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STUDIES ON THE PHYSIOLOGY OF THE PARATHYROID GLANDS

II. THE RELATION OF THE SERUM CALCIUM TO THE SERUM PHOSPHORUS AT DIFFERENT LEVELS OF PARATHYROID ACTIVITY.¹

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In 1922 Howland and Kramer (1) emphasized the fact that the deposition of calcium in the bones depends not alone on the calcium level in the blood, nor alone on the phosphorus level in the blood, but on the levels of both calcium and phosphorus. They refrained from any long physical-chemical discussion of ion products, etc., but contented themselves with multiplying the serum calcium in milligrams by the serum phosphorus in milligrams and arriving at the very useful clinical fact that, when this product was below 30 in young children or young rats, active rickets was present. When the product was above 40, rickets was either absent or healing had set in. Shipley, Kramer, and Howland (2) showed that when the product of $\text{Ca} \times \text{P}$ is 35 calcification is obtained in vitro, not only when the calcium is 10 mgm., and the phosphorus is 3.5 mgm., but also when the calcium is 5 mgm., and the phosphorus is 7 mgm. The original clinical observation of Howland and Kramer has stimulated many attempts from the laboratory to elucidate the physical-chemical laws which govern the calcium and phosphorus levels in the blood and the precipitation of these elements in the bone. Although much progress has been made, the subject is not as yet entirely clear. We believe that a return to the analysis of clinical data may throw further light on this subject. In this paper an analysis is made of the inter-relation of serum calcium

¹ The first publication of this series is 8 in the bibliography.

to serum phosphorus during varying degrees of hypo- and hyperparathyroidism.

There seems to be a growing conviction that normally the circulating fluid contains about all the calcium phosphate which that particular fluid system can hold at that particular time and that calcification is somewhat analagous to a precipitation of a calcium salt due to some local change in the environment favoring precipitation at the point of calcium deposit. The work of Robison, Soames, Kay, and Martland (3) (4) (5) (6) makes it appear likely that this local change at the point of precipitation is an increase in inorganic phosphates due to the hydrolysis of an organic phosphorus compound by a phosphatase. They find this phosphatase in growing bones and teeth, but not in ones before growth begins. With some such conception in mind one would perhaps be justified in dividing disorders of calcium metabolism (we might better say calcium phosphate metabolism) into three fundamental groups, viz.:

1. Conditions where the body fluids, as compared with normals, are deficient with respect to calcium phosphate. The serum calcium, the serum phosphorus, or both may be low—either actually or relatively to each other. As a result there is a failure of deposition of calcium phosphate in the osteoid matrix of bone and the pathological pictures of rickets or osteomalacia result.

2. Conditions where the body fluids contain more than the normal amount of calcium phosphate. This condition is less common but is met in certain destructive processes in the bones such as osteoclastic metastases and multiple myeloma and is also seen in ergosterol poisoning. It is associated with calcium phosphate deposits in tissues other than bones. In other words calcium deposits occur even where no precipitating factor is present.

3. Finally, conditions where the body fluids contain the normal amount of calcium phosphate, but where the relation of the calcium to the phosphorus is abnormal. Such, it will be seen, is our conception of the states existing in hypo- and hyperparathyroidism. If this concept is correct, an analysis of the relation of serum calcium to serum phosphorus here should give a clue as to what laws were governing their levels.

EXPERIMENTAL

Part I

We will first investigate the relation of serum calcium to serum phosphorus at various degrees of hypoparathyroidism. The data

TABLE 1

Data on patient with idiopathic hypoparathyroidism showing effect of parathormone medication on serum calcium and serum phosphorus

Day of experiment	Period of day*	Serum			Units of parathormone
		Ca	P	Ca × P	
		<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>		
2	2	5.0	10.7	53.5	
4	1	5.3	10.6	56.2	
4	2	5.3	10.4	55.1	
4	3	5.2	10.9	56.7	
6	1	5.4	10.9	58.9	50
6	2	6.2	9.5	58.9	
6	3	6.7	8.8	59.0	
7	1	7.1	8.4	59.6	50
7	2	8.5	7.8	65.9	
8	1	9.4	7.0	65.8	50
8	3	9.8	6.6	64.7	
9	1	9.8	6.0	58.8	50
9	2	10.5	5.4	56.7	
9	3	11.2	5.7	63.8	
10	1	10.1	5.7	57.6	
10	2	9.3	5.9	54.9	
10	3	8.8	6.5	57.2	
11	1	7.8	7.0	54.6	
11	2	7.8	7.6	59.3	
12	2	7.0	8.6	60.2	
13	1	7.0	8.8	61.6	
14	1	7.1	8.7	61.8	
15	1	7.7	8.7	67.0	
16	1	7.3	8.8	64.2	
18	1	7.7	8.6	66.2	
20	1	7.5	8.8	66.0	
21	1	7.4	8.6	63.6	
22	1	7.4	8.7	64.4	
Average.....				60.4	

* The days were divided into 3 eight-hour periods.

(table 1) consist of the 28 simultaneous serum calcium and serum phosphorus determinations taken in a boy with idiopathic hypoparathyroidism while the serum calcium was first being raised to normal by parathormone² and was later being allowed to fall as a result of cessation of parathormone medication (Albright and Ellsworth (8)—experi-

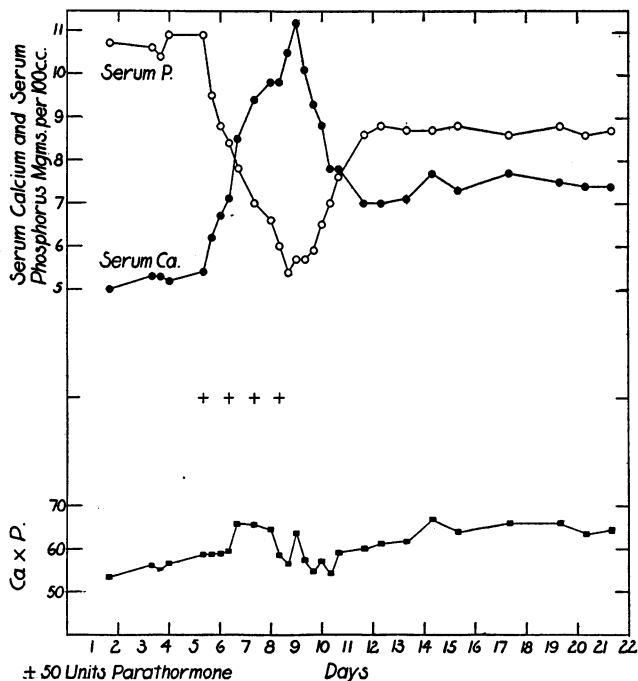


CHART 1. EFFECT OF PARATHORMONE ADMINISTRATION TO A PATIENT WITH IDIOPATHIC HYPOPARATHYROIDISM ON SERUM Ca, SERUM P, AND PRODUCT OF Ca \times P

ment 1). In chart 1 these data are given in graphic form. It will be noted that, as the serum calcium rises and falls, the serum phosphorus falls and rises. Further, it will be seen that the changes in the serum calcium and phosphorus are such that the product of Ca \times P neither rises nor falls, but merely fluctuates about the base line. In other

²Preparation of parathyroid extract introduced by Collip (7) and supplied by Eli Lilly Company.

words the product of $\text{Ca} \times \text{P}$ tends to remain about constant. We have constructed chart 2 to show better what such a constancy implies. The curve in chart 2 shows to what degree the serum phosphorus must fall as the serum calcium rises if the average calcium phosphorus product (60.4) is to be maintained. The curve is a rectangular hyperbola, the general formula for which is $xy = C$. The practical importance

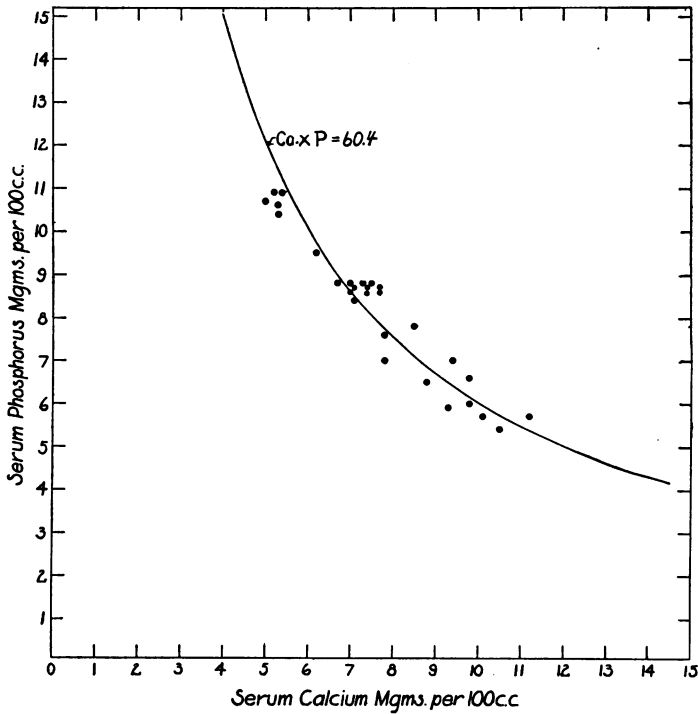


CHART 2. SHOWING HOW DATA FROM TABLE 1 FIT CURVE OF $\text{Ca} \times \text{P} = 60.4$

of the nature of the curve is that at low levels of calcium there must be a greater change in phosphorus for a given change in calcium than at high levels of calcium if the product is to remain constant. This has little significance with the figures now under consideration, but becomes important at the higher levels of calcium (*v. infra*). In chart 2 it will be noted that the individual determinations of serum calcium and serum phosphorus vary surprisingly little from such a theoretical curve.

TABLE 2

Data from eleven essentially normal patients who received parathormone medication and from two patients with hypoparathyroidism who received thyroid medication showing effect of medication on serum calcium and serum phosphorus

Group	Range of serum Ca	Number of determinations in group	Average serum Ca	Average serum P	Average Ca × P product	Condition
			<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>		
1	4.0-4.5	9	4.26	7.19	30.6	2 cases parathyroid tetany
2	4.5-5.0	20	4.79	6.50	31.1	
3	5.0-5.5	17	5.19	6.42	33.3	
4	5.5-6.0	19	5.79	5.76	33.4	
5	6.0-6.5	19	6.17	5.54	34.2	
6	6.5-7.0	8	6.68	5.60	37.4	
7	7.0-7.5	10	7.17	5.61	40.2	
8	7.5-8.0	9	7.69	5.63	43.3	
9	8.0-8.5	5	8.28	5.46	45.2	
10	8.5-9.0	7	8.70	5.18	45.1	
11	9.0-9.5	6	9.41	4.78	45.0	
12	9.5-10.0	4	9.81	4.61	45.2	
13	9.0-10.0	13	9.63	3.28	31.6	11 cases receiving parathormone
14	10.0-10.2	12	10.07	3.66	36.9	
15	10.2-10.4	14	10.28	3.39	34.8	
16	10.4-10.6	12	10.47	3.64	38.1	
17	10.6-10.8	13	10.66	3.65	38.9	
18	10.8-11.0	8	10.88	3.47	37.7	
19	11.0-11.3	12	11.12	3.43	38.1	
20	11.3-11.5	11	11.36	3.28	37.3	
21	11.5-12.0	15	11.75	3.10	36.4	
22	12.0-12.4	9	12.22	3.01	36.8	
23	12.4-12.9	9	12.66	2.79	35.3	
24	12.9-13.4	5	13.11	2.40	31.5	
25	13.4-14.0	3	13.65	3.84	52.4	
26	14.0-15.0	5	14.4	2.64	38.0	
27	15.0-16.0	5	15.52	2.87	44.5	
28	16.0-17.0	3	16.82	4.03	67.8	
Group A*		3	14.37	2.15	30.8	
Average of 13-24.....					36.1	

* This is a group of three determinations taken from groups 25 and 26 to show that a few points follow the curve as high as a serum calcium of 14.4.

The conclusion suggested from Part I is:

A. As the serum calcium varies between the level in the hypoparathyroid state and that in the normal state, or vice versa, the phosphorus varies in such a way that the product of $Ca \times P$ remains about constant.

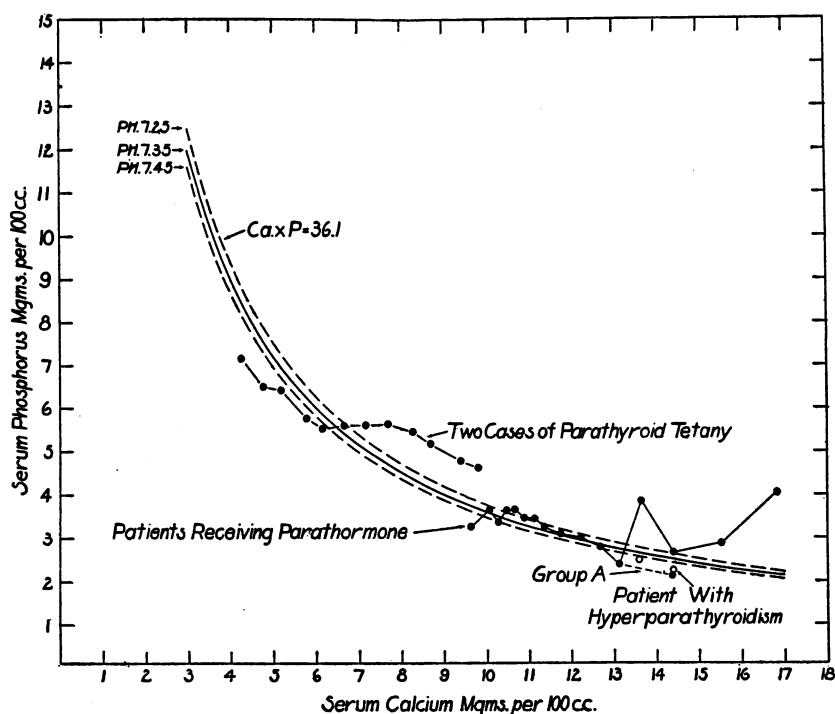


CHART 3. SHOWING HOW DATA FROM TABLES 2 AND 3 FIT CURVE OF $Ca \times P = 36.1$ AND INCLUDING (SEE BROKEN LINES) A GRAPHIC REPRESENTATION OF CORRECTION WHICH A 1/10 OF A pH WOULD ENTAIL

Part II

We now turn to the data which deal with the relation of serum calcium to serum phosphorus at varying degrees of hyperparathyroidism. (See lower half of table 2—groups 13–28.) The data consist of 149 simultaneous determinations of serum calcium and phosphorus before, after, and during a parathormone administration to eleven essentially normal patients. The data are taken from the experiments reported by Albright, Bauer, Ropes, and Aub (9). The 149 blood determina-

tions have been arranged in order of increasing values of serum calcium and averaged by groups. The increment rise in calcium for each group has been made to vary in order that enough points to be averaged fall within any one increment. For each group the average values for the corresponding serum phosphorus and $\text{Ca} \times \text{P}$ product were also obtained. These data are shown graphically in chart 3 which is constructed similarly to chart 2. It will be seen that as the calcium rises from 9.6 to 13.1 the phosphorus falls sufficiently so that the product of $\text{Ca} \times \text{P}$ again remains about constant. The fall in the phosphorus, while definite, is small and corresponds to the fact that the slope of the theoretical curve is gradual at these higher ranges of calcium. Beyond calcium levels of about 13.5, the phosphorus suddenly rises abruptly from the smooth curve suggesting that some secondary phe-

TABLE 3
Data from patient with hyperparathyroidism showing relation of serum calcium to serum phosphorus

Group	Range of serum calcium	Number of determinations in group	Average serum Ca	Average serum P	Average $\text{Ca} \times \text{P}$ product	Condition
	<i>mgm. per 100 cc.</i>		<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>		
1	13.0-14.0	11	13.6	2.5	34.0	Hyperparathyroidism
2	14.0-15.3	12	14.4	2.25	32.4	Hyperparathyroidism

nomenon has entered in. Group A (see table 2 and chart 3) is a selected group of three determinations out of groups 26, 27, and 28, showing that a few bloods continue to follow the curve to a serum calcium level of 14 mgm. per 100 cc., suggesting that the critical point varies slightly in different individuals. This phenomenon of a sudden rise of the serum phosphorus at very high calcium levels will be discussed below.

In table 2 and chart 3 are recorded in a similar manner 133 blood determinations on two patients suffering from hypoparathyroidism (groups 1 to 12). Here we see much less correspondence with the theoretical curve. This is not surprising as many factors other than the degree of hypoparathyroidism were varied during the study. What some of these factors were, will be discussed below.

The conclusions suggested from Part II are:

B. As the serum calcium varies between the level in the normal state and that in the hyperparathyroid state, the phosphorus varies in such a way that the product of $Ca \times P$ remains about constant, except that,

TABLE 4

Data from patient with postoperative hypoparathyroidism showing effect of parathormone medication on serum calcium and serum phosphorus

Date	Time	Serum			Parathormone	Remarks
		Ca	P	Ca \times P		
1930		<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>		<i>units</i>	
March 15.....	7 a.m.	5.0	10.0	50.0	100	These first nine determinations were taken on the same day. The patient was fasting
	10 a.m.	5.1	10.0	51.0		
	11 a.m.	6.4	9.5	60.8		
	12 noon	5.9	9.8	57.2		
	1 p.m.	5.9	9.7	56.8		
	2 p.m.	7.0	8.3	58.0		
	3 p.m.	7.1	8.0	57.0		
	4 p.m.	6.6	7.8	51.2		
	5 p.m.	7.1	7.7	55.0		
May 19.....	8 a.m.	8.9	6.9	61.4	40 (daily)	The last twelve determinations were taken while the patient was receiving a high calcium diet
May 22.....	8 a.m.	8.6	7.3	62.7		
May 26.....	8 a.m.	8.8	6.8	60.1		
May 27.....	8 a.m.	8.4	7.3	61.3		
May 28.....	8 a.m.	10.5	4.9	51.4		
May 29.....	8 a.m.	10.9	4.9	53.4		
May 31.....	8 a.m.	10.2	5.4	55.4		
June 2.....	8 a.m.	12.2	5.3	65.4		
June 3.....	8 a.m.	11.2	4.7	53.1		
June 5.....	8 a.m.	11.8	4.2	50.2		
June 6.....	8 a.m.	11.8	4.0	47.7		
June 7.....	8 a.m.	11.6	3.8	44.5		
Average.....				53.0		

C. At very high levels of serum calcium resulting from hyperparathyroidism, the serum phosphorus no longer falls but abruptly rises suggesting some secondary phenomenon.

D. Whereas low serum calcium levels in hypoparathyroidism are associated with much elevated serum phosphorus levels, high serum calcium values in hyperparathyroidism are associated, with only moderately

reduced serum phosphorus values, which is in entire agreement with the nature of the curve if $Ca \times P$ is to be a constant.

Part III

It is of interest to see what happens in hyperparathyroidism occurring pathologically rather than as a result of medication. In table 3

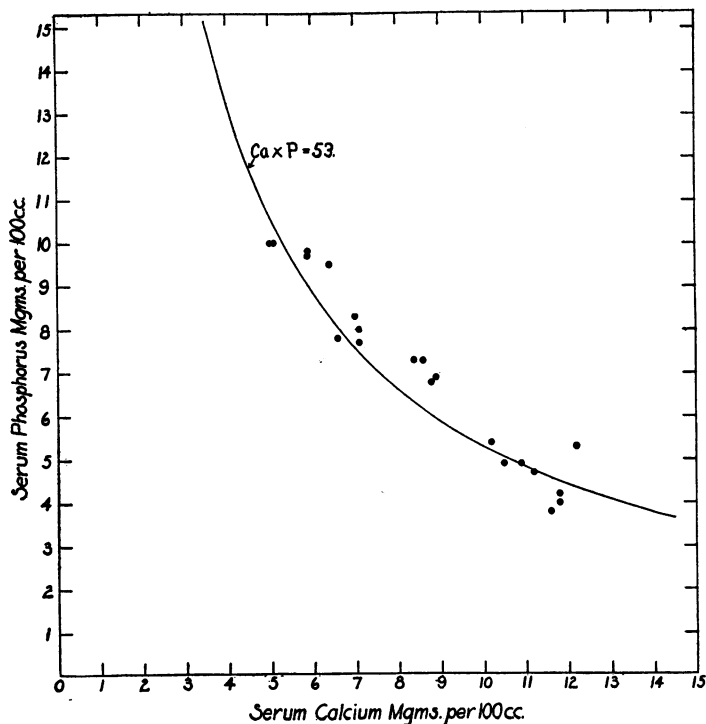


CHART 4. SHOWING HOW DATA FROM TABLE 4 FIT CURVE OF $Ca \times P = 53.0$

are given the data from 23 blood determinations on the patient suffering from hyperparathyroidism, reported by Bauer, Albright, and Aub (10). The values are represented in chart 3 by circles (q. v.). One sees that here again the values follow the theoretical curve.

Part IV

In table 4 and chart 4 are given the data from a patient with post-operative parathyroid tetany who with parathormone medication was

brought from the hypoparathyroid state through the normal state into the hyperparathyroid state. Whereas the other investigations recorded above were done on patients while on a low calcium diet, during the latter part of this study (see table 4) this patient was on a high calcium diet. Here, again, the product of $\text{Ca} \times \text{P}$ tended to remain constant, although there was some tendency for the phosphorus to fall relatively more than the calcium rose. If, as suggested by Albright and Ellsworth (8), parathormone acts by causing an increased excretion of phosphorus in the urine with a resulting lowering of the blood phosphorus, one would expect parathormone to lower the product of $\text{Ca} \times \text{P}$ temporarily until equilibrium was reestablished. It was their belief that equilibrium was as a rule so rapidly established that this lowering of the product was seldom observed. However, in the latter part of the present experiment, such a lowering did occur.

DISCUSSION

Obviously from data such as ours only graphs, showing the effect of the parathyroid hormone on the relation of serum calcium to serum phosphorus in actual clinical cases, can be constructed and the general type of curve outlined, but no definite conclusions as to the exact type of curve can be made. For instance, several years ago when some of these data were first assembled, we were influenced by the then recent work of Holt, LaMer, and Chown (11) in believing that the solubility product of tertiary calcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$) determines the amounts of calcium and phosphate in the blood. One had to assume that normally there was a marked but fairly constant degree of supersaturation. The equation to be satisfied (or rather exceeded by a constant amount) was:

$$[\text{Ca}^{++}]^3 \times [\text{PO}_4^{==}]^2 = \text{K}.$$

By making the further assumption that all the blood calcium was ionized, one obtained the simpler equation:

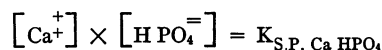
$$[\text{Ca}] \times [\text{P}]^{\frac{2}{3}} = \text{Constant}.$$

We found as a matter of fact that such a curve is sufficiently similar to $\text{Ca} \times \text{P} = \text{K}$ to fit our rough figures. One cannot escape the very

strong impression, however, that the general type of curve is such as would occur if phosphorus were varying with calcium in order to satisfy some solubility product constant,—be this that of secondary calcium phosphate, that of tertiary calcium phosphate, or that of some more complex salt. It would follow as a corollary to this, as suggested in the introduction, that the states of hypo- and hyperparathyroidism are both associated with an approximately normal degree of saturation of the blood with calcium phosphate, the only abnormality being a variation in the proportion of the calcium to the phosphate.

We have shown how our data tend to fit the curve $\text{Ca} \times \text{P} = \text{K}$ with the warning, again, that our data far from establish this curve. It may be more than coincidence that the same calcium phosphorus product which Howland and Kramer from *clinical* studies found valuable in determining whether or not rickets was healing we have found to fit the *clinical* findings in parathyroid dysfunctions. We are confronted with the question whether this product has any real significance or is merely a close approximation to some still obscure truth. We will not be able to answer this question, but a short survey of some of the pertinent facts may be helpful.

The suggestion of Shear and Kramer (12) that calcium and phosphate are precipitated as secondary calcium phosphate (CaHPO_4) has much in its favor to attract attention. The marked degree of supersaturation of the blood which one had to assume on the basis that they were precipitated as tertiary calcium phosphate no longer exists. Moreover, we are no longer dealing with a reaction of the third order which would make the rapid fluctuations in calcium and phosphorus resulting from parathyroid extract difficult to account for. When a solution is saturated with CaHPO_4



If all the calcium in such a solution is in the form of calcium ions and all the phosphate is in the form of ionizable phosphate salts, the simpler equation also holds:

$$\text{Ca} \times \text{P} = \text{Constant}$$

There is, however, very strong evidence that at least all the calcium is not ionized. Thus we would have no justification in using this second formula unless we could show that the error in so doing is constant. The constancy of our calcium-phosphorus products in that case would not be effected by a constant error.

What is the evidence for such an assumption? Salvesen (13) pointed out that

the amount of calcium in body fluids varies with the amount of protein. Cameron and Moorehouse (14) believed that the calcium of the spinal fluid, a practically protein free substance, represents the diffusible calcium of the plasma. It is not unlikely that the diffusible calcium and the ionizable calcium are approximately the same fractions. Shear, Washburn, and Kramer (15) (16) recently showed that, when protein free serum ("inorganic serum solution") is shaken with CaHPO_4 , much less CaHPO_4 is taken up than when serum containing protein is used. It would seem, therefore, that the amount of unionized calcium is roughly or perhaps exactly proportional to the amount of serum protein (if the phosphate is kept constant). But it has been repeatedly shown in this laboratory (unpublished data) that the level of serum protein is not effected by the parathyroid hormone. Since the unionized calcium is roughly proportional to the serum protein, it follows that this also would be little effected by the parathyroid hormone. The situation with the phosphates is less clear. Whereas normally the spinal fluid calcium is about one-half the serum calcium, likewise normally the spinal fluid phosphorus is about one-half the serum phosphorus (17). This by itself would suggest that the protein of the serum inactivates some phosphates as well as some calcium.

Furthermore, in hypoparathyroidism the difference between the serum calcium and the spinal fluid calcium diminishes, and the difference between the corresponding levels of phosphorus increases. These observations with respect to the relation of spinal fluid phosphorus to serum phosphorus have been under-emphasized in the literature. They strongly suggest that protein effects phosphates as well as calcium in body fluids. The actual figures obtained in a case of idiopathic hypoparathyroidism were as follows: with a serum calcium of 4.5 and a serum phosphorus of 6.2, there was a spinal fluid calcium of 4.5 and a spinal fluid phosphorus of 2.0; and later with a serum calcium of 6.7 and serum phosphorus of 4.4 there was a spinal fluid calcium of 4.7 and a spinal fluid phosphorus of 1.8. It would appear that in hypoparathyroidism the inactivated calcium decreases and that the inactivated phosphorus increases. Their product may be constant. In that case we would be dealing with a constant error due to inactivation of calcium ions and phosphate ions by proteins. One obtains the impression that protein by some process of interference alters the solubility product of CaHPO_4 . The error introduced by protein in using the quotient of serum calcium times serum phosphorus as an index may, consequently, be constant, in which case it could be disregarded. There is, therefore, some evidence other than empiricism to justify multiplying serum calcium by serum phosphorus.

There is some conflicting evidence as regards the effect of protein on inactivating phosphate ions. Grollman (18) showed that at normal ranges of calcium, 100 per cent of the serum phosphorus is filterable. Pincus, Peterson, and Kramer (19) found that the concentration of phosphorus in ultrafiltrates was the same as that in the original serum. Thus, if protein prevents some of the phosphates from exerting their full ionic values, it probably cannot be thought of as a strong union of protein and phosphates as has been considered in the case of calcium.

Even if one grants that the product of $\text{Ca} \times \text{P}$ tends to remain about constant at varying degrees of parathyroid activity, this could only be so if all other factors which effect this product were kept constant. We do not as yet know what all these factors may be. One can only hope to get consistent results if all possible factors such as diet, activity, exposure to ultraviolet light, etc., are kept as constant as possible, as in the experiments reported in Part I. The marked discrepancy, for instance, shown by the two cases of hypoparathyroidism discussed in Part II, may be due to any one of the many factors which were altered between the time when the calcium was low and the time when it was high. The elevation of the calcium in both of these cases was brought about by the thyroid hormone. The six cases of myxedema studied by Aub, Bauer, Heath, and Ropes (20) likewise showed an increase in the product of $\text{Ca} \times \text{P}$ under thyroid treatment as did the one case studied by Albright, Bauer, and Aub (21). Conversely, the case of Grave's disease in this latter study showed a reduction in the product of $\text{Ca} \times \text{P}$ coincident with treatment and reduction of metabolism. There is, then, some evidence that the thyroid hormone tends to increase the product of $\text{Ca} \times \text{P}$.

What are some of the other more important factors which may influence the product of $\text{Ca} \times \text{P}$? The serum protein requires no further discussion. There are three of special interest: (1) species of animal, (2) growth factor, and (3) hydrogen ion concentration.

In the rat the product of $\text{Ca} \times \text{P}$ is almost double that found in the human and the dog. If one assumes that this product is governed by physical-chemical laws there must be some modifying factor in the serum of the rat. The increase in the product is due to an increase in the phosphorus. Probably each species has its characteristic product depending on certain modifying variables. Likewise, to a lesser extent each individual in a species probably has its characteristic product.

It will be noted that the curve in chart 2 has a product of $\text{Ca} \times \text{P}$ of 60.4 while that in chart 3 has one of 36.1. The discrepancy is probably partly connected with the fact that chart 2 deals with a growing boy while chart 3 deals with adults. Hess and Lundagen (22) emphasized that during growth the serum phosphorus is elevated more than at other times. Shear and Kramer in their equilibration experiments

showed that the serum of normal young animals is more nearly saturated with respect to CaHPO_4 than the serum of older animals.

Whereas Shipley, Kramer, and Howland have demonstrated that, when the product of $\text{Ca} \times \text{P}$ is 35, calcification is obtained in vitro, Kramer, Shelling, and Orent (23) showed that when the pH is below 7.0, calcification is not obtained even with a product of 50. Shear and Kramer point out that at the reduced pH the product of $[\text{Ca}^{2+}] \times [\text{HPO}_4^-]$ is reduced. This results because at a reduced pH the same amount of P produces fewer HPO_4^- ions. The degree of this change can be quantitatively determined from the equation taken from Shear, Washburn, and Kramer (15):

$$[\text{HPO}_4^-] = \frac{[\text{P}]}{1 + 10^{(\text{pK}'_2 - \text{pH})}}$$

In chart 3, two broken line curves are constructed to show what difference a 1/10 of a point in pH makes. They are so constructed that their ion products equal that of the full line when allowance is made for the shift in pH. It will be seen that by this method of calculation a shift in the pH of a degree which one might find pathologically in the blood will account for only a small change in the product of $\text{Ca} \times \text{P}$. Thus, if there is an alkalosis in parathyroid tetany or an acidosis in hyperparathyroidism, it would not account for a marked shift in $\text{Ca} \times \text{P}$ product. Wilson, Stearns and Thurlow (24) from a study of the dissociation of oxyhemoglobin following parathyroid tetany in dogs, concluded that there was a tendency to alkalosis, in hypoparathyroidism. McCann (25) found a rise in blood CO_2 in two dogs suffering from parathyroid tetany. Hastings and Murray (26) were unable to substantiate these findings. In one of our cases the CO_2 combining power of the serum which was done at a time when the serum calcium was low (4.5 mgm.), was found to be high (75 volumes per cent). Brehme and György (28) found a slight lowering of pH as a result of administering parathormone.

As further evidence of the slight effect of changes in pH on the calcium-phosphorus product, table 5, is included. Here the effect of an ammonium chloride acidosis on a patient with idiopathic parathyroid tetany is illustrated. Although the acidosis caused a rise in

serum calcium as so often is the case, the calcium-phosphorus product was only slightly raised.

There remains to be discussed the abrupt rise in serum phosphorus at the very high levels of serum calcium. This is in entire agreement with the work of Collip (7). He has emphasized that after the serum calcium has risen to a certain critical point, there is a shut-down in kidney function with a rapid rise in serum phosphorus, nonprotein nitrogen, etc. The work of Grollman (18) may be significant here. He showed that whereas normally 100 per cent of serum phosphate is filtrable, at high levels of calcium this is no longer true. He further showed that injection of parathormone into a dog produced a state

TABLE 5

Data from patient with hypoparathyroidism showing effect of the production of an acidosis on serum calcium and serum phosphorus

Date	Serum						
	Ca	P	Ca × P	CO ₂	Cl	Protein	Total/ base
	<i>mgm. per 100 cc.</i>	<i>mgm. per 100 cc.</i>		<i>volumes per cent</i>	<i>mgm. per 100 cc.</i>	<i>per cent</i>	<i>cc. of N/10</i>
1927							
May 11.....	4.5	6.2	27.9	75.3	550	6.7	156
May 18.....	4.6	6.7	30.8	52.1	614		150
May 25.....	5.2	5.9	30.7	54.6	614	7.7	156
June 2.....	6.7	4.4	29.5	44.0	632	8.0	153
June 14.....	5.3	5.3	28.1	85.5	540	6.9	150

(calcium = 17.9) where only 63 per cent of the inorganic phosphorus was filtrable. This rather suggests that, at high levels of calcium, it may be difficult to excrete the inorganic phosphorus through the glomeruli. A diminution in phosphorus excretion in the urine at high levels of calcium was apparent in the patients receiving large doses of parathormone ((9), observation XXVIII, p. 159). As a result phosphorus may pile up in the blood. When this phenomenon does occur, it would appear that there must be a marked supersaturation of the blood with CaHPO₄. This is supported by the work of Hueper (27), which has been repeated by one of us (F. A.), who found calcification in the thyroid glands, mucous membrane of stomach, lungs, and kidneys of dogs dying from parathormone overdosage. We would

emphasize that this whole phenomenon is a secondary one, a complication of kidney shut-down as it were, and has probably nothing to do with the fundamental action of parathormone. It leads to a disorder of calcium and phosphorus metabolism where the body fluids contain more than the normal amount of calcium phosphate and thus may be compared with the ergosterol poisoning where similar pathological calcifications are produced.

SUMMARY

1. From an analysis of 354 simultaneous determinations of serum calcium and serum inorganic phosphorus in patients at varying degrees of hypo- and hyperparathyroidism, it would appear that one rises as the other falls to such a degree that their product remains roughly constant.

2. It is pointed out that such a constancy implies a *slight* reduction of phosphorus at high levels of calcium but a *marked* increase of phosphorus at low levels of calcium.

3. The question is raised whether this constancy represents the direct expression of a law or whether it is merely a close approximation to some law. In this connection it is pointed out that if calcium and phosphate are precipitated in the bones as secondary calcium phosphate and if the effect introduced by serum protein can be shown to be constant there may be chemical support to such a constancy.

4. The effects of serum protein, the thyroid hormone, the species of organism, the phenomenon of growth and pH on the product of $\text{Ca} \times \text{P}$ are discussed.

5. It is believed that dysfunctions of the parathyroid glands belong to that group of calcium disorders in which the body fluids contain a normal amount of calcium phosphate but in which the relation of the calcium to the phosphate is abnormal.

6. However, at very high levels of calcium a secondary phenomenon occurs. Phosphorus is no longer excreted in the urine and serum phosphorus abruptly rises. This results in a disorder of calcium metabolism where the body fluids contain an increased amount of calcium phosphate and leads to calcium phosphate precipitation in tissues other than bone.

7. The data give no clue as to whether with parathyroid administra-

tion the serum calcium rises because the serum phosphorus falls, or whether the serum phosphorus falls because the serum calcium rises. Based on this data alone one supposition is as logical as the other.

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