Etiology of Hyperparathyroidism and Bone Disease during Chronic Hemodialysis

II. FACTORS AFFECTING SERUM IMMUNOREACTIVE PARATHYROID HORMONE

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ABSTRACT Plasma concentration of immunoreactive parathyroid hormone (IPTH) was measured in 18 patients who had been on a hemodialysis program for longer than 6 months. A negative correlation was found between the predialysis plasma concentration of IPTH and the mean concentration of calcium in the dialysate previously used: plasma concentrations of IPTH were higher in patients dialyzed against a calcium concentration between 4.9 and 5.6 mg/100 ml than in patients dialyzed against a calcium concentration of 6.0 mg/100 ml or more. Plasma concentrations of IPTH also were higher in patients with bone disease than in patients without bone disease. Furthermore, a positive correlation was found between predialysis plasma concentrations of IPTH and calcium, and between mean predialysis concentration of IPTH and phosphate. To obviate the possibility that individual differences in susceptibility could have accounted for the observed effects of plasma phosphate and of dialysate calcium, a 2×2 factorial study was conducted in seven of these patients to examine the independent effects of perturbation of each of these factors. It was observed that plasma concentration of IPTH was lowest with the combination of high dialysate calcium and low plasma phosphate, highest with the combination of low dialysate calcium and high plasma phosphate, and intermediate with the two other combinations. It is concluded that both dialysate calcium and plasma phosphate are important determinants of parathyroid function in these patients.

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Received for publication 8 May 1970 and in revised form 6 August 1970.

INTRODUCTION

Systematic evaluation of factors of possible etiologic importance in the development of bone disease during chronic hemodialysis has disclosed that only the concentration of calcium in the dialysate is of statistical significance; roentgenographically demonstrable bone disease occurred almost exclusively in patients dialyzed against a calcium concentration of less than 5.7 mg/100 ml (1). It also was observed that the mean predialysis serum concentration of calcium was significantly higher in the patients with bone disease than in those without, which suggests that the degree of secondary hyperparathyroidism might be greater. The present study was designed to evaluate this possibility by examining plasma levels of immunoreactive parathyroid hormone (IPTH) in relationship to the development of bone disease and to various factors which might influence secretion of PTH.

In support of the hypothesis, plasma IPTH concentration was greater in patients with bone disease than in those without and was positively correlated with the concentration of calcium in the same plasma sample. Furthermore, a stepwise regression analysis demonstrated that the plasma IPTH concentration was significantly correlated with the following factors, enumerated in order of decreasing significance: (*a*) mean dialysate calcium concentration during the entire period of dialysis (negative), (*b*) plasma calcium concentration measured before the start of long-term dialysis (positive), and (*c*) mean predialysis plasma phosphate concentration during the entire period of dialysis (positive). The results of this study support the concept that the rate of PTH secretion is primarily responsive to the dialysate

TABLE I
Design of 2 × 2 Factorial Study

Period	Dialysate Ca	$Al(OH)_3$	Duration
	mg/100 ml		*wk*
I	6.4	No	4
II	6.4	Yes	2
III	5.3	No	3
IV	5.3	Yes	2

calcium concentration although the degree of response may be predetermined to some extent by the level of parathyroid hyperfunction before the start of long-term dialysis. Finally, the study suggests that phosphate retention may stimulate PTH secretion.

Because plasma IPTH had not been measured in these patients before the institution of the dialysis program, it was not possible to exclude the possibility that preexisting individual differences in IPTH concentration could have been responsible for the differences which were interpreted as being primarily a response to the concentration of calcium in the dialysate and the concentration of phosphate in the plasma. A further study was designed to define more precisely the influence of the dialysate calcium concentration on plasma IPTH; each patient was studied during dialysis against high (6.4 mg/100 ml) and against low (5.3 mg/100 ml) calcium concentrations. This study also incorporated an evaluation of the effect of decreasing plasma phosphate by the use of oral phosphate-binding agents. The final design of the study was a 2 × 2 factorial in which each patient was studied after 2–4 wk on each of four regimens. Plasma IPTH was influenced significantly by both the dialysate calcium and the plasma phosphate concentration: highest levels of IPTH were observed during use of the lower dialysate calcium without any specific attempt to decrease plasma phosphate, and lowest levels of IPTH were produced during combined use of the higher dialysate calcium and phosphate-binding agents. During none of the regimens, however, was plasma IPTH decreased to the normal range.

METHODS

Patient selection. IPTH was measured, in 18 of the 28 patients in the preceding report (1), before and after single dialyses, after 8–60 months of dialysis. The remaining 10 patients could not be included because they had already received renal transplants. Of the 18 patients, 10 were dialyzed at home or in an affiliated hospital against a low calcium dialysate (mean Ca, < 5.7 mg/100 ml). Eight patients were dialyzed against a high calcium dialysate, seven in the center (mean Ca, 6.0 mg/100 ml) and one at home (mean Ca, 7.4 mg/100 ml). None of these patients was taking phosphate-binding agents. In 13 of these 18 patients, an additional study was conducted to evaluate the separate effects on serum IPTH of short-term (2–4 wk) changes in dialysate calcium and plasma phosphate (see below). During this study, all patients were given an oral calcium supplement (Neo-Calglucon),[1] in amounts sufficient to increase their total oral calcium intake[2] to 1 g/day, and a multivitamin preparation containing 1000 IU of vitamin D.

Design of short-term 2 × 2 factorial study. In seven patients, the sequence shown in Table I was used to assess the separate effects on serum IPTH of changes in dialysate calcium and plasma phosphate. In an additional six patients, only a portion of the sequence could be completed. The two levels of dialysate calcium were 6.4 ±0.3 mg/100 ml (mean ±SD) and 5.3 ±0.3 mg/100 ml. Dialysate magnesium was held constant at 2.1 ±0.2 mg/100 ml. Plasma phosphate was decreased by administration of $Al(OH)_3$ gel (Amphojel).[3]

Analytical methods. Blood samples for analysis were drawn directly from the arterial cannula into heparinized Vacutainers (Becton-Dickinson & Co., Rutherford, N. J.) before dialysis. After centrifugation, a sample of plasma was drawn into a tuberculin syringe for determination of ionized calcium, and the remainder was frozen for subsequent analysis.

Ionized calcium was measured with the Orion flow-through calcium electrode. Previous studies have demonstrated that the small amount of heparin used produced no alteration in ionized calcium as measured by the electrode. The usual maximal error between duplicate measurements was 0.05 mg/100 ml. The details of this method will be reported elsewhere.[4]

IPTH was measured with an anti-porcine PTH antibody and ^{131}I-labeled bovine PTH (2). The results are expressed in microliter equivalents of a standard plasma. The sensitivity is such that IPTH can be measured in plasma of 94% of normal persons; the normal range is from undetectable to 40 μlEq/ml. All the samples used in this study were evaluated in one single assay. The coefficient of variability of a measurement within the same assay was 8%.

Concentrations of calcium and magnesium in plasma and dialysate were measured by atomic absorption spectrophotometry (3). Plasma concentration of phosphate was measured by the method of Fiske and SubbaRow (4) adapted for the AutoAnalyzer.

Statistical methods. To compare the plasma levels of IPTH in the two groups (low and high calcium dialysates), the rank sum test of Wilcoxon (5) was used because the distribution of the data did not appear to be Gaussian.

All of the factors which were considered to be possible influences on the IPTH level were included in a stepwise regression analysis (6) in which a sequence of multiple linear regression equations is computed in a stepwise manner, one variable being added to the regression equation at each step. The variable added is the one which produces the greatest reduction in the error sum of squares or, equivalently, has the highest partial correlation with the dependent variable (IPTH) partialed on the variables which have already been added.

[1] Neo-Calglucon was supplied through the generosity of Sandoz Pharmaceuticals (Hanover, N. J.) by its representative, Mr. J. F. Bahnemann.

[2] Mrs. Joyce D. Margie, dietitian, estimated the dietary calcium intakes.

[3] Amphojel was supplied through the generosity of Wyeth Laboratories (Marietta, Pa.) by its representative, Mr. W. Tournat.

[4] Dube, W. J., and R. S. Goldsmith. Unpublished data.

TABLE II

Summary of Relevant Clinical and Analytical Data

Patient	Dialysate Ca		Plasma concentration before and after dialysis*							
	Mean, previous dialyses	On study day	IPTH		Ca		P		Mg	
			Before	After	Before	After	Before	After	Before	After
	mg/100 ml		*μEq/ml*		*mg/100 ml*		*mg/ml*		*mg/100 ml*	
3‡	5.5	5.5	1630	1680	9.4	9.4	10.8	6.3	4.4	3.9
5‡§‖	4.9	4.9	2340	2165	9.5	9.9	6.9	4.6	3.8	3.5
6‡¶	5.6	5.2	562	604	9.4	9.1	7.1	4.7	3.0	2.8
7§¶	5.4	5.4	4060	4400	8.6	9.6	7.0	4.4	3.8	3.0
8‖¶	5.1	5.6	4175	3280	11.2	10.9	10.8	7.4	3.9	3.1
9¶	5.6	5.6	3060	1880	8.8	9.7	6.2	4.6	2.8	2.7
12§‖	5.6	5.4	875	510	8.8	9.7	6.1	4.6	3.4	3.1
13§	5.6	5.6	481	230	9.0	9.4	6.1	3.4	3.6	3.4
14	5.4	5.2	915	1050	6.9	6.9	7.5	5.6	3.7	3.7
15	5.4	5.6	730	490	8.8	9.5	10.5	5.5	4.3	3.7
18	6.0	6.6	697	463	7.9	10.0	7.2	4.4	3.8	3.4
20	6.0	6.6	690	150	8.9	9.0	10.2	6.8	4.7	3.8
21	6.0	6.0	235	148	8.2	8.7	5.4	3.8	3.4	3.0
24	6.2	6.3	465	465	7.0	8.6	6.3	3.0	4.3	2.8
25	6.0	6.8	5000	4838	8.8	10.1	6.3	4.0	4.6	4.0
26	6.0	7.1	356	167	7.9	10.1	8.1	4.0	3.7	3.3
27§	6.0	6.5	835	385	8.0	9.1	8.7	2.9	3.7	3.3
28‡	7.4	6.2	336	196	8.4	9.6	7.5	3.5	2.4	2.2

* Before and after denote immediately before and after a single hemodialysis treatment.

‡ Roentgenographic evidence of rib fracture.

§ Roentgenographic evidence of soft tissue calcinosis.

‖ Calcification of cornea (band keratopathy).

¶ Roentgenographic evidence of subperiosteal bone resorption (phalanges).

For the 2×2 factorial study, the sign test was chosen because the individual variability in the absolute levels of IPTH was so great and because the distribution of data was not Gaussian. In order to reduce the possibility of assigning significance to spurious changes in IPTH, differences between analyses were considered to be meaningful only when they exceeded twice the coefficient of variability of the assay method, that is, when ΔIPTH was greater than 16%. Similarly, change in total calcium or magnesium was considered to be meaningful when it was greater than 0.2 mg/100 ml, and a change in ionized calcium was considered to be meaningful when it was equal to or greater than 0.1 mg/100 ml. Applying this restriction on the data has the effect of decreasing the sensitivity of the statistical method used while increasing the rigorousness of this nonparametric technique.

RESULTS

Plasma IPTH. Both before and after dialysis, plasma IPTH was significantly higher in the low dialysate calcium group than in the high dialysate calcium group (Tables II and III). The decrease in IPTH concentration during dialysis was significantly greater in the high calcium group ($P < 0.01$).

Patients with bone disease had significantly higher IPTH values, before and after dialysis, than did patients without roentgenographic evidence of bone disease. In these two groups, however, there was no statistically significant difference between the mean values for the decrease in IPTH (ΔIPTH%) during single dialyses ($P < 0.10$). For this comparison, one patient was not included because fluorosis was considered to be a major factor in his bone disease (see reference 1).

There were no significant differences in pre-or postdialysis IPTH or ΔIPTH% in patients with and without calcinosis. It should be pointed out, however, that the predialysis IPTH values of the few patients studied with calcinosis (5 of 18) tended to be higher ($P < 0.10$).

A significant positive correlation ($P < 0.05$) was found between predialysis plasma concentrations of calcium and IPTH (Table IV) but not between the postdialysis values or the change in plasma concentrations during dialysis. However, there was a significant negative correlation between ΔIPTH% during dialysis and the dialysate concentration of calcium.

Factors possibly influencing predialysis plasma IPTH. Of the factors which may have influenced IPTH before the start of long-term dialysis, the following were introduced into the stepwise regression study: age at the beginning of dialysis, duration of kidney disease, duration of azotemia, and serum calcium before the start of long-

TABLE III

Plasma Concentrations of Immunoreactive Parathyroid Hormone (IPTH): Comparisons between Groups

Groups	No. of patients	Predialysis* IPTH, geometric mean and range	Postdialysis* IPTH, geometric mean and range	ΔIPTH%, arithmetic mean and range‡
		μlEq/ml	*μlEq/ml*	
Low dialysate calcium	10	1413	1122	−15.9
		481–4175	230–4400	+15 to −52
High dialysate calcium	8	631	355	−37.5
		235–5000	148–4838	0 to −78
P for difference§		0.05	0.02	<0.01
Bone disease‖	6	2140	1950	−7.9
		562–4175	604–4400	+8.4 to −38
No bone disease	11	692	471	−33.5
		235–5000	148–4838	+15 to −78
P for difference§		<0.05	0.01	<0.10
Calcinosis	5	1260	832	−29
		481–4060	230–4000	+8.4 to −54
No calcinosis	13	892	617	−27
		235–5000	148–4838	+15 to −78
P for difference§		<0.10	NS	NS

* Predialysis and postdialysis denote immediately before and after a single hemodialysis treatment, respectively.

‡ $\Delta IPTH\% = \frac{\text{postdialysis IPTH} - \text{predialysis IPTH}}{\text{predialysis IPTH}} \times 100.$

§ Rank sum test.

‖ Patient 28 not included (see text).

term dialysis (as an index of preexisting parathyroid function). Of the factors which may have influenced PTH secretion during long-term dialysis, the following were studied: duration of dialysis, mean predialysis serum creatinine concentration (as an index of dialysis efficiency), mean predialysis plasma phosphate concentration, mean predialysis plasma pH, mean predialysis plasma bicarbonate concentration, mean dialysate concentrations of calcium and fluoride, and serum fluoride concentration measured during the same week as IPTH.

The factor which was best correlated with predialysis IPTH concentration was mean dialysate calcium concentration (negative), followed by serum calcium concentration before long-term dialysis (positive), mean predialysis plasma phosphate concentration during the entire period of dialysis (positive), and, finally, at a borderline level of significance ($P < 0.10$), mean predialysis pH (negative). The remaining factors did not contribute significantly to the regression.

Effect of decreasing the dialysate calcium concentration. The effect of decreasing the dialysate calcium concentration from 6.4 to 5.3 mg/100 ml was assessed in seven patients both with and without the use of the phosphate-binding agent and in one patient only during the use of the binding agent (Table V). An increase in IPTH of greater than 16% occurred in 11 of the 15 trials ($P < 0.05$), whereas a decrease in IPTH of more than 16% occurred only once; variation within ±16% occurred three times. There was no significant change in plasma calcium and magnesium concentrations.

Effect of decreasing the predialysis plasma phosphate concentration. The effect of administration of $Al(OH)_3$ could be assessed with both high and low dialysate calcium concentrations in seven patients, with only high calcium in four, and with only low calcium in two (Table VI). Among these 20 observations, a decrease in IPTH of greater than 16% occurred 11 times ($P < 0.01$), whereas an increase in IPTH of more than 16% occurred only once; there was no significant variation in IPTH in 8 instances. An increase in plasma calcium concentration of more than 0.2 mg/100 ml was observed 13 times; there was no significant change in 4 instances, and it decreased in 3 instances.

The variation of predialysis plasma concentration of ionized calcium could be assessed in only 10 cases, and in most of these the dialysate calcium concentration was low. An increase of 0.1 mg/100 ml or more was observed seven times, whereas a decrease of more than 0.1 mg/100 ml occurred three times. There was thus a suggestive trend for association between increase in ionized calcium and a decrease in phosphate, but it was not statistically significant.

No significant association was found between the decrease in phosphate and variation in plasma magnesium.

No significant association could be found between the variation in IPTH and the variation in total calcium, ionized calcium, or magnesium when the predialysis plasma concentration of phosphate was decreased by administration of phosphate-binding agents. However, there was a suggestive trend that a decrease in IPTH was associated with an increase in ionized calcium. Of the seven instances in which ionized calcium increased significantly, IPTH decreased significantly four times, remained the same twice, and increased significantly only once.

DISCUSSION

The impetus for this study arose from the observation (1) that the mean predialysis serum calcium concentra-

TABLE IV

Simple Correlations between Plasma Concentrations of Calcium and IPTH: Effect of Dialysate Calcium Concentration

Correlation	Coefficient, *r*	*P*
Predialysis plasma Ca and IPTH	0.495	<0.05
Postdialysis plasma Ca and IPTH	0.267	NS
ΔIPTH% and ΔCa*	0.183	NS
ΔIPTH% and dialysate Ca (day of study)	−0.503	<0.05

* ΔCa = postdialysis Ca − predialysis Ca.

tion (during the entire period of dialysis) was higher in patients who developed bone disease and who, for the most part, were being dialyzed against calcium concentrations of less than 5.7 mg/100 ml. This suggested the possibility that the bone disease developing during chronic hemodialysis might be due in large measure to secondary hyperparathyroidism and that this might be prevented to a great extent by dialysis against higher concentrations of calcium. In confirmation, it was found that plasma concentrations of IPTH were significantly higher in the patients dialyzed against the lower calcium concentration (< 5.7 mg/100 ml). Similarly, plasma concentrations of IPTH were significantly higher in patients with bone disease than in patients without bone disease.

This finding suggests that dialysate calcium concentration is a factor which significantly influences the plasma IPTH. When the various possible factors were evaluated in a stepwise regression analysis, dialysate calcium concentration had the highest correlation with plasma levels of IPTH. Because the coefficient of correlation was negative, it confirmed the suggestion that low dialysate calcium either stimulates or less effectively inhibits secretion of PTH. Furthermore, dialysate calcium concentration was correlated with IPTH even when all of the other significantly correlated factors were kept constant, which thus suggests that it is the major factor influencing plasma levels of IPTH.

TABLE V
*Effect of Decreasing Dialysate Calcium Concentration**

Patient	Plasma P	Change in plasma values		
		ΔIPTH	ΔCa	ΔMg
		%	*mg/100 ml*	*mg/100 ml*
18	High	+96	+1.2	−0.2
	Low	+123	+0.1	−0.7
20	High	+9	+0.6	−1.3
	Low	+47	+0.8	+0.7
21	High	+131	+0.9	−0.2
	Low	+33	+0.7	+0.7
24	High	−10	−0.1	−0.4
	Low	+23	−0.7	+0.7
25	High	+8	−0.8	−0.8
	Low	+43	−0.1	−0.1
27	High	+23	−0.4	−1.2
	Low	+19	−0.2	−0.3
29	High	+21	−0.8	+0.5
	Low	−30	+0.8	+1.1
30	Low	+40	0	+0.6
P		<0.05	NS	NS

* From 6.4 to 5.3 mg/100 ml.

TABLE VI
Effect of Decreasing Plasma Phosphate Concentration

Patient	Dialysate Ca	Change in plasma value				
		ΔP	ΔIPTH	Δ Total Ca	Δ Ionized Ca	ΔMg
		mg/100 ml	%	*mg/100 ml*	*mg/100 ml*	*mg/100 ml*
18	High	−6.7	−32	+0.7		+0.7
	Low	−2.2	−22.5	−0.4	+0.5	+0.2
20	High	−5.6	−8.3	+0.8		−1.4
	Low	−3.3	+6	+1.0	+0.3	+0.6
21	High	−3.6	−16	+0.8		−0.6
	Low	−3.3	−46	+0.6	+0.8	+0.3
24	High	−3.9	−7	+1.8		−0.3
	Low	−4.8	+24	+1.2	+0.6	+0.8
25	High	−4.8	−30	−0.2		−0.4
	Low	−1.1	−7.7	+0.5	−0.3	+0.3
27	High	−3.8	−2	0		−0.8
	Low	−7.0	−6	+1.4	+0.7	+0.1
29	High	−2.2	−31	−0.5		−0.2
	Low	−2.1	−60	+1.1	−0.5	+0.4
30	High	−2.7	−68	0	+0.1	+0.2
5	High	−2.3	−8	+0.2	—	−0.3
31	High	−3.6	−49	+0.4	−0.8	0
32	High	−6.6	−66	+2.7	—	−0.2
12	Low	−4.6	−47	−0.3	—	−0.4
33	Low	−2.2	−43	+2.1	+0.1	0
P			<0.01	<0.05	NS	NS

Similarly, in the short-term study, a significant increase in IPTH was observed when dialysate calcium concentration was decreased from 6.4 to 5.3 mg/100 ml in the same patients, which demonstrates directly its influence on plasma IPTH. An acute study previously reported by Kaye, Cohen, Chatterjee, and Mangel (7) had shown that dialysate calcium concentration influences the IPTH level during dialysis: a calcium concentration of 3.5 mg/100 ml caused an increase in plasma IPTH, whereas 8.5 mg/100 ml caused a decrease. However, the dialysate calcium concentrations used by Kaye et al. were beyond the usual therapeutic range and generally have not been advised for routine use. Our data show that a minor change (1.1 mg/100 ml) within the usual therapeutic range clearly affects the plasma IPTH.

What is the mechanism by which dialysate calcium concentration influences parathyroid function? During dialysis, plasma IPTH usually decreased, but the amount of decrease was significantly less in the low dialysate calcium group; in fact, the amount of the decrease was positively correlated with the dialysate calcium concentration during dialysis. The probable reason for this phenomenon is that a greater increase in plasma concentration of ionized calcium would be expected with the use of a higher dialysate calcium concentration (8–12). Calcium infusion has been shown to suppress somewhat the hyperplastic parathyroid glands found in uremic patients (13). There is, however, a difference between calcium infusion and dialysis: during calcium infusion there is a negative correlation between ΔIPTH% and Δserum calcium, whereas in our dialyzed patients such a correlation was not observed. The absence of such a correlation was very likely due to the fact that the rate of calcium gain during dialysis (12) was considerably less than that obtained during calcium infusion as reported by Reiss, Canterbury, and Egdahl (13).

The positive correlation observed between predialysis plasma concentrations of IPTH and calcium suggests strongly that an increased rate of PTH secretion is essential to maintain plasma concentrations of calcium within the "normal range" under these conditions. In contrast with the normal state (14), many factors presumably are acting to decrease the plasma calcium, and PTH secretion increases in response. Our observation agrees with the association which has been shown by Stanbury and Lumb (15) to exist between increased serum calcium concentration and increased hyperplasia of the parathyroid glands.

It is noteworthy that no significant change in predialysis plasma calcium concentration was observed when dialysate calcium was decreased. This does not necessarily contradict the finding that patients who had been dialyzed against 6.0–6.5 mg/100 ml had a lower mean predialysis plasma calcium concentration than those dialyzed against a lower concentration. In the latter observation, plasma calcium concentrations were compared after considerably longer periods, and it is possible that the differences in the plasma calcium require longer than 3 wk to develop.

The stepwise regression study also showed that other factors were important influences. The most important of these factors was the serum calcium concentration before the start of long-term dialysis. Because we found that plasma calcium during long-term dialysis was an index of the degree of parathyroid hyperfunction, it appears probable that parathyroid status before institution of long-term hemodialysis was a major determinant of the parathyroid response to dialysis.

The next most important factor which yielded a significant partial correlation with plasma IPTH was the mean predialysis plasma phosphate concentration throughout the entire period of dialysis. Since the coefficient was positive, this suggests that retention of phosphate also may stimulate parathyroid function, most likely by decreasing plasma ionized calcium.

The observation in this study that a decrease in predialysis plasma phosphate concentration is significantly associated with a decrease in predialysis plasma IPTH is, to our knowledge, the first reported evidence that control of the plasma concentration of phosphate between dialyses is of importance in the control of parathyroid hyperfunction in patients being treated by long-term hemodialysis. Increase of plasma phosphate between dialyses is well known, as is the usually concomitant decrease in plasma total calcium concentration. Although it has been suggested (16–19) that this phenomenon could lead to stimulation of parathyroid function, no evidence for it in man has been reported. Bilinsky and associates[5] have shown that phosphate depletion decreased PTH in mild renal insufficiency but not when the renal failure was severe.

Sherwood et al. (14) have reported previously that the plasma calcium level is the primary factor in the regulation of PTH secretion, whereas plasma phosphate concentration has no direct effect. In these studies, phosphate infusions led to a delayed increase of plasma IPTH coincident with the delayed decrease in plasma calcium concentration. In our patients, a decrease in plasma phosphate concentration was significantly associated with an increase in plasma total calcium concentration.

No significant associations were found, however, between the decrease in plasma phosphate and the increase in plasma ionized calcium or the decrease in IPTH and the increase in ionized calcium. Appropriate trends were

[5] Bilinsky, R., A. Kanter, J. M. Canterbury, and E. Reiss. 1968. Spectrum of hyperparathyroidism in chronic renal insufficiency (abstract). Read at the second annual meeting of the American Society of Nephrology, Washington, D. C., November, 1968.

observed, but the number of measurements of plasma ionized calcium was insufficient to confirm or refute these trends.

At the present stage of our investigations, we believe that certain firm conclusions can be made: (*a*) a dialysate calcium concentration of 6.0–6.2 mg/100 ml more effectively controls the parathyroid hyperfunction of patients during chronic hemodialysis than does a concentration between 4.9 and 5.6 mg/100 ml; (*b*) this is one reason why roentgenographic evidence of bone disease is less frequent with the use of higher dialysate calcium concentrations; and (*c*) phosphate retention is an additional factor which may stimulate PTH secretion, perhaps by its effect of decreasing serum calcium. Although it is clear from the present studies that the higher concentrations of dialysate calcium are to be preferred for long-term hemodialysis, it is not equally apparent that long-term phosphate withdrawal is beneficial. The potential value of reducing secretion of PTH by decreasing the serum phosphate concentration must be weighed against possible protective effects of the hyperphosphatemia (20). Only long-term extensions of the present studies will provide the appropriate answer.

ADDENDUM

Since submission of the present paper, a report by O'Riordan, Page, Kerr, Walls, Moorhead, Crockett, Frauz, and Ritz has appeared (Hyperparathyroidism in chronic renal failure and dialysis osteodystrophy. 1970. *Quart. J. Med.* **33**: 359.). These authors address themselves to questions which are similar to those which we have examined, but their results have led them to conclusions which, in many respects, are at odds with ours. We are of the opinion that these discrepancies are most probably related to differences in experimental design, the rigidity with which dialysate calcium concentrations were monitored, possible geographic differences in etiologic factors involved in the production of "renal osteodystrophy," and differences in the sensitivity and specificity of the radioimmunoassay for parathyroid hormone used in the two studies.

ACKNOWLEDGMENTS

We thank Miss Judith A. Hess, Mrs. Karen Laakso, and Miss Julianna Bischoff for expert technical assistance.

This investigation was supported in part by Research Grant No. AM-12302 and Research Contract 69-2168 from the National Institutes of Health, U. S. Public Health Service.

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