STUDIES OF CALCIUM AND PHOSPHORUS METABOLISM

XIV. The Relation of Acid-Base Balance to Phosphate Balance Following Ingestion of Phosphates.[1]

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(Received for publication November 23, 1931)

OUTLINE

The effect of phosphate-feeding upon the calcium metabolism of man has been reported in experiments previously described in this journal (1). It appeared that over a relatively short period (ten days) the addition of inorganic phosphate to the control diet produced no obvious alteration of the endogenous calcium excretion, fecal or urinary. This was true whether the phosphate administered was acid phosphate (mono-sodium), basic phosphate (di-sodium), or a mixture of these two salts. Such additions to the neutral control diet, however, did produce definite alterations in the total acid-base economy of the body, not previously described, which it is the purpose of this paper to report.

The chemical principles which present themselves as the logical guides to such studies of mineral metabolism have long been recognized, but it is only within recent years that work like that of Gamble, Blackfan, and

[1] Aided financially in part by the Lead Fund of the Harvard School of Public Health.

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Hamilton (2) has afforded a sound scientific interpretation of the salt action of acid-producing salts. Much emphasis has hitherto been laid upon alterations in the economy of fixed base or upon the fate of the specific ions administered. The comparative rôle of phosphate in this process has received but little scrutiny, however, particularly as reflected in the metabolism of phosphate at various levels of acid elimination. Some authors (3) have suggested that when inorganic phosphate is fed, the metabolic fate of the phosphorus is to some degree predetermined by the potential acidity of the salt fed. Sodium acid phosphate is, indeed, a natural physiological waste product: does the administration of this acid salt provoke diuresis or loss of fixed base? The companion buffer salt disodium phosphate exists in all body fluids. What is the effect of its administration on bodily economy?

PLAN OF STUDY

In order to determine the effect of the potential acidity of ingested phosphate upon its assimilation and subsequent fate, we have studied three adult humans whose clinical conditions are described in the addenda. These subjects were placed on a potentially neutral diet, low in phosphorus content, which was continued (essentially) unvaried throughout the experiment. One week was allowed in each case to permit the body to readjust itself to this constant diet before the experiment was begun. After control levels of excretion had been determined, weighed amounts of chemically pure inorganic phosphate were added to the diet, and the resulting change in excretion observed. Three types of inorganic orthophosphate were fed, viz., sodium acid phosphate, disodium phosphate, and an equimolecular mixture of the two. The object was to administer as much phosphate as possible without producing catharsis. Subject RN was given these salts in sequence, so that there are two observations on acid phosphate (subjects WN and RN).

Because of the well recognized lag in excretion following the administration of most medication, the metabolism of phosphorus was followed after the inorganic phosphate was omitted. In all cases, the resumption of control excretion levels indicated that a "steady state" had again been reached in the second period following the last in which phosphate was fed. In this paper, therefore, the acid-base balance was struck as soon as the phosphate balance had approached its former level. It was essential in so doing not to delay too long lest the immediate metabolic response to phosphate feeding be obscured by subsequent readjustments. In evaluating the response of the organism to these phosphate additions, it is assumed that the effect of the control diet on the total metabolism remained constant; and that increases in the potential acidity of the diet (in the form of added phosphate) would be reflected by corresponding alterations in acid excretion.

In these experiments the method suggested by Sherman and Gettler (4) for calculating the potential acidity of food-stuffs was utilized, and the relative amounts of various food-stuffs so balanced that the total potential acidity (when oxidized) would be zero. The actual arithmetical operations and sources of error have been illustrated elsewhere (5). The use of such a "control" diet, constantly continued throughout the experiment, obviates any gross errors due to inaccuracy in the composition of the food. Our control diets were low in calcium and phosphorus but adequate with respect to other inorganic salts, vitamins, fat, carbohydrate, protein, and total caloric content.

EXPERIMENTAL METHODS

The technic followed in these experiments has been given in a description of the special study ward on which our subjects were kept (6). Ammonia and titratable acidity were, as usual, determined within a few hours after mixing of the combined twenty-four-hour urine. The possibility of an important change occurring under these conditions was excluded (7) by comparing the twenty-four-hour analysis with the summated results of successive specimens freshly voided.

Diuresis was excluded by recording nude weight at the same time each day, and showing this to be constant. The time of the experiments was the early (New England) spring months when perspiring was at a minimum. Basal metabolic rates were determined with the Benedict-Roth apparatus.

The analytical methods employed were outlined in our previous publication (1). Through the courtesy of Dr. Arlie V. Bock the blood CO_2 level of subject RN was established (with the apparatus of Neill and Van Slyke) before and at the end of acid phosphate administration. Haldane's negative experiment (8) determining the effect on blood CO_2 of large doses of basic phosphate obviated the necessity of such determinations in the basic phosphate experiments.

EXPERIMENTAL RESULTS

Our analysis of the experimental results is based upon the assumption that when an organism exhibits a constant excretion in response to a constantly continued "control" dietary regimen, additions to the diet will be reflected by changes in excretion, the quantitative value of which should be measured from the original excretion-level. In presenting results, therefore, emphasis has been laid in this paper upon intakes or outputs *over and above* the corresponding figures for the preliminary "control" (basal) diet. The justification for this procedure will appear in the results cited below.

In presenting these results, furthermore, we have departed from the usual procedure of sharply separating analytical figures from the dis-

cussion of their significance. This method seemed advisable because the paper is in essence a mathematical analysis of metabolic balances and derived equivalents. The massed results of the laboratory determinations may be had (for reference) in our previous paper (1).

I. The influence of the potential acidity of ingesta on inorganic phosphorus metabolism

Studies on the storage of calcium and phosphorus in rickets have demonstrated that the potential acidity of the diet is an important factor in phosphate metabolism. Zucker, Johnson, and Barnett (3) reported that the change in the acidity of diets from the alkaline toward the acid side might result in healing of the rachitic lesions. Conversely, McClendon (9) reported that adding alkali to a diet increased its power to produce rickets. The fact that most rickets-producing diets are potentially alkaline is of significance.

Most illuminating from this point of view are experiments which determine the fate of phosphate of known potential acidity added to a consistently continued basal or control diet. Karelitz and Shohl (10), in studying the metabolism of phosphate in rachitic rats to whose diet (a potentially alkaline one) acid phosphate was added, found that this addition resulted in a reversed excretion ratio between urine and feces. In the period preceding the feeding of phosphate only 7 per cent of the excretion was urinary, whereas with increase of phosphate in the diet the urinary moiety was about half, being increased both relatively and in an absolute sense. Despite the fact that their animals were in a state of phosphorus starvation, only one-fourth of the phosphate eaten was retained on this diet (which was potentially alkaline, even though acid phosphate had been added). The possibility that the greater excretion of phosphate in the urine under a more acid regimen might be due to greater absorption from the intestines was investigated in man by Zucker (11), who added NaOH and HCl to the control diet; which, however, was evidently potentially acidic as indicated by a titratable acidity of over 700 cc. N/10 acid daily. The greater absorption and retention of phosphorus under the influence of acid was also confirmed by Scheer (12).

From the massed analytical results previously published (1), the phosphate determinations have been abstracted and combined in Table I to indicate the respective phosphorus balances for the three types of salt fed, i.e., acid, basic, and the equimolecular mixture of the two. Stress is laid upon the values headed "balance above control," because these derived values indicate the extent of fluctuation above the basal level. In italics (beside the excretion figures for each three-day period) is given the relative participation (expressed as percentage) of urine and feces, respectively, in the combined phosphate excretion for that period.

TABLE I

Excretion of phosphate in urine and feces following ingestion of inorganic phosphate

Subject	Three-day period	Phosphorus balance				Phosphorus balance above control						Phosphorus retained above control	Calculated† acid equivalent of retained phosphorus
		Urine	Feces	Total output	Total intake	Urine*		Feces*		Total* output	Total* intake		
		grams	*grams*	*grams*	*grams*	*grams*	*per cent*	*grams*	*per cent*	*grams*	*grams*	*grams*	*cc. N/10*
WN Acid phosphate alone	(I)	(1.1)	(0.5)	(1.7)	(1.9)								
	(II)	(1.3)	(0.6)	(1.8)	(1.9)								
	III¶	1.3	0.6	2.0	1.9								
	IV‡	2.2	0.6	2.8	3.9	0.8		−.0		0.8	2.0	1.2	316
	V‡	7.3	1.6	9.0	10.8	6.0	*86*	1.0	*14*	7.0	8.9	2.0	530
	VI‡	6.8	2.1	8.8	10.8	5.4	*79*	1.4	*21*	6.8	8.9	2.1	564
					Total	12.2	*83*	2.4	*17*	14.6	19.8	5.3	1410
	VII	1.6	0.9	2.5	1.3	0.2		0.3		0.5	−0.6		

TABLE I (*continued*)

Subject	Three-day period	Phosphorus balance				Phosphorus balance above control						Phosphorus retained above control	Calculated† acid equivalent of retained phosphorus
		Urine	Feces	Total output	Total intake	Urine*		Feces*		Total* output	Total* intake		
		grams	*grams*	*grams*	*grams*	*grams*	*per cent*	*grams*	*per cent*	*grams*	*grams*	*grams*	*cc. N/10*
RN Acid phosphate alone	X‡	4.8	2.6	7.4	9.0	3.8	*67*	1.9	*33*	5.7	7.1	1.4	385
	XI‡	5.4	1.3	6.8	8.9	4.4	*86*	0.7	*14*	5.0	7.1	2.1	562
	XII	2.5	0.8	3.3	1.8	1.5	*94*	0.1	*6*	1.6		−1.6	−419
					Total	9.7	*78*	2.7	*22*	12.3	14.2	1.9	528
	XIII¶	1.2	0.7§	1.8	1.6								
	XIV¶	1.0	0.7	1.6	1.8								
	Average¶	1.1		1.7	1.7								
Basic phosphate alone	(I)	(1.4)	(0.5)	(1.9)	(1.8)								
	II¶	1.3	0.7	2.0	1.8								
	III¶	1.3	0.6	1.9	1.8								
	Average¶	1.3	0.6	2.0	1.8								
	V‡	3.2	3.3	6.5	7.5	1.8	*40*	2.7	*60*	4.5	5.6	1.1	− 61
	VI‡	5.3	1.9	7.3	8.7	4.0	*75*	1.3	*24*	5.3	7.0	1.6‖	− 85
	VII‡	5.0	1.3	6.3	8.4	3.7	*86*	0.6	*14*	4.3	7.0	2.3‖	−124
					Total	9.5	*67*	4.6	*33*	14.1	19.6	5.0	−270
	VIII	1.6	0.8	2.4	1.6								

TABLE I (*continued*)

Subject	Three-day period	Phosphorus balance				Phosphorus balance above control						Phosphorus retained above control	Calculated† acid equivalent of retained phosphorus
		Urine	Feces	Total output	Total intake	Urine*		Feces*		Total* output	Total* intake		
		grams	*grams*	*grams*	*grams*	*grams*	*per cent*	*grams*	*per cent*	*grams*	*grams*	*grams*	*cc. N/10*
LZ Equimolecular mixture of basic and acid phosphate	(I)	(1.8)	(0.6)	(2.4)	(2.1)								
	(II)	(2.1)	(0.4)	(2.4)	(2.1)								
	XI¶	2.0	1.1	3.1	2.1								
	XII‡	3.3	0.7	4.0	5.4	1.7	*100*	−.0		1.6	3.3	1.7	
	XIII‡	3.6	1.7	5.2	5.4	1.9	*66*	1.0	*34*	2.9	3.3	0.4	
	XIV‡	3.3	1.4	4.7	5.4	1.6	*69*	0.7	*31*	2.4	3.3	1.0	
					Total	5.2	*75*	1.7	*25*	6.9	9.9	3.0	
	XV¶	1.6	0.5	2.1	2.1								
	XVI¶	1.3	0.4	1.8	2.1								
	Average of 3 controls¶	1.6	0.7	2.3	2.1								

Data in parentheses not used because of the possibility of metabolic flux before "steady state" is attained.
* Derived from the corresponding columns under phosphorus balance, preceding.
† Derived from the preceding column.
‡ Phosphate fed during these periods.
§ Actual analysis lost. Assume figure of period XIV.
|| Corrected for slight variations in diet.
¶ Taken as control.

The corrected phosphorus balance appears in the next column (next to the last). The final column indicates the acid equivalent of the phosphorus retained, calculated with reference to blood pH = 7.4; alkali retention is indicated (in the basic phosphate experiment, subject RN) by minus signs.

The first two experiments (subjects WN and RN) are devoted to sodium acid phosphate, the third to disodium phosphate; and the fourth to an equimolecular mixture of the two.

When inorganic phosphate is fed, does the potential acidity of the salt fed influence the phosphorus balance?

In sodium acid phosphate experiment WN, 5.3 grams out of the 19.8 grams of phosphorus fed were presumably retained, i.e., 27 per cent. In sodium acid phosphate experiment RN, 1.9 grams out of the 14.2 grams of phosphorus fed were presumably retained, i.e., 13 per cent. The average of the two experiments is 20 per cent (roughly one-fifth) presumably retained.

In disodium phosphate experiment RN, 5.0 grams out of the 19.6 grams of phosphorus fed were presumably retained, i.e., 25 per cent (roughly one-fourth).

In the equimolecular phosphate experiment LZ, 3.0 grams of the 9.9 grams of phosphorus fed were presumably retained, i.e., 30 per cent (roughly one-third).

One might summarize these various results by stating that irrespective of the potential acidity of the inorganic phosphate fed, one-fourth of the phosphate fed is presumably retained in these relatively short observations.

When inorganic phosphorus is fed, what is the partition of phosphate excreted in urine and feces?

It will be observed that considerable fluctuations occurred from period to period in the division of phosphate between urine and feces. It will be more profitable, therefore, to consider the total excretion for each experiment.

In sodium acid phosphate experiment WN, 2.4 grams out of the 14.6 grams of phosphorus recovered appeared in the feces, i.e., 17 per cent; leaving 83 per cent as urinary. In the duplicate experiment on subject RN, 2.7 grams out of the 12.3 grams of phosphorus recovered appeared in the feces, i.e., 22 per cent; leaving 78 per cent as urinary. The average values for sodium acid phosphate excretion, therefore, are fecal, 19 per cent (roughly one-fifth), and urinary, 81 per cent (roughly four-fifths).

In disodium phosphate experiment RN, 4.6 grams out of the 14.1 grams of phosphorus recovered appeared in the feces, i.e., 33 per cent (roughly one-third); leaving 67 per cent (roughly two-thirds) as urinary.

In the equimolecular mixture experiment LZ, 1.7 grams out of the 6.9 grams recovered appeared in the feces, i.e., 25 per cent (roughly one-fourth); leaving 75 per cent (roughly three-fourths) as urinary.

One might summarize these results by stating that irrespective of the potential acidity of the extra inorganic phosphate fed, one-fourth of the excreted phosphorus is fecal. During the control periods, on a potentially-neutral mixed diet, one-third of the total phosphorus excretion was fecal.

The net result of the phosphorus balance presented in Table I is (first) that irrespective of the potential acidity of the salt fed, one-fourth of the phosphorus is retained; and (secondly) that irrespective of the potential acidity of the salt fed, one-fourth of the excreted phosphorus is fecal.

II. The influence of the potential acidity of ingesta upon total fixed base metabolism

The relation of phosphate excretion to the excretion of total acid, especially from the viewpoint of its bearing on urinary acidity, has occupied the interests of many investigators of acid-base economy. Folin (13) in 1903, in discussing the acidity of urine, pointed out the convenience of the assumption that the titratable acidity of urine is due to acid phosphate. The classical work of Henderson (14) on the excretion of acid catabolites emphasized the importance of using the hydrion concentration of the blood as a point of reference in titrating acid excretion; and clarified the significance of urinary hydrion concentration in terms of the titration curve of orthophosphoric acid. The chemical mechanisms by which phosphate is metabolized, however, demand further clarification.

The neutralization of phosphate within the bowel

When an inorganic salt or acid is fed, fixed base is added or withdrawn by the intestinal juices so that the potential acidity of the original salt is altered. If the potential acidity be far removed from neutrality, this process may be spoken of as "neutralization" of the salt by the bowel. The analogy is admittedly crude: first, because the pH to which the salt is neutralized is not known exactly; and secondly, because complex organic buffer-substances within the gut make exact physicochemical reasoning impossible. Nevertheless, such a concept may be profitably applied to the fate of ingested phosphate when analyses are made on aqueous extracts of fecal ash by assuming that "neutralization" occurs with reference to blood pH = 7.4, or intestinal pH = 8. It is not easy to decide which of these hydrogen ion values is the preferable reference point. Fortunately, however, the base bound by phosphate between these two limits is relatively small and either point may, therefore, be used for practical purposes.

The original potential acidity of the phosphorus found (in feces) can be calculated as its base equivalent, i.e., 1.8 times the mols of phosphorus involved. When fecal fixed base is determined, the extent of "neutralization" of the unabsorbed inorganic phosphate may be estimated. From the massed analytical data previously published (1), the values for fecal phosphorus and fecal fixed base have been abstracted; and are presented in Table II for comparison. Because of fluctuations from period to period only totals are discussed.

In sodium acid phosphate experiment WN, the extra fixed base (967 cc. N/10) more than neutralized the potential acidity (*b*) of the phosphate present (637 cc. N/10, referred to pH = 7.4). The extra base (*c*) is in fact greater than the molal equivalent (*a*) of the extra phosphorus present (768 cc. M/10). In sodium acid phosphate experiment RN, the extra fixed base (897 cc. N/10) more than neutralized the potential acidity (*b*) of the phosphate present (718 cc. N/10, referred to pH = 7.4). The extra base in this instance is approximately equal to the molal equivalent of the extra phosphorus present (865 cc. M/10).

These results may be explained on the basis that the acid phosphate which escaped absorption (or was re-excreted) was excreted chiefly in the form of disodium phosphate. The figures, indeed, indicate for WN a fraction excreted as tertiary phosphate, and for RN a small fraction excreted as primary phosphate. Such differences, however, are probably not significant in a metabolic procedure of this sort.

In the disodium phosphate experiment RN, the extra fecal phosphorus (*a* = 994 cc. M/10) would theoretically have carried with it, if excreted unchanged, 1988 cc. N/10 fixed base (i.e., sodium). The extra fixed base (*c*) actually found (2167 cc. N/10) is in fair agreement, and indicates that this phosphate was excreted chiefly in the form in which it was fed.

The conclusion indicated by these three experiments is that fecal inorganic phosphate was excreted chiefly as the disodium salt irrespective of the form in which it was fed. It is interesting that Berg (15) believed calcium phosphate to be excreted by bowel in tribasic form. It is clear, however, that such a condition cannot be ascribed to the total fixed base of the feces when phosphate is fed. The fact that calcium is a weaker base than sodium may explain this apparent discrepancy.

The neutralization of phosphate in the urine

In the preceding section, the base equivalent of the fecal phosphate excreted was found to serve as a rough measure of the extra fixed base excreted (by bowel) when inorganic phosphate was fed. In the case of urinary excretion, an even more precise relationship exists—at least for acid phosphate. For the sake of clearness and brevity the analytical values for individual successive periods have been omitted from Tables III and IV, and only the summated values (representing nine consecutive

TABLE II

Fecal base following inorganic phosphate feeding

Subject	Three-day period	Fecal phosphorus	(a) Fecal phosphorus above control*	Calculated acid equivalent of fecal phosphorus‡	(b) Estimated acid due to phosphorus lost in feces above control*	Calculated sodium due to extra phosphorus above control	Actual fecal fixed base	(c) Fecal base above control*
		cc. M/10	*cc. M/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*
WN Sodium acid phosphate	III§	205		170			970	
	IV†	200	−5	166	−4		836	−134
	V†	522	317	433	263		1431	461
	VI†	661	456	548	378		1610	640
			Total 768		Total 637			Total 967
RN Sodium acid phosphate	X†	836	623	694	517		1740	1000
	XI†	426	213	354	177		775	35
	XII	242	29	201	24		602	−138
			Total 865		Total 718			Total 897
	XIV§	213		177			740	

TABLE II (*continued*)

Subject	Three-day period	Fecal phosphorus	(*a*) Fecal phosphorus above control*	Calculated acid equivalent of fecal phosphorus‡	(*b*) Estimated acid due to phosphorus lost in feces above control*	Calculated sodium due to extra phosphorus above control	Actual fecal fixed base	(*c*) Fecal base above control*
		cc. M/10	*cc. M/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*
RN Disodium phosphate	II§	208		−35			893	
	III§	203		−34			868	
	Average§	205		−35			881	
	V†	107	−99	−183	−147	−198	2050	1169
	VI†	686	483	−106	− 71	966	1964	1083
	VII†	413	610	− 70	− 34	1220	796	−85
			Total 994		Total −252	Total 1988		Total 2167

* Derived from the preceding column.
† Phosphorus fed during these periods.
‡ Referred to the pH value of the blood.
§ Taken as control.

days) are presented. Because of lack of adequate analytical data, the intermediate experiment with an equimolecular mixture of phosphates is not discussed.

Acid phosphate in urine

When an acid salt is absorbed and excreted, the kidney must excrete additional fixed base in order to neutralize it to the pH of the urine. The amount of extra fixed base excreted would be the base equivalent of the salt excreted provided that the kidney did not exercise its powers of base-conservation either by increased titratable acidity or by ammonia output. Titratable acidity might, indeed, be expected to play a large rôle in the elimination of phosphate, but the observations of Marriott and Howland (16) would lead one to expect the amount of extra ammonia to be rather small. The sum of these two increases should indicate the extra fixed base saved by the kidney, and this sum should be subtracted from the base equivalent of the extra urinary phosphate in order to estimate the increase to be expected in urinary fixed base. When this is done, in Table III and Figure 1, comparison with the analytical results shows a

TABLE III

The urinary fixed base response to acid phosphate feeding can be predicted quantitatively

Excretion values above control levels	Patient WN		Patient RN	
	Extra base excreted as phosphate	Extra fixed base conserved	Extra base excreted as phosphate	Extra fixed base conserved
	cc. N/10	*cc. N/10*	*cc. N/10*	*cc. N/10*
Extra phosphorus excreted, P, in cc. M/10	3927		3110	
Its base-equivalent, 1.8 × P	7190		5698	
Extra ammonia excreted, N		465		− 20
Increased titratable acid, T		+ 1868		+ 1230
Extra base saved, N + T	*2333*	2333	*1210*	1210
Predicted excretion of fixed base = 1.8 × P − (N + T)	4857		4488	
Actual analytical finding	4615		4290	

difference which is not over 5 per cent in either of the two experiments presented. The difference, in fact, is probably less than the maximal error to be expected from the combination of chemical analyses involved. The detailed analytical figures are appended in Table III*A*.

This calculation involves the tacit assumption that the underlying "control" acid-base metabolism (in response to the basal "control" diet)

remains undisturbed by the addition of phosphate. The results make it likely that the premise is justified.

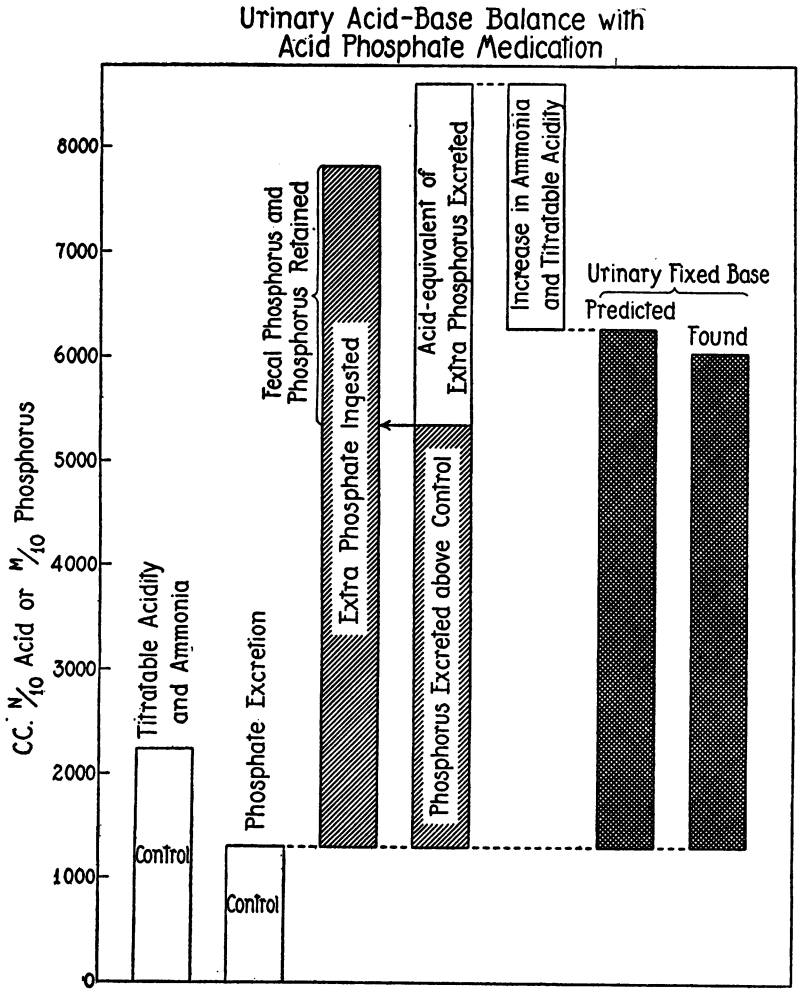

FIG. 1. PATIENT WN—THE ACTUAL INCREASE IN URINARY FIXED BASE IS APPROXIMATELY EQUIVALENT TO THAT THEORETICALLY PREDICTED.

The control excretions are pictured at the left of the chart. The superimposed phosphorus excretion is indicated by the hatched areas.

Basic phosphate in urine

The foregoing prediction of fixed base excretion depended upon the assumption that the underlying general trend of inorganic salt metabolism remained undisturbed by the feeding of acid phosphate. When given a constant control diet, each subject had eventually arrived at a plateau level of excretion for the several dietary constituents measured. The

TABLE IIIA *

Urinary acid balance due to acid phosphate fed

Subject	Three-day period	Urinary phosphorus	Urinary phosphorus above control			Neutralization of extra acid above control			Total extra base predicted excreted	Analyses of actual total fixed base of urine	Actual extra fixed base†
					Acid equivalent = 0.83 × molal equivalent‡	By extra ammonia§	By extra titratable acidity§	Remaining extra acid. Neutralized by base supplied by body			
		grams	*grams*†	*cc. M/10*† (*a*)	*cc. N/10* (*b*)	*cc. N/10* (*c*)	*cc. N/10* (*d*)	*cc. N/10* (*e*) =*b*−*c*−*d*	*cc. N/10* (*f*) =*a*+*e*	*cc. N/10*	*cc. N/10* (*g*)
WN	(I)	(1.1)									
	(II)	(1.3)									
	III‖	1.35								3780	
	IV	2.18	.83	267	222	41	160	20	287	4594	814
	V	7.33	5.98	1920	1596	202	1030	364	2284	5221	1441
	VI	6.77	5.42	1740	1445	222	678	545	2285	6140	2360
			Totals	3927	3263	465	1868	929	*4857*		*4615*
	VII	1.57									
	(VIII)	(0.8)									
	(IX)	(1.3)									

TABLE IIIA (*continued*)

Subject	Three-day period	Urinary phosphorus	Urinary phosphorus above control			Neutralization of extra acid above control			Total extra base predicted excreted	Analyses of actual total fixed base of urine	Actual extra fixed base†
					Acid equivalent = 0.83 × molal equivalent‡	By extra ammonia§	By extra titratable acidity§	Remaining extra acid. Neutralized by base supplied by body			
		grams	*grams*†	*cc. M/10*†	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*	*cc. N/10*
RN	X	4.83	3.77	1220	1014	72	616	326	1546	3570	810
	XI	5.44	4.38	1410	1178	−52	486	744	2154	4740	1980
	XII	2.54	1.48	480	396	−40	128	308	788	4260	1500
			Totals	3110	2588	−20	1230	1378	*4488*		*4290*
	(I)	(1.4)									
	XIII‖	1.15								2840	
	XIV‖	0.97								2680	
	Average‖	1.06								2760	

* This table gives in full the data summarized in Table III.
† Derived from the column immediately preceding.
‡ Referred to the pH value of the blood (= 7.4).
§ Data taken from Table 2, first two columns, published in this Journal, Vol. X, 256.
‖ Taken as control.

various factors which had determined the height of the plateau level are, of course, no better understood than are the factors which determined the phosphorus balance itself. The addition of acid phosphate to the control diet, merely produced an incremental change in the excretion plateau values which was assumed to be additive.

This assumption could not be maintained, however, when basic phosphate was fed. Table IV indicates that a fundamental shift in the

TABLE IV

(Patient RN)—Phosphate balance and acid-base balance following the ingestion of disodium phosphate

	Intake	Output			Balance	Remarks
		Urine. Change from control level	Feces. Change from control level	Total. Change from control level		
Phosphorus grams...	19.6	9.5	4.6	14.2	(4.9)*	
cc. N/10 anion...	11560	5600	2712	8320	(2890)*	
Per cent...	100	49	24	72	28	
Titratable acid cc. N/10...	−1090	−1732			642	Gamble's "base economy." More alkalinity appears in the urine than was fed
Ammonia cc. N/10...		−1041				
Titratable acid plus ammonia cc. N/10...		−2773				Henderson's "total acid," the best measure of saving of fixed base, apparently indicates much less saving of fixed base
Fixed base cc. N/10...	12670	2565	2167	4732	7938	A large positive fixed-base balance
Per cent...	100	20	17	37	63	
Total anion (calculated)..		−208				Gamble's "total acid" drops, even though there are 5600 milliequivalents additional HPO_4 present

* This figure has been modified by a slight correction for refused food.

electrolytes of the body occurred when the alkaline salt was administered. In short, the fundamental excretion plateau was altered. That this was so is suggested by several facts shown in the table. More titratable alkalinity appeared in the urine than the alkali equivalent of the salt fed. Henderson's "total acid" (14), which is the best measure of saving of

fixed base, indicated less base economy than before; but on the contrary the actual analyses showed a large positive fixed base balance. Moreover, Gamble's "total acid" (17) (i.e., total anion) dropped from its control level, despite the fact that much extra phosphate ion was present.

This last fact makes it seem likely that the extra phosphate was excreted in preference to other anions (e.g., chloride or carbonate). Unfortunately, it was not possible in this study to have a complete analytical synopsis of anion excretion. Such observations would of necessity entail analyses for the high carbonate content of alkaline urines (described by Gamble (18)). Our findings, inadequate as they are, are reported here to show the need of more detailed study, which the phenomenon merits in view of its bearing upon the effect of alkaline diuretics.

DISCUSSION

This investigation was undertaken with the supposition that phosphate and acid exerted reciprocal effects upon their mutual and respective metabolisms. The object of this study was to measure the extent of this mutual influence when inorganic phosphate was fed to adult humans over a relatively short period.

The first question to be answered was: How does the potential acidity of the inorganic phosphate fed affect the assimilation of phosphorus? The answer given by these experiments is essentially negative. No definite influence of potential acidity could be discerned upon the absorption or retention of inorganic phosphorus.

The second question to be answered was: How does the potential acidity of the inorganic phosphate fed affect the fixed base metabolism while the extra phosphate is being excreted? In analyzing this problem, two rational mechanisms were encountered which explained quantitatively the excretion of total fixed base (i.e., cation considered in its rôle as an electrolyte, apart from its alkaline properties). The first of these assumed that fecal phosphate was excreted chiefly as disodium phosphate, regardless of its potential acidity when fed. The second of these assumed that when the kidney failed to neutralize acid phosphate completely (either with ammonia or by altering titratable acidity), the deficiency was made up quantitatively by draught upon the body's reserve stores of fixed base.

It is of passing interest that the subjects here described apparently retained about one-fourth of the phosphate fed (irrespective of the potential acidity of the salt administered). Of more moment is the discrepancy between the respective amounts of acid (or base) recovered and the corresponding portions of phosphate recovered. In the acid phosphate experiments four-fifths of the extra phosphate was found in excreta, in which only one-third of the corresponding acid could be measured. In the basic phosphate experiment, three-fourths of the

administered phosphate was recovered, but only about one-third of the fixed base.

CONCLUSIONS

The influence of the ingestion of sodium acid phosphate and disodium phosphate on the balance of inorganic electrolyte was studied in subjects on a constant, potentially neutral diet.

1. About one-fourth of the phosphate fed was stored. Approximately one-fourth of the excess phosphate excretion was fecal.

2. Fecal inorganic phosphate was excreted chiefly as the dibasic salt irrespective of the form in which it was fed.

3. With acid phosphate there was an increased excretion of inorganic base which was mainly urinary. It was equivalent to the theoretical amount of base necessary to neutralize the excess phosphoric acid excretion, not conserved by titratable acidity and ammonia.

4. This simple mechanism, however, did not hold when disodium phosphate was administered. The mechanisms here involved are not yet obvious.

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DESCRIPTION OF PATIENTS

A brief description of each of the patients used in this investigation follows:

WN: A married female of 34 years of age, weighing 89 kilos, suffering from chronic atrophic arthritis of 2 years' duration. (M. G. H. number 289324.)

RN: A single female of 39 years of age, weighing 56 kilos, suffering from rheumatic heart disease (mitral stenosis), chronic bronchitis, and bronchial asthma. During the period of observation she had no cough, her chest was clear, and there were no signs of myocardial failure. (M. G. H. number 286369.)

LZ: A male, aged 18, weighing 60 kilos, recovering from chronic multiple neuritis; confined to bed because of weakness of extremities, but feeling well. (M. G. H. number 274029.)