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Growth and Renal Control of Plasma Phosphate

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ABSTRACT. Glomerular filtration rate (GFR), maximal tubular reabsorption of phosphate ($TmPO_4$), and fasting plasma phosphate have been measured in states of normal growth (childhood) and pathological growth ("active" acromegaly, pituitary dwarfism) and in adult controls. GFR and $TmPO_4$ were corrected for a mean body area of 1 m^2 73. GFR, $TmPO_4$ and $TmPO_4/U$ of GFR were higher in active acromegalics than in adult controls and successfully treated acromegalics. $TmPO_4$ and $TmPO_4/U$ of GFR were higher in normal children than in adult controls. GFR was not significantly different. GFR and $TmPO_4$ were lower in pituitary dwarfs than in normal children, whereas $TmPO_4/U$ of filtrate was not significantly different.

Fasting plasma phosphate was significantly higher in "active" acromegaly and normal children than in adult controls. A highly significant correlation was found between fasting plasma phosphate and $TmPO_4/U$ of GFR in the acromegalics, the normal children, the adult controls and also when all groups were pooled.

It is concluded that the renal handling of phosphate regulates the concentration of phosphate in the plasma in normal and pathological growth as well as in normal adults. Chronic oversecretion of growth hormone alone can account for the raised tubular reabsorption capacity for phosphate seen in "active" acromegaly. From the data obtained in the pituitary dwarfs, it is apparent that the powerful tubular phosphate transport system in children is little dependent on growth hormone secretion and that additional factors must be operative. (*J Clin Endocr* **34**: 452, 1972)

GROWTH is generally associated with high blood phosphate. It has been long recognized, indeed, that fasting blood phosphate was higher in normal children (1) and in "active" acromegalics (2) than in normal adults. The cause of this phenomenon is not clear but some experimental data implicate growth hormone. Administration of growth hormone raises the level of blood phosphate in normal man (3–6) and in normal and thyroparathyroidectomized dogs (7). This rise in blood phosphate is most likely secondary to an increase in phosphate reabsorption by the kidney (4–7).

As patients with "active" acromegaly are in the state of chronic oversecretion of growth hormone and as a slight oversecretion of growth hormone has been found in children, as compared to normal adults (8), it is tempting to ascribe at least partly the high blood phosphate found in the two states to the renal action of growth hormone.

In order to test this hypothesis we measured glomerular filtration rate (GFR) and maximal tubular reabsorption of phosphate ($TmPO_4$) in patients with "active" acromegaly or successfully treated acromegaly, in normal children, in pituitary dwarfs and in adult controls, and tried to correlate these renal indices with fasting plasma phosphate concentrations.

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Materials and Methods

Renal studies were performed in 15 patients with acromegaly, 19 normal adult subjects, 15 normal children and five children with pituitary dwarfism. In the group of patients with acromegaly, structural changes characteristic of the disease were present, and enlargement of the sella turcica was demonstrated by x-ray. Twelve out of 15 were untreated: all 12 were considered to be in an "active" phase of their disease at the time of the study. They were selected on the following basis:

1. The serum concentration of growth hormone (GH) measured at 9:00 AM at rest, and in the fasting state was higher than normal (> 10 ng/ml).

2. Plasma inorganic phosphate value (as P) above 4 mg/100 ml was obtained on several occasions in the weeks preceding the renal studies.

3. One or more clinical signs of GH oversecretion were present, such as recent enlarge-

ment of hands or feet, impairment of glucose tolerance, or hyperhydrosis.

4. There was no sign of thyroid dysfunction as judged from physical examination and serum concentration of protein bound iodine.

The three remaining patients with acromegaly had been previously treated, one (M 44) by hypophysectomy, one (F 37) by section of the pituitary stalk, and one (M 48) by irradiation. In these three subjects, the serum GH was normal or undectectable. The fasting plasma phosphate was constantly below 4 mg/100 ml and there were no clinical signs of GH oversecretion.

The adult controls were 19 patients with benign functional disorders in whom careful examination, including biological and x-ray exploration, failed to reveal any organic disease.

The 15 children considered to be normal were convalescent from benign illnesses and free of metabolic, endocrine or renal abnormalities. They were all prepubertal. The five pituitary dwarfs were untreated at the time of the study. The diagnosis was made by the usual physical and biological criteria. The fasting blood GH was low or undetectable, and showed no significant response to insulin hypoglycemia. They were all subsequently treated with HGH and exhibited the expected spurt of growth.

Renal Studies. All subjects were hospitalized.

Renal studies were begun at 9 AM after food had been withheld for 14 hr. The bladder was catheterized and the catheter remained in place throughout the experiment. Blood was drawn for blank determination and for control blood phosphate. A priming dose of inulin and phosphate was administered. It was followed by a "sustainer" solution containing inulin and phosphate infused at a rate designed to give a slowly-rising serum phosphate value in the range of 7–12 mg/100 ml and a serum inulin value of about 30–50 mg/100 ml. The composition of the administered solution was similar to that used previously in our laboratory (5). Thirty min. after the infusion was begun, urine was collected for 6 consecutive periods varying in length from 10–15 min. In the middle of each period, blood was drawn from an antecubital vein. Each period was ended by washing the bladder with distilled water and air.

Calculations. Plasma phosphate and inulin were plotted against time to permit interpolation. It was assumed that the plasma value for a given collection period was 2.5 min before the midpoint. The clearance of inulin was calculated in the usual manner. Filtered phosphate was calculated as the product of the inulin clearance and plasma phosphate. Reabsorbed phosphate was calculated as the difference between the filtered and the excreted phosphate. The ratio of filtered phosphate to reabsorbed phosphate was always above 2. Therefore a maximal tubular reabsorption rate of phosphate ($TmPO_4$) was thought to have been reached in each experiment. Reabsorption of phosphate ($TmPO_4$)/U of filtrate was also calculated, as the ratio of $TmPO_4$ to GFR, multiplied by 100.

The correlation coefficients have been calculated with a computer GE 235.

Chemical methods. Inulin was determined in plasma and urine by the method of Roe *et al.* (9), inorganic phosphorus by the method of Fiske and Subbarow (10). Growth hormone was estimated by the radioimmunoassay of Glick *et al.* (11). Human growth hormone was labelled with I^{131} by the method of Hunter *et al.* (12).

Results

1. *Fasting plasma phosphate on the day of renal studies*

a. *Adult subjects*: controls, patients with "active" acromegaly and with treated acromegaly.

As seen in tables 1 and 2, the plasma phosphorus during fasting was higher in the patients with "active" acromegaly (mean 4.50 mg/100 ml $\pm$ 0.50 SD) than in control subjects (3.14 mg/100 ml $\pm$ 0.51. $P < 0.001$).

Although data from only three treated acromegalics were available, it is apparent that the values were lower than those of any

TABLE 1. "Active" acromegalics

Sex	Age	Body Area m^2	GFR* ml/min	$TmPO_4$* mg/min	$\frac{TmPO_4}{GFR} \times 100$	Plasma PO_4 mg/100 ml	Plasma GH ng/ml
M	44	1.97	132.2	6.34	4.80	4.50	41
M	20	2.16	153.8	8.88	5.78	5.60	76
F	30	1.88	138.0	5.97	4.30	4.20	78
F	57	1.49	160.5	7.40	4.58	4.60	70
F	45	2.00	146.6	6.06	4.10	3.72	34
M	36	1.96	117.0	5.23	4.46	4.80	51
M	34	2.00	208.5	10.66	5.08	4.50	36
F	57	1.74	206.7	9.22	4.45	4.22	125
M	28	1.94	122.0	5.89	4.83	4.80	14
F	38	1.98	131.4	5.58	4.24	3.90	38
M	38	1.80	125.4	6.26	4.99	4.70	70
F	75	1.70	137.1	6.71	4.90	4.48	240
Mean			148.3 ± 32†	7.02 ± 1.8	4.71 ± 0.49	4.50 ± 0.50	
			Treated Acromegalics				
F	37	1.78	100.0	2.92	2.92	2.68	
M	48	2.20	85.8	3.22	3.74	3.59	
M	44	2.13	92.3	2.62	2.83	3.35	
Mean			92.7	2.92	3.16	3.21	

* Corrected for a mean body area of 1 $m^2$73.
† SD.

TABLE 2. Adult controls

Sex	Age	Body Area m^2	GFR* ml/min	$TmPO_4$* mg/min	$\frac{TmPO_4}{GFR} \times 100$	Plasma PO_4 mg/100 ml
M	43	1.61	106	3.56	3.34	3.91
M	23	2.40	127	3.91	3.08	3.25
M	24	1.90	167	5.95	3.50	3.50
M	26	1.80	131	4.18	3.20	3.31
M	29	1.70	123	3.35	2.71	2.81
M	33	1.70	118	2.99	2.52	3.13
M	33	1.65	107	2.77	2.59	2.74
M	26	1.80	126	4.34	3.45	3.65
M	27	1.70	139	4.33	3.10	2.80
M	53	1.74	110	3.41	3.08	3.08
M	40	2.16	128	4.81	3.74	3.09
F	50	1.59	116	2.49	2.14	3.28
F	56	1.49	87	1.99	2.27	2.93
F	23	1.43	133	5.43	4.09	3.78
F	29	1.47	115	3.71	3.30	3.95
F	32	1.67	121	3.51	2.89	2.48
F	44	1.37	113	3.19	2.83	2.97
F	55	1.44	115	3.78	3.29	3.55
F	50	1.65	88	2.39	2.72	2.46
Mean			119.5 ± 18†	3.69 ± 1.01	3.04 ± 0.49	3.14 ± 0.51

* Corrected for a mean body area of 1 $m^2$73.
† SD.

of the "active" acromegalics. It is also evident that they are indistinguishable from the values for control patients.

b. *Normal children and adult controls* (Tables 2 and 3). As usual plasma phosphorus was higher in children (4.84 mg/100 ml ± 0.64) than in adults. The difference was significant. ($P < 0.001$).

c. *Normal children and pituitary dwarfs* (Table 3). Although the mean plasma phosphorus was lower in the pituitary dwarfs (4.21 mg/100 ml ± 0.40) than in normal children (4.84 mg/100 ml ± 0.64) the difference is not significant ($0.05 < P < 0.10$).

d. *Pituitary dwarfs and adult controls* (Tables 2 and 3). The mean plasma phosphorus was higher in the pituitary dwarfs (4.21 mg/100 ml ± 0.40) than in adult controls (3.14 mg/100 ml. $P < 0.01$).

2. *Renal handling of phosphate*

a. *Patients with acromegaly and adult controls* (Tables 1 and 2). GFR/U of body area was significantly higher in the patients with "active" acromegaly (148.3 ml/min ± 32) than in adult controls (119.5 ml/min ± 17.8) ($P < 0.005$). The patients with treated acromegaly have values of GFR lower than those of any of the patients with "active" acromegaly, and also lower than in 17 of the 19 normal subjects. These patients might have been rendered slightly hypopituitary.

$TmPO_4$/U of body area was also significantly higher in the patients with "active" acromegaly (7.02 mg/min ± 1.8) than in the two other groups (Adult controls: 3.69 mg/min ± 1.01. $P < 0.001$, patients with treated acromegaly: 2.92 mg/min. $P < 0.005$). Also $TmPO_4$/U of filtrate $\left(\frac{TmPO_4}{GFR} \times 100\right)$ was significantly higher in "active" acromegaly (4.71 ± 0.49) than in adult controls (3.04 ± 0.49. $P < 0.001$) or in patients with treated acromegaly (3.16. $P < 0.001$).

TABLE 3. Normal children

Sex	Age	Body Area m^2	GFR* ml/min	$TmPO_4$* mg/min	$\frac{TmPO_4}{GFR} \times 100$	Plasma PO_4 mg/100 ml
F	11	1.24	112	6.04	5.35	5.09
M	11	1.10	115	5.35	4.67	4.67
F	10	0.94	90	3.66	4.01	4.69
M	14	1.27	136	6.46	4.87	5.33
M	11	1.01	146	6.99	4.68	4.04
M	15	1.52	170	10.07	5.89	5.07
M	6	0.71	119	6.43	5.38	5.62
M	13	1.24	128	7.60	5.68	5.54
M	6	0.70	138	7.36	5.29	4.73
M	7	0.80	108	4.84	4.49	5.28
F	7	0.97	146	8.57	5.83	5.93
F	5	0.71	124	5.53	4.42	4.03
M	8	0.88	124	6.53	5.23	4.48
F	5	0.86	131	6.24	4.75	4.18
M	5	0.75	128	5.10	3.98	3.87
Mean			127.7 ± 18.8†	6.45 ± 1.57	4.97 ± 0.61	4.84 ± 0.64
			Pituitary Dwarfs			
M	13	0.71	72.0	2.50	3.47	4.60
M	11	0.79	97.0	5.00	5.10	4.60
M	15	0.88	77.0	3.80	4.93	3.80
F	14	0.79	88.9	3.70	4.15	4.25
M	17	1.00	88.0	3.60	4.09	3.80
Mean			84.6 ± 9.9	3.72 ± 0.89	4.34 ± 0.69	4.21 ± 0.40

* Corrected for a mean body area of 1 $m^2$73.

† SD.

b. *Normal children compared to adult controls* (Tables 2 and 3). Mean GFR/U of body area in children (127.7 ml/min ± 18.8) was not significantly different from that of adult controls (119.5 ml/min ± 18.0; $P > 0.05$). $TmPO_4$/U of body area and $TmPO_4$/U of filtrate were significantly higher in the children ($TmPO_4$: 6.45 mg/min ± 1.57, $\frac{TmPO_4}{GFR} \times 100$: 4.97 ± 0.61) than in the adults ($TmPO_4$: 3.69 mg/min ± 1.01; $P < 0.001$, $\frac{TmPO_4}{GFR} \times 100$: 3.04 ± 0.49; $P < 0.001$).

c. *Pituitary dwarfs compared to normal children* (Table 3). GFR and $TmPO_4$/U of body area were significantly lower in the pituitary dwarfs (GFR: 84.6 ml/min ± 9.9, $TmPO_4$: 3.72 mg/min ± 0.89) than in the normal children (GFR 127.7 ml/min ± 18.8. $P < 0.001$, $TmPO_4$ 6.45 mg/min ± 1.57. $P < 0.005$). The difference in $TmPO_4$/U of filtrate between the pituitary dwarfs (4.34 ± 0.69) and the normal children (4.97 ± 0.61) was not significant.

d. *Pituitary dwarfs compared to adult controls* (Tables 2 and 3). There was no difference in $TmPO_4$/U of body area between the pituitary dwarfs (3.72 mg/min ± 0.89) and adult controls (3.69 mg/min ± 1.01). GFR/U of body area was lower in the pituitary dwarfs (84.6 ml/min ± 9.9) than in adults (119.5 ml/min ± 17.8. $P < 0.001$). $TmPO_4$/U of GFR was higher in the pituitary dwarfs (4.34 ± 0.69) than in the adult controls (3.04 ± 0.49. $P < 0.01$).

3. *Correlation between fasting plasma phosphate and renal function*

a. *GFR*. There was no significant correlation between fasting plasma phosphate and GFR or GFR/U of body area within any group of subjects, or when values for all groups were pooled.

b. *$TmPO_4$*. Correlation coefficient between fasting plasma phosphate and $TmPO_4$ not corrected for body surface was not significant in any group of subjects. Only in normal subjects does a correlation become significant when $TmPO_4$ is expressed/U of body surface ($P < 0.05$). When values for all groups are pooled, a correlation is found for $TmPO_4$ not corrected for body surface ($P < 0.05$. T: 2.27) and for $TmPO_4$/U of body area ($P < 0.01$. T: 6.64).

c. *$TmPO_4$/100 ml of GFR*. There is a correlation between fasting plasma phosphate and $TmPO_4$/U of filtrate in the adult controls ($P < 0.01$), in the normal children ($P < 0.01$) and in the "active" acromegalics ($P < 0.001$). There is no correlation between these two variables in the group of pituitary dwarfs. The correlation is very significant when all values for the groups are pooled ($P < 0.001$. $T = 13.15$). The values of fasting plasma phosphate have been plotted against corresponding values of $TmPO_4$/U of filtrate in adult controls, in patients with acromegaly and in children (Fig. 1). The figure illustrates well the obvious positive correlation existing between these two values. If on the other hand the relationship between plasma phosphate and $TmPO_4$/U of body area rather than $\frac{TmPO_4}{GFR}$ is examined (Fig. 2), a regression is seen only in normal adults. It disappears in children as well as in acromegalics where plasma phosphate fails to increase at high values of $TmPO_4$.

Discussion

The observations reported here demonstrate that maximal resorptive capacity for phosphate/U of body surface and /U of GFR is higher in active acromegaly and in normal children than in control adults. Several factors may be involved in the increase of tubular phosphate transport seen in acromegaly. One is hypertrophy of the kidney with enlargement of proximal tubules (13). Another is a rise in GFR which is known to occur in acromegaly (13,14) and has been observed in our own series.

The rise in GFR is probably not entirely

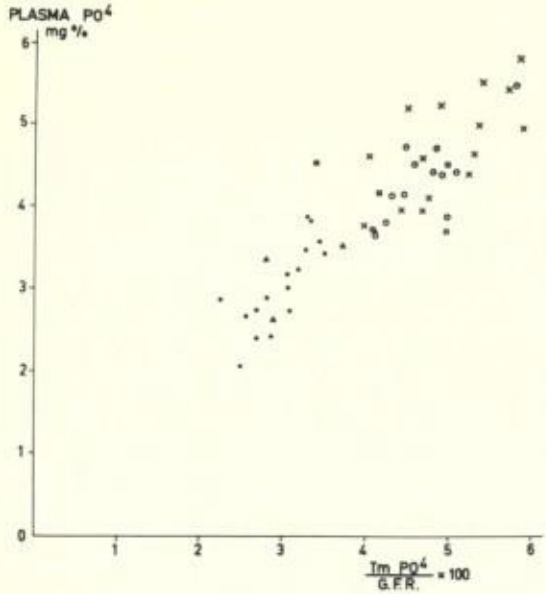

FIG. 1. Mass plot of plasma phosphate values versus phosphate reabsorption expressed as $\frac{TmPO_4}{GFR} \times 100$ in:

- ● Normal adults
- X Normal children
- □ Pituitary dwarfs
- ○ "Active" acromegalics
- ▲ Treated acromegalics

a result of an increase in the size of the glomeruli. It is probably caused also by an independent rise in renal blood flow. Indeed, growth hormone can elicit a rise in GFR within a period of time too short for the occurrence of significant hypertrophy of the kidney with concurrent increase in the cellular area available for filtration (5).

Since increase in GFR produced experimentally by different means in dogs has been shown to be often associated with a rise in $TmPO_4$ (15), it appears that both hypertrophy-hyperplasia of the glomeruli and the hemodynamic increase of GFR could explain an increase in $TmPO_4/U$ of body surface. These two factors, however, cannot account for the increase in $TmPO_4/U$ of GFR. The increase in tubular reabsorption of phosphate/U of GFR seen here in "active" acromegaly as well as in normal subjects treated for 4 days with human GH (5) should be independent of an increase in kidney mass affecting proportionally glomeruli and tubules or of hemodynamic changes.

Because the same pattern of change in renal phosphate transport is observed in acromegaly and in normal subjects after short term administration of GH, it is likely that the renal transport of phosphate in acromegaly depends on a chronic oversecretion of GH.

GH action may involve an increase in the number of active transport sites for phosphate in the proximal tubules or an increased synthesis of carrier molecules specific for phosphate transport. The effects of GH on

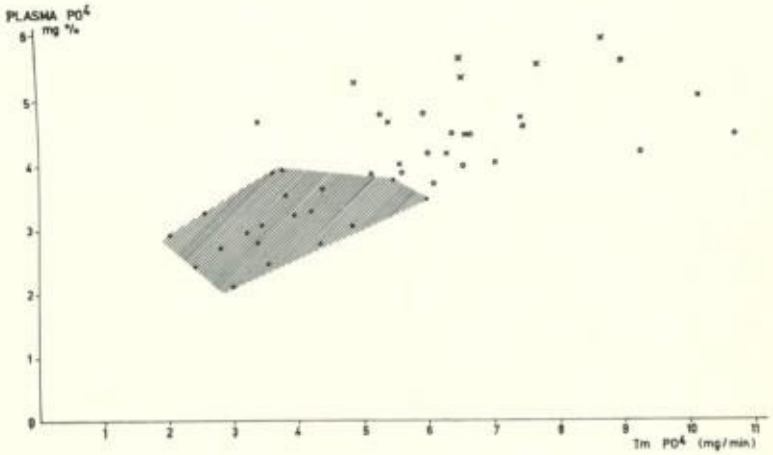

FIG. 2. Mass plot of plasma phosphate values versus phosphate renal reabsorption expressed as $TmPO_4$. For symbols see Fig. 1. Shaded area includes all data from normal adults.

the kidney in acromegaly appear to be reversible, GFR, $TmPO_4$ and $TmPO_4/U$ of GFR were normal in 3 patients treated successfully for their disease.

A $TmPO_4$ larger than in adults has been previously noted in normal children (16). In our series, $TmPO_4/U$ of body surface and $TmPO_4/U$ of GFR were much higher than in normal adults; GFR was not significantly different. The reason for the comparatively potent tubular phosphate transport system in children is not quite clear. There may be an effect on the kidney of relative endogenous GH excess. Brauman *et al.* (17) report a mean blood GH of 4.5 ng/ml in children between 5 and 14 years of age and 2 ng in adults, after 12 hr fasting, while values reported by Greenwood *et al.* (8) are 10.8 ng in children and 0.55 ng in adults 2 to 3 hr after a meal. However, Glick *et al.* think that basal levels of GH may actually be no different in children and in adults (18).

Since the increase in $TmPO_4/U$ of body surface and /U of GFR are of the same order of magnitude in acromegalics and children, one may postulate a greater sensitivity of the young kidney to growth hormone. However, this should be restricted to tubular phosphate transport, since GFR/U of body surface is the same as that in adults and lower than that in acromegaly.

Both $TmPO_4$ and GFR/U of body area are lower in pituitary dwarfs than in normal children and the $TmPO_4/U$ of GFR does not show in the pituitary dwarfs the sharp drop one would expect if GH played a major role in the increased $TmPO_4/U$ of filtrate of childhood. It is also worth noting that $TmPO_4/U$ of GFR is higher in pituitary dwarfs, who are deprived of GH, than in normal adults who have GH.

However, pituitary dwarfism is not a state of pure GH deficiency and it is possible that other factors such as cortisol and thyroid deficiency tend to cancel the effect of GH deficiency. Indeed, administration of these compounds results in phosphaturia (19–21).

Therefore we can conclude that our findings in pituitary dwarfs do not support the hypothesis that GH is responsible for the high $TmPO_4/U$ of GFR seen in normal children but do not exclude it completely.

Since there were differences in $TmPO_4$ and $TmPO_4/U$ of GFR between some of our groups of subjects, it is necessary to analyse the possible relevance of these differences to the differing plasma phosphate during fasting.

As expected, normal children had higher plasma phosphate values than control adults. Plasma phosphate was also higher in patients with "active" acromegaly; indeed, the patients had been selected partly on that basis.

We estimated the correlation between fasting plasma phosphate and the different indices of renal function in each individual group of subjects and in all subjects taken together.

No correlation between GFR/U of body area and fasting plasma phosphate was found.

We found a correlation with $TmPO_4/U$ of body area only in one group of subjects, the adult controls and that correlation was poor. It became significant, however, when values for all subjects were pooled. A highly significant correlation was present between plasma phosphate and $TmPO_4/U$ of filtrate in adult controls, in normal children and in patients with acromegaly. When all groups of subjects are considered together, correlation between plasma phosphate and $TmPO_4/U$ of filtrate was highly significant and better than that between plasma phosphate and $TmPO_4$. Figs. 1 and 2 illustrate this well and show that heterogeneity between groups fades out if the relationship between plasma phosphate and $TmPO_4/U$ of GFR is examined. This implies that the latter renal index regulates plasma phosphate in each group.

We are well aware that by dividing $TmPO_4$ by GFR, errors made in $TmPO_4$ estimation because of errors in measurement in GFR, are minimized, thereby improving the correlation with plasma phosphate.

However, it is quite evident that GFR and

tubular phosphate transport tend to influence urinary phosphate excretion and therefore plasma phosphate level in the opposite direction. Any effect of a change of tubular phosphate transport on plasma phosphate will be buffered by a similar change in GFR. $TmPO_4/U$ of GFR appears therefore as the best single renal index to relate with plasma phosphate.

The importance of the renal excretion of phosphate in regulating the concentration of phosphate in the plasma was stressed 30 yr ago by Harrison and Harrison (22). Bijvoet (23), studying normal subjects and patients with thyrotoxicosis and hyperparathyroidism, also showed a correlation between $\frac{TmPO_4}{GFR}$ and plasma phosphate. He discussed the validity of assessing renal handling of phosphate under phosphate loading conditions, showing its relevance to phosphate transport and plasma phosphate during fasting.

The plasma concentration of phosphate may of course be influenced also by extra renal factors such as phosphate absorption from the intestinal tract and movement of phosphate between bones, cells and extracellular fluids. In a steady state however, such as occurs during fasting, the plasma concentration of phosphate tends to approach the level at which filtered phosphate equals $TmPO_4$ because any excess of filtered phosphate will appear in the urine. Clearly it is because the tubular reabsorptive system for phosphate is near saturation at existing plasma phosphate concentration that the latter can be modulated by the interplay between filtration and reabsorption. It is in this way that the high plasma phosphate shown by children and patients with "active" acromegaly and some of the individual variation of plasma phosphate seen in each group of subjects can be explained.

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