PARATHORMONE DOSAGE AND SERUM CALCIUM AND PHOSPHORUS IN EXPERIMENTAL CHRONIC HYPERPARATHYROIDISM LEADING TO OSTITIS FIBROSA[1]

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Clinical ostitis fibrosa cystica (von Recklinghausen's disease) has been found to be associated with parathyroid enlargements. In experimental rickets and other conditions the enlargement of these glands seems to be secondary to the deficiency. However, accumulated clinical evidence favors hyperparathyroidism as the cause of von Recklinghausen's disease.[2] We have attempted to furnish experimental evidence for this view. The relative tolerance of guinea pigs to parathormone enabled us to induce in this animal a condition of severe but non-fatal chronic hyperparathyroidism, leading to ostitis fibrosa (3, 4).

We proceeded on the working assumption that while hypercalcemia is one indication of parathormone action, its reported absence in guinea pigs was not a proof of immunity to parathormone, for parathormone might cause the mobilization and excretion of calcium, as well as produce its other associated effects, without necessarily raising the serum calcium. Single injections of large doses (20 units per 100 gm.) of parathormone resulted not only in hypercalcemia but also in hyperphosphatemia, which were most pronounced in young guinea pigs fasted for 60 hours; severe and extensive bone resorption, with injury of the bone marrow, occurred only in young guinea pigs. Prolonged treatment with parathormone resulted in varying degrees of bone

[1] A preliminary report of this work has been published (1). The bone changes were reported in a companion paper (2), to which reference may also be made for protocols and for details which have been omitted from the present paper in order to avoid unnecessary duplication.

[2] Barr and Bulger recently reviewed the literature of this subject in the *Am. J. Med. Sc.*, 1930, **179**, 449.

resorption and marrow fibrosis, depending on the daily dose and the length of treatment; bone resorption occurred in young animals even in the absence of hypercalcemia; hypercalcemia was found after the largest doses, but toxic symptoms (with hyperphosphatemia) were absent even after the largest doses when these had been preceded by treatment with smaller doses, some compensation having apparently been established by this means.

A procedure similar in principle was employed to produce chronic hyperparathyroidism in the dog. The dog, as is well known, is very sensitive to moderate doses of parathormone as well as to overdosage (5). While this sensitiveness has been an advantage in studies of acute hyperparathyroidism, it has limited the dog's usefulness in prolonged experiments. Greenwald and Gross (6) found negative calcium and phosphorus balances (in adult dogs after a prolonged period of parathormone treatment) of such magnitude as to be clearly due to bone depletion, though this was not demonstrable by the X-ray (7). Histological studies were not made. The dosage had necessarily been limited by the need of avoiding fatal effects.[3]

It was our aim not only to induce a condition of chronic hyperparathyroidism, but also to maintain this condition for periods as long as possible, in order to allow the most definite development of the bone lesions. We preferred young animals on an *a priori* assumption that bone changes may be expected to be more pronounced in an actively growing animal. This assumption has found its experimental justification in the standard methods for the production of rickets. The more pronounced effects of parathormone upon the serum calcium which we have observed in actively growing animals may be related to the greater availability of their calcium reserves.

After having established the limits of safe and effective parathormone dosage at different levels of calcium intake (9), we studied the responses of serum calcium and phosphorus to single parathormone

[3] The results of Morgan and Garrison (8), showing the influence of vitamin D on response to parathormone, were reported after most of the present study had been completed. Among their dogs there was one 3.5 months old at the beginning of the experiment, on an adequate diet, which received repeated parathormone treatment for 5 weeks. They did not report on the mineral metabolism of this dog, or on the bone changes.

injections, which are different in chronic hyperparathyroidism from the typical responses of normal dogs, and tested in dogs the assumption of immunity that has been advanced to explain the absence of hypercalcemia in man after repeated parathormone injections (10, 11). The bone changes were studied by histological methods and the findings are given here very briefly, as an indication of a negative mineral balance under the various conditions, in presence as well as in absence of hypercalcemia. They have been reported in detail in another paper (2). A chemical study of the effects of chronic hyperparathyroidism upon bone composition will be published later.

Experimental Methods

The puppies, 6 to 9 weeks old, and weighing 1 to 2 kg. at the beginning of the experiments, were of the same series as those reported in the companion paper (2), where brief diet notes were given. We have found our diet—lean meat supplemented with about 10 per cent canned tomato and 1 cc. cod liver oil—adequate for rapid growth over long periods, even when no calcium supplement was given, although in the latter case osteoporosis developed in controls not receiving parathormone (12).

Calcium Supplement.—In order to ascertain the effects of calcium intake, the basal (low calcium) diet was given without calcium supplement, and with small, adequate and liberal calcium supplements (10 per cent calcium lactate solution by stomach tube, or bone meal and calcium lactate mixed with a small portion of the meat mixture). Calcium supplement was sometimes omitted for 1 day before a special interpolated test (see page 594), in order to avoid possible effects of ingested calcium. An interval of almost 48 hours was thus allowed, although the serum calcium rise after the ingestion of calcium disappeared in parathormone treated animals within a few hours (12).

Parathormone Injections.—Parathormone (Lilly) was injected subcutaneously, usually at about 4 p.m., unless contraindicated. Anorexia, even in the absence of hypercalcemia, was a generally reliable indication of overdosage, and of the imminence of more urgent symptoms.

Blood Analyses.—The food was removed about 18 hours before the blood was drawn for analysis. Blood was drawn from the jugular vein. Serum calcium was determined by the Clark-Collip modification of the Kramer-Tisdall method. The Benedict-Theis method was employed in the serum phosphorus analyses.

We adopted intervals of about 18 hours after injections of parathormone as most suitable for the determination of overdosage effects on the serum calcium and phosphorus (see Discussion, page 601). To study the effects of a single dose in detail we employed shorter intervals.

Recovery Periods and Special Tests.—Parathormone was sometimes discontinued or reduced during recovery periods (indicated in the tables as R-1, R-2, etc.)

when overdosage was suspected. Parathormone doses were sometimes increased in special interpolated tests. In the experiments that were thus interpolated (E-1, E-2, etc.) care was taken not to interfere with the principal object of producing and maintaining a state of chronic hyperparathyroidism.

Serum Calcium and Phosphorus in Chronic Hyperparathyroidism

In preliminary experiments (9) to establish the limits of safe—or highest non-fatal doses,—and effective—or the lowest doses with which bone resorption could be demonstrated—we found that daily parathormone injections of 1 unit per kg. at no time resulted in overdosage or hypercalcemia at the 18 hour interval, even on a liberal calcium diet; slight bone resorption indicated a negative mineral balance. On a low calcium intake an initial dose of 2 units per kg. could be employed, which could be raised gradually to 6 units per kg. without symptoms of overdosage; bone resorption and fibrosis were definite. An initial dose of 4 units per kg. produced hypercalcemia and overdosage both on low and liberal calcium intakes, presumably due to an abundant store of readily available calcium in the tissues.

The experience gained in the preliminary tests enabled us to avoid fatal overdosage and to maintain a group of puppies in a condition of chronic hyperparathyroidism on varying calcium intakes.

Liberal Calcium Intake.—Puppy 7 (initial weight 1.3 kg.) received an average calcium supplement of 0.65 gm. daily and during most of the period of treatment (106 days) received 2 units of parathormone per kg. daily. (The details are given in Table I.)

Daily injection of 1.5 to 4 units per kg. was found at first to produce symptoms of overdosage, although hypercalcemia was absent (Periods 1, 2 and 3). Doses of about 5 and 4 units per kg. (Periods 5 and 7, respectively) resulted in more pronounced symptoms, with hypercalcemia, while hypercalcemia had been absent or slight and no symptoms of overdosage had appeared in the intervening Period 6, on 2.5 units per kg. The animal was therefore continued on about 2 units per kg. Its condition remained good.

The puppy was sensitive to parathormone throughout: On the 67th day of the experiment (Period E-1), on the 97th day (Period E-2c) and the 105th day (Period E-3b) single doses caused the serum calcium to rise about 1 mg. per unit per kg.

It is noteworthy that in experimental Periods E-2c and E-3b the rise of serum calcium after a single dose of parathormone was accompanied or followed by a rise of serum phosphorus (see Discussion, page 601).

The typical changes of ostitis fibrosa were found at autopsy.

TABLE I[4]

Course of Chronic Hyperparathyroidism on a Liberal Calcium Intake

Period No.	Duration	Weight (end of period)	Daily treatment			Serum analyses				Remarks
			Average food intake	Calcium supplement	Parathormone	Day	Hrs. after injection	Calcium	Phosphorus	
	days	*kg.*	*gm.*	*gm.*	*units*					
1	7	1.5	110	1.3	2					Vomited repeatedly
2	17	1.8	150	.60	4	4	18	11.9		" "
3	4	2.0	200	.60	8	3	18	11.3		" "
4	2	2.0	250	.60	12	1	20	Lost		No food taken on 2nd day
R-1	4	2.0	110	.60	0	3	18	11.4		Recovery period
5	4	2.1	240	.60	10	4	18	15.6	6.3	Anorexia on last day
R-2	2		210	.60	0					Recovery period
6	21	3.5	360	.60	8	1	18	12.2	8.9	Condition good
						4	18	12.6		
						12	24	13.7	9.0	
						19	21	11.1	8.6	
7	3	3.2	120	.20	14	1	20	14.5	7.8	Appetite failed rapidly
R-3	1		140		0					Recovery period
E-1	1			0	12		22	17.1	5.2	Test of effects of a single dose
R-4	2	3.0	0		0					Recovery period. Refused food, but active
8	7	3.3	300	.65	6	5	21	11.5	7.0	Condition good henceforth
9	18	4.0	370	.65	8	5	18	11.2	8.5	
						12	18	11.0	8.0	
E-2a	1		320	.65	0					
2b	1		0	0	0					
2c	1			0	8		Init.	10.8	8.7	Test of effects of a single dose
							3	12.8	8.5	of parathormone
							6	12.6	8.9	
							9	12.0	9.3	
							12	11.2	9.3	
							24	9.8	8.5	
10	6	4.4	465	.65	8					
E-3a	1		0	0	0					
3b	1			0	8		Init.	12.0?	6.4	Test of effects of a single dose
							3	13.4	7.2	of parathormone
							24	12.0	6.5	

Serum calcium and phosphorus are stated in mg. per 100 cc.

[4] For convenience of presentation periods of treatment with a given dose are distinguished by number in the tables from periods of recovery from overdosage (R-1, R-2, etc.) and from experimental periods (E-1, E-2, etc.) interpolated to elucidate certain special problems.

Liberal Calcium Supplement after a Control Period on a Low Calcium Supplement.—Another puppy (No. 6, initial weight 1.1 kg.) was placed for 6 weeks on an average daily calcium supplement of 0.125 gm. and on daily doses of parathormone increasing from 2 to 6 units per kg. As usual, hypercalcemia associated with symptoms of overdosage was found early in the treatment. The serum calcium was, however, normal (10.6 mg. per 100 cc.) during the last week of the period, on 6 units per kg. daily; the serum phosphorus was 7.5 mg. per 100 cc.; the puppy had been eating well and gaining weight.

The daily calcium supplement was then increased to 1.2 gm., the dose of parathormone remaining the same. Pronounced hypercalcemia (15.3 mg. of calcium per 100 cc.) followed. The calcium supplement was reduced to 0.65 mg. daily and the parathormone to 4 units per kg. Hypercalcemia (19.0 and 18.5 mg. of calcium per 100 cc.), was followed later by evidence of compensation (12.6 and 11.3 mg.). The animal, however, declined with loss of appetite and other symptoms of overdosage. Bone and soft tissue changes due to terminal acute hyperparathyroidism were found, superimposed upon some bone resorption with marrow fibrosis due to chronic hyperparathyroidism.

Thus, even after a long period of treatment, doses well tolerated on a lower calcium intake proved fatal on a liberal calcium intake.

Calcium Deficient Diet.—Puppy 8 (initial weight 1.1 kg.) received no calcium supplement except during a short period of recovery, when calcium administration seemed necessary to prevent the animal's decline and death (R-2), and during a final experimental period (E-6). In this animal some of the characteristic phenomena of chronic hyperparathyroidism were observed most clearly and the data (given in Table II) are therefore discussed in greater detail.

The low calcium diet apparently enabled this animal to tolerate relatively large doses of parathormone (up to 6 units per kg. in Period 4) without hypercalcemia or symptoms of overdosage. Prolonged parathormone administration resulted eventually in a striking hypocalcemia, which was associated with hyperphosphatemia, which was particularly pronounced when the animal developed tetany or rigor (Periods 6, 7 and R-2). It is noteworthy that when the puppy went into tetany its serum calcium was considerably higher and its serum phosphorus lower than in tetania parathyreopriva (about 8 and 12 mg. per 100 cc., respectively, as compared with about 6 and 15 mg.) (12). Calcium lactate by stomach tube gave prompt relief from tetany; as a result of continued calcium treatment, the postabsorptive serum calcium rose from about 8 mg. per 100 cc. to over 9 mg. at the end of Period R-2 and during Period E-1. To save the life of the animal, parathormone was discontinued for 44 days (Periods 8 and 9); the animal gained weight for about 5 weeks; the serum calcium remained consistently low and the serum phosphorus rose. After parathormone administration had been resumed (Period 10) the serum calcium remained low when not under the influence of the last dose of parathormone. The serum phosphorus was definitely lower during the late part of the treatment.

TABLE II[4]

Course of Chronic Hyperparathyroidism on a Calcium Deficient Diet

Period No.	Duration	Weight (end of period)	Daily treatment			Serum analyses				Remarks
			Average food intake	Calcium supplement	Parathormone	Day	Hrs. after injection	Calcium	Phosphorus	
	days	*kg.*	*gm.*	*gm.*	*units*					
1	7	1.2	110	0	2					Condition good
2	17	1.6	130	0	4	4	18	13.0		" "
3	5	1.7	180	0	6	3	18	11.4		" "
4	5	2.0	220	0	12	4	18	10.9		" "
5	5	2.1	300	0	16					Vomited on last day
R-1	1		80	0	0					Recovery period
6	8	2.4	240	0	6	1	18	9.6	9.4	
						8	18	8.1		Sensitive to handling
7	3	2.4	300	0	10	3		8.1	9.4	Tetanic seizures, frequent at
R-2	9	2.6	240	.60	0	1		7.8	10.7	first, with respiratory fail-
						2		9.9	7.1	ure, spasmodic defecation
						3		8.7	11.0	and urination; marked
						4		8.9	9.4	weakness. Gradual im-
						7		9.4	9.1	provement in Period R-2
E-1a	1			0	0			9.2		Controls on values in Period
								9.0		E-1b below, at the same
								8.7		hours
								8.7		
E-1b	1			0	10		Init.	8.7		Test of effects of a single dose
							3	8.7		of parathormone
							9	11.0		
							22	9.3		
8	32	3.3	340	0	0	3		9.9		Condition relatively good at
						6		8.2	7.5	first, but getting weaker to-
						9		8.4	8.5	ward the end of the period,
						14		9.2	8.1	and more sensitive to han-
						17		8.5	9.0	dling
						24		8.5	10.0	
E-2	1			0	6		Init.	8.0	10.0	Test of effects of a single dose
							3	9.2	12.4	of parathormone; tetanic
							6	8.4	10.0	seizure when handled at the
							9	8.8	10.5	3 hour interval
							12	8.2	10.1	
							24	7.8	10.1	
9	11	3.1	220	0	0	7		7.8		
10	2	3.1	215	0	3					

Serum calcium and phosphorus are stated in mg. per 100 cc.

TABLE II[4]—*Concluded*

Period No.	Duration	Weight (end of period)	Daily treatment			Serum analyses				Remarks
			Average food intake	Calcium supplement	Parathormone	Day	Hrs. after injection	Calcium	Phosphorus	
	days	*kg.*	*gm.*	*gm.*	*units*					
11	20	3.3	245	0	8	8	13	8.0	6.7	Note higher calcium value at the 8 hour interval
						12	8	9.2	6.3	
						20	20	8.0	7.3	
E-3a	1		300	0						
3b	1			0	16		Init.	7.9	7.8	Test of effects of a single dose; rigid when handled
							9	8.6	8.5	
12	25	3.4	230	0	8	5	22	7.6	8.6	Progressively increasing weakness and skeletal deformities
						19	22	7.5	8.0	
E-4a	1		110	0	0					
4b	1			0	30		Init.	7.7	7.2	Test of effects of a single dose of parathormone
							9	8.6	8.9	
13	2		0	0	8					Animal refused to eat
E-5	1			0	70		20	10.7	7.2	Test of a single large dose
E-6	7	2.9	90	.10	20	3	20	9.6	6.2	
						6	20	7.8	6.4	Bloody diarrhea

The puppy remained sensitive to single doses of parathormone even in the late stages of chronic hyperparathyroidism, as shown by its serum calcium about 9 hours after the injection. (Periods E-1b, 62nd day; E-2, 95th day; 11, 121st day; E-3b, 130th day; E-4a, 157th day of the treatment). Plateau effects were obtained with very large doses (E-5 and 3rd day of Period E-6). The serum phosphorus also rose after single doses of parathormone (E-3b and E-4b).

Thus, even toward the end of the experiment immunity to parathormone had not been established, although, due to the reduction of the readily available calcium reserves, the conditions were obviously not favorable to a demonstration of a marked calcium rise from the usually hypocalcemic level, except with very large doses. The serum calcium rise (per 100 cc.) was at first about 0.5 mg. per unit per kg., decreasing later.

The typical changes of ostitis fibrosa were produced in this animal in the severest form. The effect of chronic hyperparathyroidism was thus enhanced by calcium deprivation, but was distinct from that of calcium deprivation as such—osteoporosis, which is easily distinguishable in the gross examination of the skeleton.

Calcium Deficient Diet Preceded by an Adequate Calcium Intake.—In another puppy (No. 10, initial weight 1.1 kg.), a period of about 60 days on a calcium

deficient diet was preceded by a period of about 100 days on an average daily calcium supplement of 0.2 gm. Hypercalcemia and anorexia were marked early in the treatment on a dose of parathormone of 1.5 to 4 units per kg., and were still observed as late as the 67th day of the treatment; hyperphosphatemia (9 to 10 mg. per 100 cc.) in absence of hypercalcemia was frequent, and hypotonia appeared. The dose was reduced to 2 units per kg., and the animal gained weight, showing a normal serum calcium but a high serum phosphorus (8 to 9 mg. per 100 cc.).

After the elimination of the calcium supplement, increasing doses (up to 4 units per kg.) were required to produce an equal serum calcium elevation, which was consistent although slight, and was associated with a characteristic serum phosphorus rise (see Discussion, page 601). The serum phosphorus rose from an average initial value of 7.0 mg. per 100 cc. to an average of 8.0 mg. within 3 to 9 hours after the injection.

During a terminal 25 day period on 20 units of parathormone daily (4 units per kg.) a consistent decline of serum phosphorus occurred from an average of about 7 mg. per 100 cc. at the beginning of the period to about 6 mg. at its end. Hypercalcemia and urgent symptoms of overdosage were absent. On the other hand, hypocalcemia was prevented by an average supplement of 0.1 gm. of calcium per day.

The typical lesions of ostitis fibrosa were produced, but not in as severe form as in Puppy 8.

Variations of Calcium Intake.—Puppy 9, initial weight 2.3 kg., received an initial daily calcium supplement of 0.2 gm. for 24 days, 0.65 gm. for 57 days, no supplement for 59 days and 0.1 gm. for 25 days. (The details are given in Table III.)

On a supplement of 0.2 gm., early hypercalcemia appeared as usual, but soon disappeared, to reappear (Period 5) when the supplement was increased to 0.65 gm., the parathormone dose remaining constant (4 units per kg.). But even on this liberal calcium intake hypercalcemia tended to disappear (Periods 5 to 7 inclusive). The puppy gained weight during Period 5, on about 3 units per kg.; when parathormone was increased to 4 units per kg. (Period 6) symptoms of overdosage appeared, without hypercalcemia, but with a slight increase in serum phosphorus (as compared with the figures in Periods 5 and R-4); after a decrease of the dose to 2 units per kg. (R-4 and 7) the animal gained weight and was otherwise in good condition.

2 and 29 days after the elimination of the calcium supplement, serum calcium showed definite effects of a single dose (Periods E-1b and E-2b), but very slight effects were shown 25 days later (Period E-3b). A tendency to hypocalcemia had already appeared, as in Puppy 8. Severe hypocalcemia, with associated extreme effects, as observed in Dog 8, was prevented by a small calcium supplement. As in Dog 10, the final long period of relative overdosage resulted in a gradual decline of serum phosphorus.

The typical changes of ostitis fibrosa were produced, not in as pronounced form as in Dog 8, and substantially identical with those in Dog 10.

TABLE III[4]

Effect of Changes of Calcium Intake upon the Course of Chronic Hyperparathyroidism

Period No.	Duration	Weight (end of period)	Daily treatment			Serum analyses				Remarks
			Average food intake	Calcium supplement	Parathormone	Day	Hrs. after injection	Calcium	Phosphorus	
	days	*kg.*	*gm.*	*gm.*	*units*					
1	6	2.0	200	.20	4					
2	4	2.0	160	.20	8	3	18	16.4		Loss of appetite
R-1	6	2.1	160	.20	0	5	18	11.3		Recovery period
3	4	2.3	255	.20	6	4	20	12.4	6.9	Overdosage suspected
R-2	2		245	.20	0					Condition good
4	2	2.1	130	.20	8	1	20	11.4	7.3	Vomited on 2nd day
R-3	2	2.1	125	1.3	0	2	68	11.0		Recovery period
5	17	3.0	265	.65	8	8	24	15.0	6.5	Appetite better; condition
						9	21	15.5	6.3	good
						15	24	10.9	6.1	
6	7	2.8	180	.65	12	1	24	12.1	7.0	Appetite decreased toward the
						5	20	11.1	7.0	end of the period
R-4	8	3.0	240	.65	6	5	21	11.0	5.8	Dose reduced; condition better
7	25	3.8	380	.65	8	4	24	10.7	5.6	Condition good
						11	18	10.9	6.1	
E-1a	1			0	0					
1b	2			0	8	1	Init.	12.4	5.4	Test of effect of single dose at
							3	13.8	5.9	the end of régime of liberal
							25	11.8	4.8	calcium intake
8	24	4.0	350	0	8	12	12	10.0	6.5	Condition good
						16	8	9.6	6.6	Note decreased parathormone
						24	20	9.6	5.1	effect at early intervals
E-2a	1		300	0	0					
2b	1			0	16		Init.	9.6	6.4	Test of effect of a single dose
							9	12.2	6.6	
9	25	5.1	450	0	8	19	20	8.5	7.4	Note hypocalcemia
E-3a	1		510	0	0					
3b	1			0	30		Init.	8.7	7.9	Test of single dose. Note
							9	9.3	7.9	continuing hypocalcemia
10	3	5.2	515	0	10					
E-4	25	5.4	370	.10	20	3	20	9.9	6.9	Gradual decrease of appetite;
						6	20	10.1	6.8	refused food on last day of
						10	18	10.8	6.9	the period. Note gradual
						17	18	10.7	6.2	decline of serum phos-
						24	24	10.7	6.1	phorus

Serum calcium and phosphorus are stated in mg. per 100 cc.

DISCUSSION

In chronic hyperparathyroidism the curves seem to be quite different from those observed in normal dogs after single injections of parathormone (11); the effect of a single moderate dose reaches its maximum before the 12th hour, and disappears within 18 hours; after large doses hypercalcemia may persist beyond that interval (plateau effect); when hypercalcemia is absent, the serum phosphorus will frequently be raised at the same late interval after an excessive dose. We therefore consider an interval of at least 18 hours after the injection of parathormone as suitable for the detection of overdosage in experimental chronic hyperparathyroidism. Earlier intervals may be employed for a more detailed study of responses to moderate as well as large doses.

While the influence of the calcium intake on the serum calcium response to parathormone which we observed was perhaps to be assumed *a priori*, the relative unimportance of this influence in young animals at the beginning of the parathormone treatment is of particular interest, indicating the influence of readily available reserves on the serum calcium after parathormone injections. The tolerance to parathormone that Morgan and Garrison (8) found in animals on a vitamin free diet is analogous in some respects to that found on a calcium poor diet later in the treatment.

While in normal dogs the serum phosphorus is lowered by a single dose of parathormone, the serum phosphorus rose in puppies suffering from chronic hyperparathyroidism at early intervals (9 hours and earlier) after a single moderate injection. Sometimes the increase of serum phosphorus was the earliest response and frequently the only response to a single parathormone injection in these dogs, when the serum calcium rose slightly, if at all. Thus, after long periods of parathormone treatment absence of hypercalcemia points not to immunity but to a modification of the response to parathormone. We are continuing the study of this phase of the subject.

The similarity between the association of low serum calcium and high serum phosphorus in chronic hyperparathyroidism on low calcium diets and that observed in renal rickets suggests further investigation.

The hyperphosphatemia distinguishing experimental chronic hyperparathyroidism in young dogs was also in contrast to the hypophos-

phatemia found in the clinical cases of ostitis fibrosa cystica (von Recklinghausen's disease). This difference may be due to the age of the animal, as well as to the method of treatment which frequently approached the limit of the dog's tolerance. There are, of course, many differences between the experimental procedure and the spontaneous clinical process. Age and species differences, as well as the duration of the state of hyperparathyroidism are among the factors that may affect the various associated phenomena.

We have found, for instance, ready bone resorption after single and repeated doses of parathormone in young guinea pigs, but not in the adult (2, 4). Hirsch (13) suggested that the clinical condition begins frequently in childhood and has a long course before it becomes clinically obvious.

The influence of the species factor is illustrated by a comparison with our results in chronic hyperparathyroidism of guinea pigs (4). As a result of previous treatment with smaller doses, a modified response to parathormone appeared both in the guinea pig and in the dog, and toxic symptoms tended to disappear. In that stage, hypercalcemia was observed in the guinea pig without hyperphosphatemia, while in the dog, hyperphosphatemia was present, while hypercalcemia was frequently absent, particularly on a limited calcium intake.

The common symptoms of chronic hyperparathyroidism were most severe in Puppy 8, on a calcium deficient diet, but were present, although in not as severe form, in the other puppies. Among these the most important were general hypotonia, muscular weakness and bone deformities with frequent fractures—also characteristic findings in clinical cases of hyperparathyroidism.

The essential bone lesions of ostitis fibrosa, which were generalized (involving all the skeletal bones studied—skull, jaw bone, long bones, ribs), were most severe on low calcium diets, but were distinct from the effects of low calcium diets as such. While calcium deficiency *per se* is quite compatible with rapid growth, parathormone administration retarded bone formation and growth in a very striking manner (2). Extensive bone and marrow fibrosis, with the production of osteoid tissue and cysts, was the end result of the drastic combined effects of calcium deficiency and chronic hyperparathyroidism. In dietary

calcium deficiency a certain economy of calcium is still possible. With chronic hyperparathyroidism added, it was rendered more difficult.

SUMMARY

1. On a low calcium intake hypercalcemia tended to disappear in chronic hyperparathyroidism on a given dose of parathormone (as large as 6 units per kg.), apparently due to the reduction of a readily available calcium reserve. An increase of either the calcium intake or of the daily dose of parathormone caused a rise of serum calcium and symptoms of overdosage.

2. Hypocalcemia developed in chronic hyperparathyroidism in young puppies on a low calcium diet. Tetany occurred at a calcium level which was higher and a phosphorus level which was lower than in tetania parathyreopriva of young puppies. About 0.1 gm. of calcium daily was apparently sufficient to maintain the serum calcium at a normal level.

3. The serum phosphorus in chronic hyperparathyroidism in young puppies continued at or rose above the high level normal for young animals. Toward the end of long periods of treatment on large parathormone doses (about 5 units per kg.) serum phosphorus approached normal levels, pronounced hypercalcemia was absent but hypotonia and other symptoms of hyperparathyroidism were present.

4. A single dose of parathormone caused early in the treatment and on liberal calcium intakes a more marked relative rise of serum calcium than in normal adult dogs, confirming previous observations (5, 8). Later in the treatment and on low calcium intakes this effect was greatly reduced. Serum phosphorus rose after a single injection of parathormone, even when the effect on the serum calcium was slight or absent.

5. The continued effect of parathormone on serum calcium after prolonged periods of treatment, and the modified response of the serum phosphorus indicate tolerance due to some compensation, rather than immunity.

6. The bone lesions, presenting the essential features of ostitis fibrosa cystica (von Recklinghausen's disease) in varying degrees of severity, depending on the relation of the parathormone dose to the calcium intake and to the duration of the treatment, were most promi-

nent on low calcium intakes, which permitted the use of large doses of parathormone without fatal hypercalcemia and without symptoms of overdosage.

7. Clinical and experimental hyperparathyroidism are compared and discussed.

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