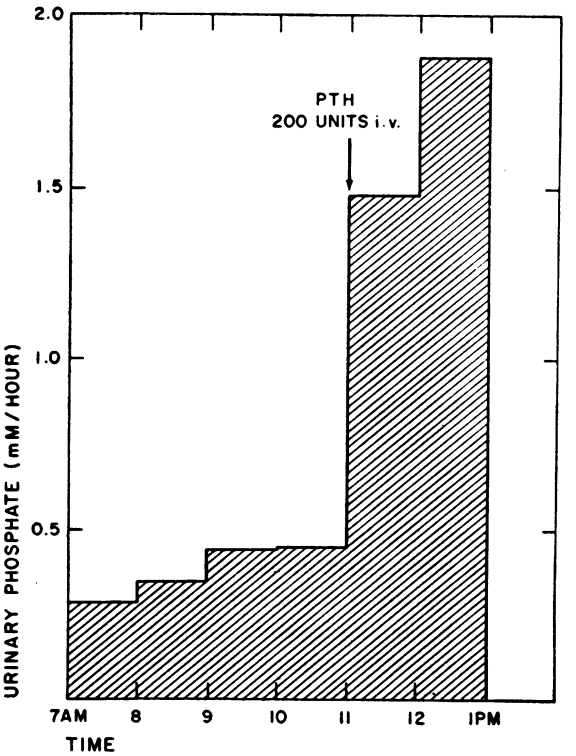

FIG. 2. URINARY PHOSPHATE EXCRETION BEFORE AND FOLLOWING THE INTRAVENOUS ADMINISTRATION OF 200 UNITS OF PARATHYROID EXTRACT TO L. D., A 52-YEAR-OLD FEMALE WITH POST-OPERATIVE HYPOPARATHYROIDISM

no evidence of sensitization or resistance, even in subjects who received several injections over a period of twelve months.

Acute effects of intravenous parathyroid extract under conditions of phosphate loading

As was noted at endogenous plasma P levels, no constant change in renal tubular reabsorption of P resulted from the administration of PTH to subjects receiving P infusions (Table III). If in the study summarized in Table III one selects two periods with comparable levels of plasma P, *e.g.*, the 6th, before the administration of PTH, and the 7th, after PTH was given, one notes that after PTH the excretion of P is increased. The rise in urinary P is ascribable to an increase in filtered P, the reabsorbed P remaining unchanged. Similar findings were noted in nine studies in five normal subjects (Table IV). The levels of TmP following the administration of PTH did not differ significantly from those seen prior to the administration of the hormone (Figure 3). D. F., who showed the greatest fall in TmP following PTH, was unique among the subjects studied in that spontaneous variations of his TmP of similar magnitude were observed on occasions when no medication was given. With but one exception a rise in GFR followed the intravenous administration of PTH, and on all occasions a striking rise in renal plasma flow was observed (Table IV). In almost all normal subjects the rise in GFR was adequate to account for the observed increase in P excretion.

In the hypoparathyroid subjects, on the other hand, the rise in urinary P which followed the administration of PTH resulted not only from an increase in filtered P, but from a striking diminution in the reabsorbed P as well (Table V). A fall in TmP was seen in all three hypoparathyroid subjects, although in A. W. a negligible decrease in response to PTH was observed on one occasion (Figure 4). The same slight but consistent rise in GFR and striking increase in RPF noted in

TABLE I

EFFECTS OF INTRAVENOUS PARATHYROID EXTRACT ON RENAL FUNCTION AT ENDOGENOUS PLASMA PHOSPHATE LEVELS

ELAPSED TIME Min.	C_{PAH} ml/min.	C_{IN} ml/min.	PLASMA P μM/ml.	PHOSPHATE		
				FILTERED μM/min.	EXCRETED μM/min.	REABSORBED μM/min.
82–106	535	122	1.01	123	8	115
106–123	518	108	1.04	113	7	106
123–152	458	106	1.03	109	6	103
152–189	838	138	1.00	138	20	118
189–217	825	130	0.96	125	24	101

J. N., 22 year old normal male.
Sustaining inulin infusion begun at 51 min.
155 – 160 min., 1000 USP units of parathyroid extract i.v.

TABLE II

ACUTE EFFECTS OF INTRAVENOUS PARATHYROID EXTRACT AT ENDOGENOUS PLASMA PHOSPHATE LEVELS IN NORMAL INDIVIDUALS

Subject	Units of Extract	C_{PAH} ml/min.		C_{IN} ml/min.		Plasma P μM/ml		Phosphate μM/min.					
								Filtered		Excreted		Reabsorbed	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
C.H.	800	550	674	121	145	1.12	1.27	136	184	2	15	134	169
E.E.	800	620	930	130	131	1.08	1.06	140	139	3	18	137	121
J.N.	1000	502	832	112	134	1.03	0.98	115	131	7	22	108	109

TABLE III

EFFECTS OF INTRAVENOUS PARATHYROID EXTRACT ON RENAL FUNCTION DURING PHOSPHATE LOADING

Period	Elapsed Time min.	Urine Flow ml/min.	C_{PAH} ml/min.	C_{IN} ml/min.	Plasma P μM/ml	Phosphate μM/min.		
						Filtered	Excreted	Reabsorbed
	0	Inulin, PAH infusion begun.						
1	41 – 59	5.45	538	142	1.09	155	4	151
2	59 – 75	8.00	500	135	1.07	144	4	140
	76	Inulin, PAH, buffered sodium phosphate infusion begun.						
3	109 – 139	8.90	543	140	2.16	302	92	210
4	139 – 170	5.00	502	142	2.52	358	152	206
5	201 – 221	4.85	463	130	3.53	459	262	197
6	221 – 243	3.18	500	141	4.02	566	329	237
	244	Maintenance inulin, PAH, phosphate infusion begun.						
	247 – 251	200 USP units of parathyroid extract i.v.						
7	279 – 301	3.45	652	152	4.15	625	386	239
8	301 – 319	2.56	591	144	4.10	590	348	242

C.H. 17-year old normal male.

TABLE IV

ACUTE EFFECTS OF INTRAVENOUS PARATHYROID EXTRACT ON RENAL FUNCTION IN NORMAL SUBJECTS

Date	Subject	Units of Extract	C_{PAH}			C_{IN}			TmP		
			Before ml/min.	After ml/min.	Percent Change	Before ml/min.	After ml/min.	Percent Change	Before μM/min.	After μM/min.	Percent Change
3/25/54	C. H.	200	682	670	− 11	149	149	0	190	215	+ 13
4/ 6/54	C. H.	200	500	620	+ 24	138	148	+ 7	217	241	+ 11
7/13/54	C. H.	500	763	865	+ 13	151	164	+ 9	138	145	+ 5
9/ 7/54	C. H.	500	561	810	+ 44	135	148	+ 10	297	204	− 15
5/25/54	E. E.	900	627	1048	+ 67	135	153	+ 13	169	208	+ 23
6/10/54	J. N.	1000	475	725	+ 53	106	118	+ 11	177	157	− 11
6/22/54	J. N.	1000				124	137	+ 10	176	185	+ 5
3/11/55	D. F.	500	387	620	+ 60	91	99	+ 9	82	59	− 28
3/31/55	E. P.	500	537	741	+ 38	96	118	+ 23	99	127	+ 28

normal subjects occurred in the hypoparathyroid patients (Table VI).

The acute administration of PTH had no discernible immediate effect on plasma calcium or potassium or on urinary calcium in any of the subjects.

Effects of prolonged treatment with parathyroid extract

Hyperparathyroidism was induced in five normal subjects on six occasions and in two hypoparathyroid patients by the administration of 1,800 to 4,500 units of extract over periods of 60 to 120 hours. In all subjects hypercalcemia, hypophosphatemia, and an increase in urinary calcium and phosphate were observed (Table VII). Two subjects complained of mild skeletal pain, anorexia, polydipsia, polyuria, and constipation.

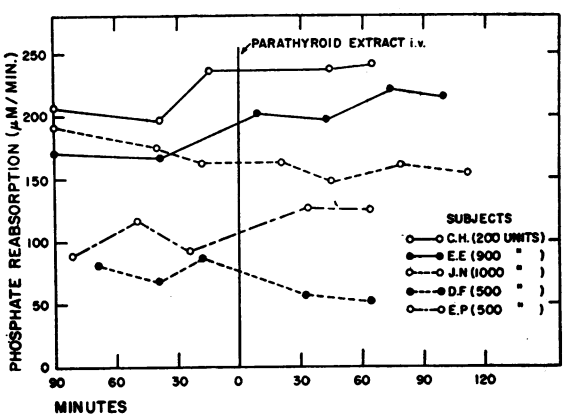

FIG. 3. VARIATIONS IN TmP IN FIVE NORMAL SUBJECTS BEFORE AND FOLLOWING THE INTRAVENOUS ADMINISTRATION OF PARATHYROID EXTRACT

These symptoms, as well as the chemical abnormalities rapidly disappeared after discontinuation of the hormone.

The hyperparathyroid state was characterized by a depression of TmP in both normal (Table VIII) and hypoparathyroid (Table IX) subjects. The fall in TmP ranged from 27 to 64 per cent below control levels (Table X). In W. R. on one occasion (5/6/55) the TmP was reduced by parathyroid extract to the level observed in the only patient with spontaneous hyperparathyroidism studied. The latter, a 72-year-old male with a plasma Ca of 14.05 mg. per 100 ml. and a plasma P of 0.53 μM per ml. was found to have a TmP of 26 μM per minute.

The effect of the prolonged administration of parathyroid extract on C_{In} and on C_{PAH}, in contrast to the results in the acute studies, was inconstant (Table X).

Renal function studies were carried out in a hypoparathyroid patient in the untreated state (plasma Ca, 7.10 mg. per cent; P, 1.42 μM per ml.), in an "isoparathyroid" state, following the daily administration of 100 units of extract for 5 days (plasma Ca, 10.05; P, 1.10), and in a hyperparathyroid state, following the daily administration of 900 units of extract for 3 days (plasma Ca, 12.90; P, 0.68). Average TmP values of 170, 150, and 70 μM per minute, respectively, were found at these times (Figure 5). In a similar series of studies in a second hypoparathyroid subject, B. C., a progressive lowering of TmP with increasing doses of extract was again noted (Table XI). Of interest is the fact that 100 units of parathyroid extract daily for 3 days served to

TABLE V

ACUTE EFFECTS OF PARATHYROID EXTRACT ON RENAL FUNCTION IN HYPOPARATHYROIDISM

ELAPSED TIME Min.	C_{PAH} ml/min.	C_{IN} ml/min.	PLASMA P μM/ml	PHOSPHATE		
				FILTERED μM/min.	EXCRETED μM/min.	REABSORBED μM/min.
77– 97	345	80.0	2.26	181	79	102
97–116	316	73.0	2.60	190	96	94
116–136	315	75.5	3.00	226	116	110
159–192	711	84.0	2.80	235	177	58
192–216	625	90.0	2.57	231	183	48

L. D., 52 year old female, post-operative hypoparathyroidism.
Continuous infusion of buffered sodium phosphate and inulin.

137 – 145 min., Parathyroid extract, (Lilly no. 628857), 500 USP units i.v.

lower B. C.'s plasma P and TmP without altering the level of plasma Ca. Hyperparathyroidism was induced in this subject by intermittent intravenous administration of extract.[4] This was the only one of the prolonged studies reported in hypoparathyroid patients in which PTH was given by other than the subcutaneous route. D. F. and W. R., two normal subjects, received three successive daily infusions, each containing 1,500 units of extract, and each given intravenously over a six-hour period. No effect on plasma Ca or P or on TmP (measured 15 hours after the last infusion of PTH) was observed. In W. R., an equal quantity of the same lot of hormone given in repeated *subcutaneous* injections over a similar period produced marked hyperparathyroidism (Table VII).

DISCUSSION

Two explanations have been offered for the increase in urinary phosphate usually observed following the administration of parathyroid extract. The evidence supporting these hypotheses, an increase in the load of phosphate filtered through the kidney, on the one hand, and a diminution in the tubular reabsorption of phosphate, on the other, has been summarized by Bartter (8). The rise in filtered phosphate has been ascribed to an increase in glomerular filtration rate, to a rise in plasma phosphate, or to both (9–11). Indeed, the demonstration that phosphaturia follows the administration to animals of formalin-inactivated (as assayed by its effect on serum calcium) parathyroid extract has been interpreted as indicating that the observed increase in urinary phosphate is an artifact ascribable to some non-hormonal component of an exceedingly heterogeneous preparation (12).

Our data indicate that the phosphaturia seen immediately following the intravenous administration of the extract to normal individuals is the result of an increase in GFR with a consequent

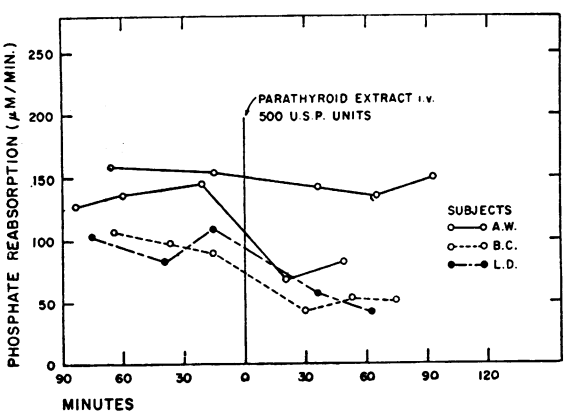

FIG. 4. CHANGES IN TmP FOLLOWING THE ADMINISTRATION OF PARATHYROID EXTRACT TO THREE SUBJECTS WITH HYPOPARATHYROIDISM

[4] The fall in C_{In} in this subject in the hyperparathyroid state was believed ascribable to mild congestive heart failure, a state known to be accompanied by a reduced GFR (7). Digitalis, with which she had been treated for signs of failure noted one year previously, had been omitted prior to the administration of parathyroid extract.

TABLE VI

ACUTE EFFECTS OF INTRAVENOUS PARATHYROID EXTRACT ON RENAL FUNCTION IN HYPOPARATHYROIDISM

Date	Subject	Units of Extract	C_{PAH}			C_{IN}			T_mP		
			Before ml/min.	After ml/min.	Percent Change	Before ml/min.	After ml/min.	Percent Change	Before μM/min.	After μM/min.	Percent Change
8/25/54	A. W.	500				96	103	+ 7	158	142	- 10
2/25/55	A. W.	500	498	852	+ 71	108	113	+ 5	137	75	- 45
2/22/55	B. C.	500	230	418	+ 75	63	69	+ 10	98	50	- 49
3/9/55	L. D.	500	325	668	+ 102	75	87	+ 16	99	51	- 48

TABLE VII

EFFECTS OF PROLONGED ADMINISTRATION OF PARATHYROID EXTRACT ON PLASMA AND URINARY CALCIUM AND PHOSPHORUS

Subject	Total Units of Extract	Hours of Administration	Plasma Ca mg. percent		Plasma P μM/ml		Urine Ca μgm/min.		Urine P μM/min.	
			Before	After	Before	After	Before	After	Before	After
Normal										
C. H. 7/13/54	4000	60	9.80	13.50	1.23	1.02			9	52
W. R. 8/19/54	4500	72	10.02	13.90	0.96	0.73			23	52
W. R. 5/6/55	4000	72	9.40	15.20	0.98	0.63	280	420	7	27
E. P. 3/31/55	2500	120	10.60	12.90	1.17	0.68	213	506	8	20
L. B. 11/22/54	2100	72	9.20	12.00	0.90	0.70	257	444	16	24
W. H. 10/22/54	1800	66	8.60	11.31	1.23	0.96	161	212	9	25
Hypoparathyroid										
A. W. 9/30/54	3000	96	7.10	12.90	1.42	0.68	35	90	0.9	21
B. C. 2/24/54	2500	60	8.08	11.95	1.35	0.74				

TABLE VIII

RENAL EXCRETION OF PHOSPHATE BEFORE (A) AND AFTER (B) ADMINISTRATION OF 1500 USP UNITS OF PARATHYROID EXTRACT DAILY FOR 3 DAYS

	ELAPSED TIME Min.	C_{PAH} ml/min.	C_{IN} ml/min.	PLASMA P μM/ml.	PHOSPHATE		
					FILTERED μM/min.	EXCRETED μM/min.	REABSORBED μM/min.
A	80 – 109	570	100	2.43	243	104	139
	109 – 139	580	102	2.74	279	143	136
	139 – 169	555	106	3.05	324	181	143
B	183 – 222	684	124	2.36	292	214	78
	222 – 243	665	107	2.61	279	225	54
	266 – 293	576	111	2.33	259	213	46

W. R. 22 year old normal male.
Continuous infusion of buffered sodium phosphate and inulin.

rise in filtered phosphate. In hypoparathyroid subjects the relative increase in phosphate excretion is even more striking, for in such individuals parathyroid extract produces not only a rise in filtration rate, but a depression of tubular reabsorption of phosphate as well. Repeated subcu-

TABLE IX

RENAL EXCRETION OF PHOSPHATE BEFORE (A) AND AFTER (B) ADMINISTRATION OF 900 USP UNITS OF PARATHYROID EXTRACT DAILY FOR 3 DAYS

	ELAPSED TIME Min.	C_{PAH} ml/min.	C_{IN} ml/min.	PLASMA P μM/ml.	PHOSPHATE		
					FILTERED μM/min.	EXCRETED μM/min.	REABSORBED μM/min.
A	168 – 205	86	86.5	2.65	229	60	169
	205 – 232	95	86.0	3.17	272	98	174
	265 – 296	95	82.5	4.36	360	188	172
B	165 – 195	206	131	1.77	232	163	69
	228 – 256	218	133	2.35	312	267	45
	256 – 286	212	129	3.07	396	295	101

A. W., 37 year old hypoparathyroid male.
Continuous infusion of inulin and buffered sodium phosphate.

TABLE X

EFFECTS OF PROLONGED ADMINISTRATION OF PARATHYROID EXTRACT ON RENAL FUNCTION

Subject	Total Units of Extract	Hours of Administration	C_{PAH}			C_{IN}			TmP		
			Before ml/min.	After ml/min.	Percent Change	Before ml/min.	After ml/min.	Percent Change	Before μM/min.	After μM/min.	Percent Change
Normal											
C. H. 7/13/54	4000	60	550	763	+ 39	135	151	+ 12	200	138	- 31
W. R. 8/19/54	4500	72	585	728	+ 24	113	121	+ 7	122	63	- 48
W. R. 5/ 6/55	4000	72	558	568	+ 2	102	95	- 7	81	29	- 64
E. P. 3/31/55	2500	120	537	430	- 20	96	85	- 11	110	64	- 42
L. B. 11/22/54	2100	72	846	837	- 1	136	131	- 4	124	91	- 27
W. H. 10/22/54	1800	66	904	889	- 2	125	129	+ 3	179	118	- 34
Hypoparathyroid											
A. W. 9/30/54	2700	72	157	200	+ 27	96	129	+ 34	175	72	- 59
B. C. 2/24/54	2500	60	236	232	- 2	74	57	- 23	131	56	- 57

taneous administration of extract, however, both to normal and to hypoparathyroid subjects induces a state of hyperparathyroidism, characterized by an invariable and striking diminution in TmP. No effort was made to determine the minimal period of extract administration required before a tubular effect is demonstrable in normal individuals; sixty hours was the shortest duration of an experiment involving the subcutaneous administration of hormone, and a 31 per cent decrease in TmP was observed. Why the tubular effect is more readily demonstrable in the hypoparathyroid than in the normal individual is unknown, but this phenomenon may have a parallel in the increased sensitivity to small amounts of thyroid noted in patients with myxedema (13).

Of considerable interest is the fact that the induced hyperparathyroid state in several of our subjects was not accompanied by a rise in GFR or in RPF. These observations strengthen the thesis that the factor in parathyroid extract exerting an action on renal hemodynamics is distinct from the hormonal principle(s) responsible for hypercalcemia and a reduction in TmP. While our data support the concept that the phosphaturia seen in normal subjects immediately after the intravenous administration of PTH is not the result of changes in renal tubular transport of phosphate, they also demonstrate that under appropriate conditions tubular reabsorption of phosphate is profoundly inhibited by the hormone. Similar findings have been noted in the dog by Handler and Cohn (14).

The fact that prolonged administration of the extract is required to depress TmP in normal individuals raises the question as to whether the

TABLE XI

EFFECTS OF PARATHYROID EXTRACT IN HYPOPARATHYROIDISM (B. C.)

Date	Parathyroid Extract	Time Elapsed min.	Urine Flow ml/min.	Plasma Ca mg. %	Plasma P μM/ml	C_{PAH} ml/min.	C_{IN} ml/min.	Phosphate (μM/min.) Filtered	Excreted	Reabsorbed
2/9/55	None	0		8.08	1.35					
		26 Continuous infusion of inulin, PAH, and phosphate								
		89 – 121	6.85	7.40	3.33	252	75.5	252	114	138
		121 – 153	8.07		3.73	234	73.6	274	143	131
		153 – 190	7.81	8.36	4.00	222	71.5	286	161	125
		Mean				236	73.5	271	139	132
2/14/55	50 u. bid for 3 days	0		7.56	0.91					
		26 Continuous infusion of inulin, PAH, and phosphate								
		93 – 124	8.32	7.09	2.67	266	84.0	224	131	93
		124 – 157	8.82		2.94	265	82.9	244	166	78
		157 – 187	9.40	6.83	3.32	258	83.3	277	194	83
		Mean				259	83.4	248	164	85
2/24/55	500 u. q. 12 hr. x 5 i.v.	0		11.95	0.74					
		109 Continuous infusion of inulin, PAH, and phosphate								
		173 – 205	3.41		2.57	220	57.7	148	98	50
		205 – 241	3.65		3.02	225	55.5	168	113	55
		241 – 270	4.01	9.03	3.52	252	56.5	199	137	62
		Mean				232	56.6	172	116	56

hormone acts directly on the renal tubule. That the hypercalcemia produced by the hormone is not responsible for the change in tubular transport of P is indicated by the demonstration that a rise in plasma Ca leads to an increase in the tubular reabsorption of P (15). In addition, the prompt and striking fall in TmP which follows the intravenous administration of parathyroid extract to hypoparathyroid subjects strongly suggests a direct effect of the hormone on the renal tubule.

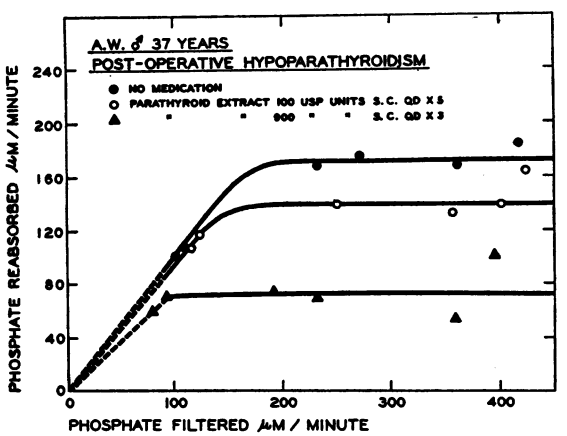

FIG. 5. TUBULAR REABSORPTION OF PHOSPHATE AT SEVERAL LEVELS OF FILTERED PHOSPHATE IN A HYPOPARATHYROID SUBJECT IN THE UNTREATED STATE, IN AN "ISOPARATHYROID" STATE, AND IN A HYPERPARATHYROID STATE

No manifestations of hyperparathyroidism were observed in W. R. following the intravenous administration of 1500 units of extract over a six-hour period on each of three successive days. Whether the renal tubule and bone of the normal individual must be constantly exposed to the extract for an even more prolonged period of time before a change in TmP or in calcium metabolism is demonstrable remains to be answered.

The demonstration of an action of PTH on the kidney does not, of course, exclude an effect on bone. Indeed, only by invoking an action of the hormone at both sites can one satisfactorily explain the chemical aberrations characteristic of patients with hyperparathyroidism. It would appear reasonable, then, to assume that the secretion(s) of the parathyroid alters metabolic processes in bone, in kidney, and possibly even elsewhere.

SUMMARY

1. The intravenous administration of parathyroid extract results in a phosphate diuresis. Such an effect in normal subjects can generally be accounted for by a rise in filtered phosphate secondary to a rise in glomerular filtration rate with-

out any decrease in phosphate Tm. In hypoparathyroid individuals there is a diminution in the tubular reabsorption of phosphate as well as an increase in filtered phosphate.

2. Repeated subcutaneous injections of parathyroid extract both to normal and to hypoparathyroid individuals lead to a diminution in the maximal tubular reabsorptive capacity for phosphate.

3. The phosphaturia seen after the *acute* administration of extract to normal individuals is usually caused by an action of the extract on renal hemodynamics and is not accompanied by hypercalcemia. Following the prolonged administration of parathyroid extract to normal individuals, however, hypercalcemia is observed as well as a decrease in TmP, but without any constant change in renal hemodynamics.

ACKNOWLEDGMENT

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

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