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Observations on the Effect of Parathyroid Hormone on Environmental Blood Lead Concentrations in Humans

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The effect of parathyroid hormone (PTH) on blood lead (Pb) concentrations was observed preliminarily in three different situations. Of 342 healthy bus drivers with no unusual exposure to Pb, 25 drivers with the highest and 25 with the lowest blood Pb were compared for serum PTH concentrations. There was no association between blood Pb and serum PTH concentrations. Eight women with postmenopausal osteoporosis enrolled in an experimental protocol to increase bone mass received daily PTH (1–34 fragment) for 1 week, calcitonin for the next 2 weeks, and oral calcium for the subsequent 10 weeks. This cycle was repeated four times during the year. Initial blood Pb concentrations averaged 6.0 μg/dl (range 2.1–8.9). Mean blood Pb concentrations decreased by 1.7 μg/dl over 1 year of therapy. The confidence interval for this change excluded zero, the mean change was significantly different from the mean change for comparative population ($P < 0.050$), and paired changes were statistically significant ($P = 0.045$). Lastly, a single subject with hyperparathyroid disease and no unusual exposures to lead demonstrated stabilized blood Pb concentrations that were 50% lower after removal of his hyperplastic parathyroid glands. These observations suggest that the effect of PTH on increasing bone turnover and releasing Pb into blood is not easily detected at low physiologic amounts of PTH, but that with pathologic increases of PTH in hyperparathyroid disease, elevation of blood Pb from bone or increased gastrointestinal absorption may be possible. Likewise, either bone building therapies (PTH + calcitonin + calcium) may move Pb from blood into bone or supplemental calcium may decrease Pb gastrointestinal absorption, thereby explaining the observed lower blood Pb concentrations.

INTRODUCTION

Most of the lead (Pb) in the body is stored in the bone. At steady state with low environmental exposures, up to 70% of the Pb in the blood is possibly due to equilibration from bone stores (Manton, 1985; Schutz *et al.*, 1987). Hormonal influences, such as parathyroid hormone (PTH) activity, on bone have long been thought to effect the mobilization of lead from bone. The direct effect of PTH on the release of bone lead from bone culture (Rosen and Trinidad, 1974) and the exchange rates for Pb in osteogenic bone cell culture (Long *et al.*, 1990; Pounds and Rosen, 1986) have been described, but only a few clinical studies have addressed this area. In 1927, Hunter and Aub showed that large doses of bovine parathyroid extract would induce a calciuria with concurrent increased lead excretion in lead-poisoned humans. Also, a role for PTH in altering Pb availability from bone due to renal osteodystrophy has been suggested (Colleoni and D'Amico, 1986; Osterloh and Becker, 1986; Van De Vyver *et al.*, 1988). Concern has also been expressed about the release of lead from bone due to pathophysiologic processes such as osteoporosis (Wittmers *et al.*, 1988; Silbergeld *et al.*,

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1988). In this paper, three preliminary observations are presented: the relationship of physiologic PTH concentrations to blood Pb concentrations in a population with low Pb exposure, the change in blood Pb concentrations in osteoporotic women receiving bone building therapy, and blood Pb concentrations in a single hyperparathyroid subject before and after hyperparathyroidectomy.

METHODS

Blood lead concentrations and serum PTH concentrations were previously measured in a population of bus drivers with environmental lead exposure who were part of an earlier study which examined the relationship between blood Pb and blood pressure (Sharp *et al.*, 1988). Briefly, this cross-sectional study of 342 bus drivers had been performed to investigate the association of blood pressure with blood Pb. Various confounders have been analyzed such as age, sex, race, body mass, smoking, and coffee use (Sharp *et al.*, 1988, 1989). The study design details, analytical techniques, and data analysis were given in the earlier reports. In order to ascertain if bone turnover might have been a covariate of blood Pb concentration, serum PTH concentrations were measured in stored serum samples from 25 subjects with the highest blood Pb concentrations and 25 subjects with the lowest blood Pb concentrations. Serum PTH concentrations were measured by the midregion PTH method (Arnaud *et al.*, 1971). Midregion PTH is a measure of intact and fragment PTH. Because only a small portion of this PTH measurement represents active PTH, it is often used as a surrogate for PTH activity in individuals without renal failure. The serum PTH concentrations in the two groups were compared with a Student t test. Analysis of covariance was performed for possible covariates of blood Pb concentrations upon the PTH concentrations. Selected covariates with complete data available were age, race, and caffeine concentrations.

In a second observation of women enrolled in a larger study for the experimental therapy of postmenopausal osteoporosis, eight women had blood lead concentrations determined over the course of therapy. Treatment consisted of daily subcutaneous injections of 400 U of teraparatide acetate, a 34-amino-acid fragment of PTH, (Parathar, Rorer Pharmaceutical Corp.), for 7 days. Daily injections of calcitonin (100 IU/day) were added for the next 14 days and oral supplementation with calcium (500 mg calcium carbonate) was given for 10 more weeks. This 13-week cycle was repeated four times during the year. Subjects would normally be enrolled for repeating cycles of therapy for a 2-year duration. Blood lead concentrations were measured prior to entering a cycle of treatment, after 3 weeks (PTH + calcitonin), and after 1 year (four cycles). Determinations were made by graphite furnace atomic absorption spectrometry. A comparison of blood Pb concentrations before and after therapy was performed with a paired Wilcoxon signed rank test.

This experimental procedure of sequential PTH, calcitonin, and calcium is intended to increase bone mass. Frost (1979) had proposed that bone building therapy might be based on the sequential events of activation, resorption, and formation which were observed experimentally in basic multicellular bone units. This concept has been extended to the experimental treatment of osteoporosis,

now called ADFR for activate, depress, free, and repeat. Current studies have used etidronate (or PTH in this study) to stimulate osteoclastic and osteoblastic activity, then calcitonin to repress osteoclastic activity, followed by a free period of coherent growth with calcium uptake and repetition of all three cycles. Studies to date using PTH or etidronate in this cyclical pattern have either reduced osteoporotic bone remodeling or resulted in gains in bone mass (Reeve *et al.*, 1987; Storm *et al.*, 1990).

A single subject with hyperparathyroid disease was studied before and after hyperparathyroid surgery. The subject was a 66-year-old male in whom an incidental measurement of serum calcium was found to be elevated. The subject had no obvious complications of hyperparathyroidism complaining only of fatigue and constipation. Elevated PTH concentrations (see Table 1) confirmed a diagnosis of hyperparathyroidism. Past medical history was unremarkable. The subject had no unusual past exposures to Pb. He was chelated with 1 g of $CaNa_2$–EDTA intramuscularly 2 weeks prior to scheduled surgery. Urine was collected for 24 hr. Blood for Pb concentration determination was drawn just prior to chelation and at the same time each day for 5 consecutive days after the injection of $CaNa_2$–EDTA. Four months after surgery, these procedures were repeated. Presurgical and postsurgical values are listed in Table 1. Blood and urine Pb concentrations were determined in triplicate by graphite furnace atomic absorption (Sharp *et al.*, 1988; Osterloh *et al.*, 1990).

RESULTS

In the healthy bus driver population, the mean blood Pb concentrations for the upper 23 individuals (one sample lost, one sample insufficient volume) and lower 24 individuals (one sample insufficient volume) were 12.0 ± 2.7 and 3.3 ± 0.7 μg/dl, respectively. Serum PTH concentrations in these two groups were the same (34.3 ± 9.0 and 34.3 ± 13.6 pg eq/ml, $P = 0.99$). The two groups were similar to

TABLE 1
PRE- AND POSTSURGICAL DATA FOR HYPERPARATHYROID SUBJECT

Sample	Analyte	Pre	Post	Normal range
S	Calcium (mg/dl)	11.9	9.5	8.5–10.7
S	Phosphorus (mg/dl)	2.0	2.7	2.5–4.5
S	Alkaline phosphatase (U/liter)	153	108	30–115
S	PTH (μg eq/ml)	300	30–67	<40
B	Pb (μg/dl), before chelation	10.0	5.2	
U	Pb (μg), 24-hr collection	52	38	
B	Pb_1	—	4.5	
B	Pb_2	9.6	5.2	
B	Pb_3	11.3	4.3	
B	Pb_4	9.6	3.9	
B	Pb_5	9.3	4.0	

Note. S, serum; B, blood; U, urine; pre, 2 weeks before hyperparathyroidectomy; post, 4 months after hyperparathyroidectomy. Subscripts are number of days after chelation. Standard error of triplicate blood Pb measurements is 1.5 at 5 μg/dl and 1.0 at 10 μg/dl.

the original cohort in age and race. The groups were not different from each other with respect to age, race, or caffeine concentrations (see Table 2). The potential covariates of age, race, or caffeine concentrations did not significantly affect the mean PTH concentration in each group as assessed by analysis of covariance.

The blood Pb concentrations in the eight postmenopausal females receiving PTH/calcitonin/calcium therapy are listed in Table 3. All eight subjects had initial blood Pb concentrations (mean = 6.0; range, 2.1–8.9 μg/dl) consistent with environmental exposure in this region (Sharp *et al.*, 1988). The mean change was a decrease of 1.7 μg/dl. The 95% confidence interval of this decrease (0.1–3.3 μg/dl) excluded zero and the paired changes from either baseline to 1 year or 3 weeks (after PTH and calcitonin only) to 1 year were significantly decreased ($P = 0.045$ and 0.014, respectively) using the Wilcoxon signed rank statistic. Comparing the mean change in blood lead in this study to that of a known population of postmenopausal women (+0.1397 μg/dl per year, Silbergeld *et al.*, 1988), the difference is also significant ($P < 0.05$, one sample t test).

For the subject with hyperparathyroid disease, the pre- and posthyperparathyroidectomy biochemical and blood lead data are given in Table 1. Five blood samples were taken to determine the stability of his blood Pb concentration and the effect of chelation, if any. The blood Pb concentrations decreased (50%) to lower concentrations after removal of his hyperplastic parathyroid glands. Blood Pb concentrations did not change as a result of chelation. The amounts of lead eliminated with chelation were not different when the hyperparathyroid and emparathyroid states were compared.

DISCUSSION

Serum PTH concentrations did not vary with high or low blood Pb concentrations in a small population of normal bus drivers with environmental blood Pb concentrations and normal serum PTH concentrations. Because of the small sample size and possible confounding, a weak association of PTH with blood Pb might have been missed. Of the limited variables available for all subjects, age, race, and caffeine were considered as possible covariates. Blood Pb will increase with age and black populations tend to have higher blood Pb concentrations. Age and race

TABLE 2
CHARACTERISTICS OF UPPER AND LOWER BLOOD Pb GROUPS

	Upper	Lower
n	23	24
Blood Pb (μg/dl)	12.0 (2.7)[a]	3.3 (0.7)
Age (years)	43.7 (7.8)	40.8 (6.9)
Race (%B)[b]	56	50
Caffeine concentration (ng/ml)	1193 (1058)	1211 (964)
PTH concentration (pg eq/ml)	34.3 (9.0)	34.3 (13.6)

[a] Standard deviation.
[b] Percentage of population as black.

TABLE 3
BLOOD Pb CONCENTRATIONS BEFORE AND AFTER TREATMENT IN EIGHT OSTEOPOROTIC WOMEN

	Blood Pb (μg/dl)			
Subject	Baseline	At 3 weeks*	At 1 year*	Change at 1 year
1	8.0	8.3	8.1	0.1
2	6.2	7.5	6.2	0
3	2.1	2.5	1.5	−0.6
4	4.3	9.4	5.1	0.8
5	6.5	3.8	3.0	−3.5
6	3.8	2.7	2.9	−0.9
7	8.4	NA	3.5	−4.9
8	8.9	7.9	4.1	−4.8
mean	6.0	6.0	4.3	−1.7**

Note. NA, not available.

* Significantly different from baseline ($P = 0.045$) and from 3 weeks time ($P = 0.014$) by Wilcoxon signed ranks test.

** 95% Confidence interval (0.1–3.3) excludes zero.

were similar in both groups and adjusting for age or race did not alter the means of PTH in each group. Caffeine can increase catecholamine release which can raise PTH concentrations slightly. Caffeine concentrations were similar in both groups.

The single hyperparathyroid subject studied showed a dramatic decrease in equilibrated blood Pb concentrations after hyperparathyroidectomy. If bone contributes up to 70% of Pb in blood (Manton, 1977, 1985; Rabinowitz *et al.*, 1973, 1976; Schutz *et al.*, 1987), then decreasing bone activity (after parathyroidectomy) may have been responsible for the decrease in blood Pb concentrations in this subject. However, decreased parathyroid activity may also cause a decrease in vitamin D-dependent gastrointestinal absorption of lead. Thus, higher levels of blood Pb during hyperparathyroidism may have been due to a greater bioavailability from the diet.

The eight postmenopausal osteoporotic women were subjects in an osteoporosis treatment trial. The sequential use of PTH, calcitonin, and calcium is considered to favor calcium incorporation into trabecular bone (Reeve *et al.*, 1987; Storm *et al.*, 1990). Thus, if Pb follows calcium into bone, this therapy might be expected to decrease blood Pb and increase trabecular bone Pb. Our observation was consistent with this hypothesis even though the small number of subjects has limited power to detect such change. However, a systematic type I bias may be at work, since this observation was uncontrolled for calcium intake. Therefore, while the net effect of PTH may result in an increase in gastrointestinal absorption of both calcium and Pb, the excess dietary calcium administered to these subjects may have prevented the usual gastrointestinal absorption of Pb, allowing for a new and lower steady state of blood Pb. Results of the larger clinical trial of PTH/calcitonin/calcium for treatment of osteoporosis are not complete. Preliminary data at 1 year suggest little or no change in bone density (personal commu-

nication with Dr. S. Harris). Recently studies using cyclic etidronate (osteoclast inhibition) and supplemental calcium have demonstrated efficacy in reversing the osteoporotic process in postmenopausal women (Storm *et al.*, 1990).

Altered physiologic or disease states might be expected to change the availability of Pb. In an overlooked manuscript by Hunter and Aub from 1927, it was demonstrated that by injecting a crude bovine parathyroid extract into patients suffering from lead intoxication, the urinary excretion of calcium and Pb (without chelation) was greatly increased in some individuals. This increase was thought to be due to the mobilization of Pb from bone sites. PTH concentrations are also elevated during chronic renal failure and may produce bone remodeling known as osteodystrophy. Van De Vyver *et al.* (1988) have shown that chelatable Pb is representative of bone lead among renal failure patients and that renal failure itself does not appear to contribute to the accumulation of Pb into bone, though Pb accumulation has been suggested to decrease its own renal clearance (Campbell *et al.*, 1981). Also, it has been shown that Pb burdens are no greater or no more prevalent in hypertensive nephropathy, a disorder where Pb may play an etiologic role, than in other causes of renal disease or in the general population (Osterloh *et al.*, 1989). However, it has been suggested that more Pb might be available for chelation due to increased bone turnover in renal osteodystrophy (Osterloh and Becker, 1986). Pb availability from bone may have been a factor in a study of Pb-related nephropathy. When gouty nephropathy patients were compared to other cases of renal disease with similar creatinine clearances (means = 40 ml/min), patients with gouty nephropathy excreted three times more chelatable Pb and had 69% greater serum PTH concentrations. In the gouty nephropathy patients, the urinary chelatable Pb correlated with the serum PTH concentration ($r = 0.73$) (Colleoni and D'Amico, 1986). PTH may have increased bone turnover and increased the availability of Pb in these subjects, or Pb may have inhibited vitamin D synthesis requiring compensatory elevation of PTH to maintain calcium homeostasis.

Other hormonal influences acting in concert with PTH may increase Pb availability. Bushnell *et al.* (1979) showed that the stress of confinement elevated cortisol and slightly raised blood Pb concentrations in monkeys. They hypothesized that Pb was mobilized from bone due to action of PTH release (via catecholamine effect) or direct action of minerocorticoids. Confinement leading to inactivity or lack of normal physical forces on bone may also produce bone demineralization as with the effects of weightlessness in space. A recently reported case of paraplegia in a child due to Pb intoxication suggested this effect. An immobilization osteoporosis with slightly elevated PTH concentrations was thought to have caused blood Pb concentrations to rise (Shannon *et al.*, 1988). The effect of PTH on the release of Pb from bone cultures *in vitro* has been demonstrated (Rosen and Trinidad, 1974). Such an effect of PTH *in vivo* might be exacerbated by the inhibitory effect of Pb on the renal synthesis of 1,25-dihydroxyvitamin D (Rosen *et al.*, 1980). Additionally, Pb itself may be responsible for retarding growth of bone by inhibiting formation more than resorption (Anderson and Danylchuk, 1977; Hass *et al.*, 1967).

One of the major concerns regarding the lifetime storage of Pb in bones is the

potential release of this toxin during normal physiologic states of osteoporosis and pregnancy. Trabecular bone is first affected by osteoporosis. The elegant data of Wittmers *et al.* (1988) have shown that trabecular bone (rib, vertebra, ilium), but not cortical bone, will lose lead content relative to calcium (Pb/Ca by weight) after the sixth decade of life in men and women. Thus, aging and the concomitant physiologic osteoporosis may produce greater Pb availability to the soft tissues, which may, in turn, increase toxicity, as well as availability for chelation. Concern for this process was recently heightened by Silbergeld *et al.* (1988). A cross-sectional analysis of blood Pb concentrations in the NHANES II database (1976–1980) for pre- and postmenopausal women was performed. After adjusting for eight blood Pb-related covariates, including age and race, and eight osteoporosis-related variables, the pre- vs postmenopausal difference in blood Pb was +12.6% for all women and +22.0% for women who were never pregnant (nulliparity is a risk factor for osteoporosis). Although this study did not study osteoporosis per se, women with clinical osteoporosis are likely to have even greater blood Pb increases.

While PTH concentrations are known to increase with age (Young *et al.*, 1987), PTH is not thought to be a major determinant of the loss of bone mass seen in osteoporosis (Raisz, 1988). Possible other causes include decreased vitamin D synthesis (Tsai *et al.*, 1984), poorer bone responsiveness, and loss of the additive effects of other steroid hormones (Raisz, 1988). PTH may also have a concentration-dependent differential effect on bone. At high concentrations, resorption will exceed formation, resulting in net bone loss. This may be the case for our result in the single patient with hyperparathyroidectomy. For intermittent low dose administration in animals, trabecular bone mass may actually increase (Gunness-Hey and Hock, 1984). The latter fact is also, in part, the strategy for the experimental treatment of postmenopausal osteoporosis in our study subjects.

The observations in this paper suggest that physiologic concentrations of PTH are an unlikely covariate of blood Pb concentration in environmentally exposed adults, but pathologic elevations in a single subject may have elevated blood Pb through increased bone activity or increased gastrointestinal absorption. Also, regimens used to increase bone mass may possibly decrease blood Pb. Further rigorously designed studies are needed to test these hypotheses.

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