Annu. Rev. Nutr. 1991. 11:93–119

PARENTERAL NUTRITION: Effect on Bone and Mineral Homeostasis

Gordon L. Klein

Department of Pediatrics, University of Texas Medical Branch, Galveston, Texas 77550

Jack W. Coburn

Medical and Research Services, Veterans Administration Medical Center of West Los Angeles and UCLA School of Medicine, Los Angeles, California 90073

KEY WORDS: total parenteral nutrition, calcium homeostasis, phosphate homeostasis, parathyroid hormone, vitamin D

CONTENTS

0199-9885/91/0715-0093$02.00

CLINICAL PROBLEMS IN MINERAL METABOLISM AND PARENTERAL NUTRITION

Metabolic bone disease has complicated the long-term use of parenteral nutrition in both adults and infants. The bone disease may be asymptomatic and associated with only roentgenographic evidence of demineralization (70). Alternatively, it may manifest itself as incapacitating periarticular pain (31), occasionally with fractures in adults (70), or as rickets with or without fractures in growing infants (28). Dynamic studies with tetracycline may show bone formation to be reduced, and histologically, the patients may exhibit osteomalacia (52) and/or reduced bone area (71). Disturbances in bone and mineral metabolism associated with parenteral nutrition likely contribute to the pathogenesis of these skeletal problems.

Table 1 Content of maintenance parenteral nutrition solutions:[a] nutrients per day

	Children	Adults
Dextrose	10–30%	10–30%
Protein[b]	2 g/kg	1–1.5 g/kg
Sodium	2–3 mmol/kg	60–150 mmol
Chloride	2–3 mmol/kg	60–150 mmol
Potassium	2–3 mmol/kg	60–150 mmol
Phosphate	1–2 mmol/kg	20–40 mmol
Calcium[c]	20–40 mg/kg (0.5–1 mmol/kg)	180–360 mg (4.5–9 mmol)
Magnesium	30–60 mg/kg (1.2–2.5 mmol/kg)	100–300 mg (4–12 mmol)
Acetate	0–2 mmol/kg	0–20 mmol
Multivitamin infusion[d]	1 vial	1 vial
Trace element solution[e]	0.3 ml/kg (up to 3 ml)	3 ml
Selenium	3 μg/kg (maximum 30 μg)	
Fat emulsion	1–4 g fat/kg	1–4 g fat/kg

[a] As used at the University of Texas Medical Branch.

[b] As crystalline amino acids.

[c] As 10% calcium gluconate.

[d] Multivitamin infusion for *pediatric* solutions contains the following per vial: vitamin A 0.7 mg, vitamin C 80 mg, vitamin D 10 μg (400 IU), vitamin E 7 mg, vitamin K1 200 μg, folic acid 140 μg, biotin 20 μg, thiamine 1.2 mg, riboflavin 1.4 mg, niacinamide 17 mg, pyridoxine 1 mg, cyanocobalamin 1 μg, dexpanthenol 5 mg. Multivitamin infusion for *adult* solutions contains the following per vial: vitamin A 1 mg, vitamin C 100 mg, vitamin D 5 μg (200 IU), vitamin E 10 μg, folic acid 400 μg, biotin 60 μg, thiamine 3 mg, riboflavin 3.6 mg, niacinamide 40 mg, pyridoxine 4 mg, cyanocobalamin 5 μg, dexpanthenol 15 mg.

[e] For *pediatrics* the trace element solution (3 ml) provides zinc 3 mg, copper 300 μg, chromium 3 μg, manganese 75 μg. For *adults* the trace element solution (3 ml) provides zinc 3 mg, copper 1.2 mg, chromium 12 μg, manganese 300 μg.

In this review we discuss the perturbation in bone and mineral homeostasis that arises as a result of long-term parenteral nutrition, and we consider how the body responds when nutrients are provided directly into the blood and bypass the intestine as the nutritional route. This review focuses on patients receiving prolonged parenteral nutrition (e.g. many months) and not on those receiving it for only a few weeks or less. Thus, greater amounts of nutrients may be required for treatment of malnutrition and marked hypophosphatemia that are encountered during the early period of parenteral nutrition than are needed later when tissue repair is no longer occurring.

COMPOSITION OF PARENTERAL NUTRITION SOLUTIONS AND METHODS OF ADMINISTRATION

In parenteral nutrition, hyperosmolar nutrient-dense solutions are administered by vein to individuals in whom intestinal dysfunction renders the alimentary tract incapable of digesting and absorbing the nutrients necessary to prevent and treat malnutrition. Generally, hospital pharmacies prepare either standardized or individualized sterile solutions under laminar flow conditions. Typical solutions used at the University of Texas Medical Branch at Galveston are shown in Table 1. The solutions include (*a*) the macronutrients carbohydrates, protein, and fat, (*b*) the micronutrient electrolytes, (*c*) the major minerals, such as calcium, phosphate, and magnesium, (*d*) vitamins, and (*e*) trace elements, such as zinc, copper, selenium, chromium, and manganese.

CALCIUM AND PHOSPHATE HOMEOSTASIS: NORMAL MECHANISMS AND EFFECT OF PARENTERAL NUTRITION

Parenteral nutrition may alter calcium and phosphate homeostasis by the following mechanisms: (*a*) the continuous provision of nutrients rather than periodic ingestion in the diet, (*b*) a lack of intestinal absorption, (*c*) alteration of urinary excretion of calcium and phosphate, (*d*) altered distribution of calcium and phosphate pools in soft tissue, bone, and intracellular spaces, (*e*) changes in secretion and/or action of parathyroid hormone, and (*f*) changes in the production and bioactivation of vitamin D. No studies have been performed comparing the effects of continuous and periodic nutrient intakes on mineral homeostasis. The other perturbations listed above are discussed below.

Intestinal Absorption

Under normal circumstances, dietary calcium enters the blood via absorption, primarily from the duodenum and jejunum; this occurs by both pericellular

nonsaturable passive diffusion and transepithelial saturable active transport, which is dependent on calcitriol, or 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) (19). This biologically active vitamin D sterol stimulates the production of intracellular calcium-binding proteins(s) (19), and it may alter the phospholipid composition of the enterocyte membrane (14). Indirectly, the intestine buffers the variation in dietary calcium intake by altering the efficiency of calcium absorption; thus, in a healthy adult, an increase in calcium intake from 220 to 2000 mg per day results in a reduction of efficiency of calcium absorption from 70 to 20% (49). This reduced efficiency occurs via a complex regulatory mechanism: First, a small rise in serum calcium is brought about by increased calcium absorption; parathyroid hormone (PTH) secretion is reduced, which in turn decreases the activity of the renal enzyme 25-hydrooxyvitamin D-1-α hydroxylase and leads to decreased production of $1,25(OH)_2D$; finally, the lower serum $1,25(OH)_2$ D concentration decreases the efficiency of calcium absorption (49).

During parenteral nutrition, this normal regulatory system is lost; the intestine is bypassed and the "dietary" calcium load is provided by the continuous infusion of a constant amount of calcium directly into the blood. An indication that this constant calcium infusion suppresses the intestinal calcium regulatory pathway is provided by observations that serum concentrations of both parathyroid hormone (PTH) and $1,25(OH)_2D$ are in the low normal range (29, 72) or even subnormal (29, 70) in patients receiving parenteral nutrition therapy.

Dietary phosphate is normally absorbed by an active transport process when luminal phosphate concentration is in the range provided by most normal diets (23). Approximately 70–80% of dietary phosphate is absorbed over a range of dietary intake from 500 to 2200 mg per day. Changes in the serum concentrations of $1,25(OH)_2D$ may affect the efficiency of intestinal phosphate transport, but the buffering capacity of the intestine for phosphate homeostasis is considerably less than that for calcium (49). For this reason, bypass of intestinal absorption of phosphate by means of parenteral nutrition is less significant than bypass of intestinal absorption of calcium by this means.

Urinary Excretion

CALCIUM Under circumstances of normal dietary intake, variations of oral calcium ingestion have little predictable effect on urinary calcium excretion. This is due in part to intestinal adaptation to the changes in oral calcium intake. However, urinary calcium excretion does vary directly with the quantity of calcium absorbed (49). Diurnal variation is normal, and more calcium is excreted during the day (11). The mechanism that explains the relationship between absorption and urinary excretion involves the calcium-

parathyroid hormone axis. With increased intestinal calcium absorption, serum calcium concentration rises by a small increment; the latter both increases the filtered load of calcium and reduces PTH secretion (49). With normally functioning kidneys, both these factors cause the tubular reabsorption of calcium to be decreased, and therefore urinary calcium excretion rises. The reverse would occur with reduced intestinal calcium absorption. Dietary sugar and protein, however, also affect urinary calcium excretion. The greater the protein intake, the greater the urinary excretion of calcium (42, 43). This phenomenon may be related to the quantity of sulfur-containing amino acids ingested (80). Other data (4) indicate that a high-protein intake can lead to glomerular hyperfiltration with a propensity to increase calcium excretion.

Patients receiving continuous parenteral nutrition demonstrate a linear relationship between infused calcium and urinary calcium excretion in a manner analogous to the data obtained for the relationship between absorbed dietary calcium and urinary calcium excretion in normal individuals (Figure 1) (39).

In parenteral nutrition patients, a direct relationship has also been demonstrated between urinary calcium excretion and (*a*) the protein infused (3, 27, 39), (*b*) the infused sodium (39), and (*c*) the glomerular filtration rate (39).

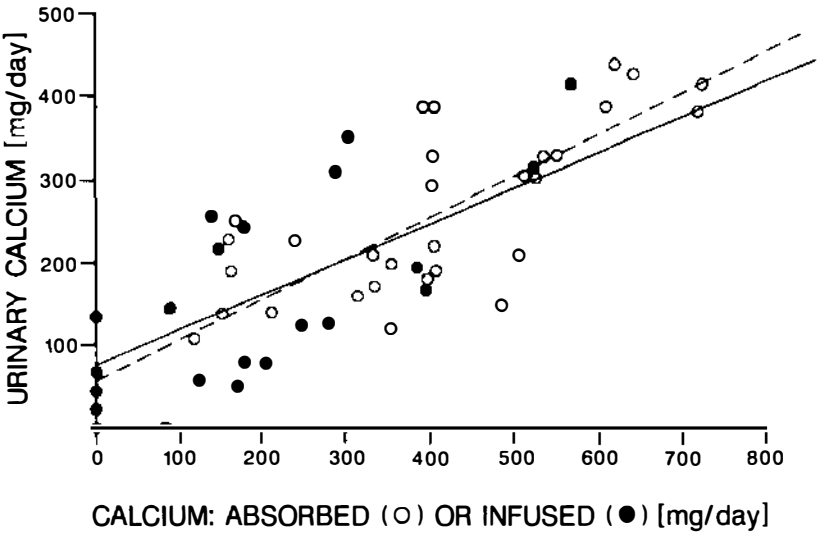

Figure 1 Relationship between urinary calcium excretion and absorbed calcium in subjects with normal dietary intake or infused calcium in patients receiving long-term parenteral nutrition without evidence of aluminum loading. The *dashed line* represents the regression for infused calcium; *solid line*, absorbed calcium. Data for absorbed calcium were collected from several sources by Neer (49); data for infused calcium were obtained from Lipkin et al (39). The similarity of the relationships is apparent.

An inverse correlation between urinary calcium excretion and the phosphate content of parenteral nutrition solutions has been reported (1, 79); this parallels a similar relationship that has been described with changes in oral phosphate intake (54); the underlying mechanism is discussed below. In a cross-sectional study, Lipkin et al described a temporal adaptation that occurred in their patients: urinary calcium exceeded calcium intake with short-term parenteral nutrition (mean duration of therapy, 3.3 months), but there was a net positive calcium balance with calcium intake surpassing urinary excretion in the long-term patients (mean duration of therapy, 55.2 months) (39).

Most patients treated with long-term parenteral nutrition receive infusions over a 12-h overnight period during the 24-h day. Under those circumstances, urinary calcium excretion during the infusion period greatly exceeds the postinfusion rate of excretion and overrides the normal diurnal variation in calcium excretion. The serum concentrations of PTH, obtained once during the infusion period and once during the post-infusion period, did not change significantly, but small alterations of PTH concentrations that are not measurable by the assay method cannot be excluded. Furthermore, a permissive role of low levels of PTH in this alteration of urinary calcium excretion cannot be discounted.

Whether or not the total 24-h urine calcium excretion associated with 12-h cyclic administration of parenteral nutrition solutions is greater than that associated with continuously infused parenteral nutrition solutions is a matter of dispute. Wood et al (78) suggest that the negative calcium balance found in some patients can be attributed to the increased filtered calcium load associated with cyclically administered parenteral nutrition. However, urinary calcium excretion during cyclic parenteral nutrition was not found to exceed urinary calcium excretion during continuous administration by either Klein et al (27) or Lipkin et al (39), both of whom studied a larger number of patients.

PHOSPHATE Under normal conditions the kidney is the chief regulator of phosphate balance. Since the intestinal absorption of phosphate is quite efficient, variations in renal excretion of phosphate preserve serum phosphorus levels within a broad normal range. The factors that produce these changes in renal tubular phosphate absorption are unknown, but they are not dependent on PTH concentrations (54). The ingestion of very large quantities of phosphate can produce transient hyperphosphatemia. In normal adults given a phosphate-supplemented diet, the elevated serum phosphorus levels gradually fell and eventually reached the concentrations observed with a normal phosphate intake. This occurred without any change in PTH levels and presumably was due to the rapidly increased urinary phosphate excretion (53, 54). With dietary phosphate restriction, urinary phosphate excretion falls within 4 h in

rats (36) and in less than 24 h in humans; this is due primarily to intrinsic renal mechanisms, as serum PTH levels did not change significantly during this time (54).

In patients receiving parenteral nutrition, phosphate excretion is primarily a function of intake. Serum phosphorus concentrations were normal or slightly elevated in patients on long-term parenteral nutrition and receiving a phosphate intake of 51 mmol/day; serum phosphorus did not change significantly when the phosphate load was reduced to 29 mmol/day, but urinary phosphate excretion decreased (76). In one patient, removal of phosphate from the parenteral solution resulted in a 69% decrease in daily phosphate excretion after 24 h (unpublished data). In none of these studies were serum phosphorus levels measured frequently during the day or night; therefore, the profound effect that small changes in serum phosphorus levels exert on urinary phosphorus excretion (53) cannot be excluded.

With regard to cyclic parenteral nutrition, neither Klein et al (27) nor Lipkin et al (39) could detect differences in urinary phosphate excretion during periods of infusion and periods of no infusion. However, when glucose was removed from the parenteral nutrition solution, urinary phosphate excretion was significantly greater during the hours of infusion than during the noninfusion hours (27). Shike et al observed negative phosphate balance ranging from 6 to 424 mg per day in 7 of 13 home parenteral nutrition patients studied, but this finding was not explained (71).

Buffering By Bone, Soft Tissue, and Intracellular Pools

Under normal circumstances, bone, soft tissue, and intracellular compartments can buffer disturbances in serum concentrations of calcium and can assist the intestine and kidneys in maintaining the serum calcium concentration within a narrow normal range (49). Under conditions that tend to increase serum calcium concentrations, uptake of calcium by the bone is increased. Also, because serum PTH concentrations fall, bone resorption is decreased and consequently the flux of calcium from bone into the blood is less (49). On the other hand, under conditions such as malabsorption, which may reduce serum calcium concentration, the higher PTH secretion can cause increased skeletal resorption with an increased flux of calcium into the blood (49).

Patients receiving parenteral nutrition were initially reported to exhibit hypercalciuria and often to be in negative calcium balance (31). However, those patients were subsequently discovered to have aluminum loading with high bone aluminum content and very low bone turnover (26, 52). It was postulated that the reduced bone turnover may have resulted in reduced bone uptake of infused calcium (76), leading to hypercalciuria. Consistent with this hypothesis, one of these patients demonstrated increased calciuria in response to an increase of calcium in the parenteral infusate (Figure 2). After the

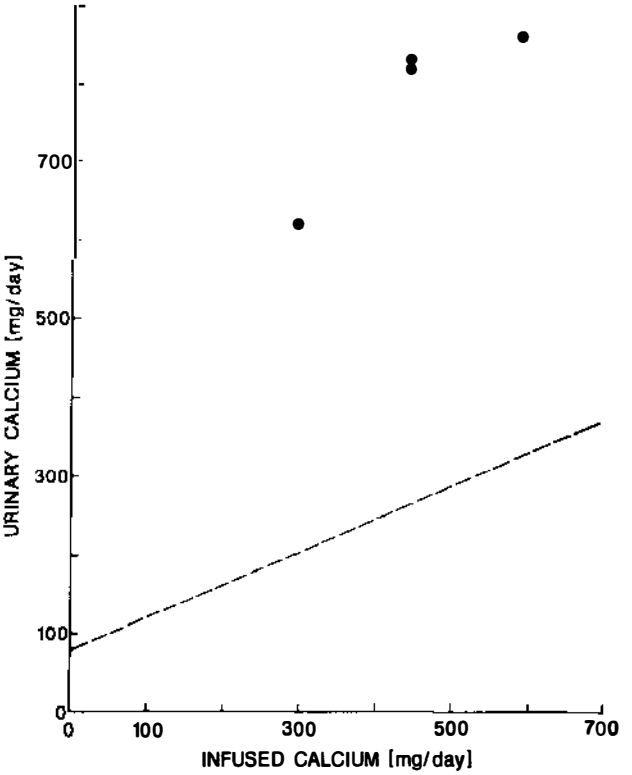

Figure 2 Relationship between urinary calcium and infused calcium in an aluminum-loaded patient managed with parenteral nutrition *(solid circles)*. These values are considerably higher than the *dashed line*, which represents the relationship between urinary calcium and infused calcium in parenteral nutrition patients lacking evidence of aluminum loading (shown in Figure 1).

aluminum contamination of parenteral nutrition solutions had been reduced, the relation between urinary calcium excretion and calcium intake was similar to that seen with intestinal absorption of similar quantities of calcium (76) (Figure 1). Thus, bone would appear to be capable of providing normal buffering activity. Further support for this conclusion comes from data demonstrating improved or normal bone formation rates (40, 76) and normal serum levels of both PTH (40, 76) and osteocalcin (41) in patients on parenteral nutrition who either never received aluminum-contaminated solutions or who had received casein hydrolysate in the distant past and then were converted to solutions with negligible aluminum.

No studies of patients receiving parenteral nutrition have examined the contribution of skeletal, soft tissue, and intracellular compartments to the maintenance of normal serum phosphorus concentration. Preliminary studies

of phosphate restriction in two patients on parenteral nutrition failed to demonstrate the expected increase in serum concentrations of $1,25(OH)_2D$, and the serum PTH levels fell slightly in only one of the two patients (29a). More information is needed before a comparison can be made with adaptation to the altered dietary phosphate absorption.

Parathyroid Hormone Secretion and Action

In normal adults, serum levels of PTH respond within minutes to acute variations in serum calcium concentrations, and with calcium levels between 7.0 and 10.5 mg/dl, both maximum and minimum PTH secretory rates are observed (49). A component of PTH secretion cannot be suppressed even in the presence of hypercalcemia. If hypocalcemic stimuli are sustained, as in chronic renal failure or other prolonged hypocalcemic states, hyperplasia of the parathyroid glands produces an even greater response of PTH to hypocalcemia (49). Furthermore, should the hypocalcemic stimulus be removed, as for example, after the adequate treatment of a cause of intestinal malabsorption, the increased basal secretion of PTH that arises because of increased parathyroid mass can actually produce hypercalcemia (49).

An acute elevation of serum phosphorus can indirectly affect PTH secretion by causing transient hypocalcemia as the solubility product of calcium and phosphate is exceeded. Conversely, marked hypophosphatemia will increase skeletal calcium release and tend to raise the serum calcium concentration (49), although elevated levels have only been identified in phosphate-depleted infants (65) and not in adults.

In addition to calcium and phosphate, $1,25(OH)_2D_3$ can regulate PTH secretion. The parathyroid cells have high-affinity receptors for this vitamin D sterol (6), and concentrations of $1,25(OH)_2D_3$ as low as 10^{-10} to 10^{-11} M can suppress PTH secretion and reduce the level of messenger RNA for pre-pro-PTH both in vitro (49) and in vivo (5).

Patients receiving parenteral nutrition have generally demonstrated circulating PTH levels in the low normal or even subnormal range (29, 72). This can be attributed in part to the maintenance of normal serum calcium concentration by either the continuous or cyclic infusion of calcium (27, 29). Neither the infusion of a parenteral nutrition solution in general nor aluminum loading in particular seems to impair the direction of the PTH response to the removal of calcium from the solution; however, the magnitude of the PTH release compared to that in normal individuals has not been studied.

In patients receiving chronic therapy with parenteral nutrition and with demonstrated aluminum loading, the transient removal of calcium from the parenteral solutions resulted in a rise in serum PTH concentrations in association with a slight fall in serum calcium levels (29, 29a). This is of particular interest because aluminum loading, both in vitro or in vivo, can impair PTH

secretion (2, 33, 47). Studies of adults receiving long-term parenteral nutrition both during and after the removal of aluminum-contaminated solution components demonstrated a small but statistically significant increase in serum PTH concentration after removal of the source of aluminum loading (Figure 3; 76). Whether or not this small increase in PTH implies that aluminum loading contributes to the low-normal serum PTH concentrations is uncertain.

No studies of the effects of PTH on either renal tubular calcium reabsorption or bone resorption have been performed in patients receiving parenteral nutrition therapy. Fractional urinary phosphate excretion (phosphate clearance/creatinine clearance) in four long-term parenteral nutrition patients was not significantly higher when calcium was removed from the parenteral

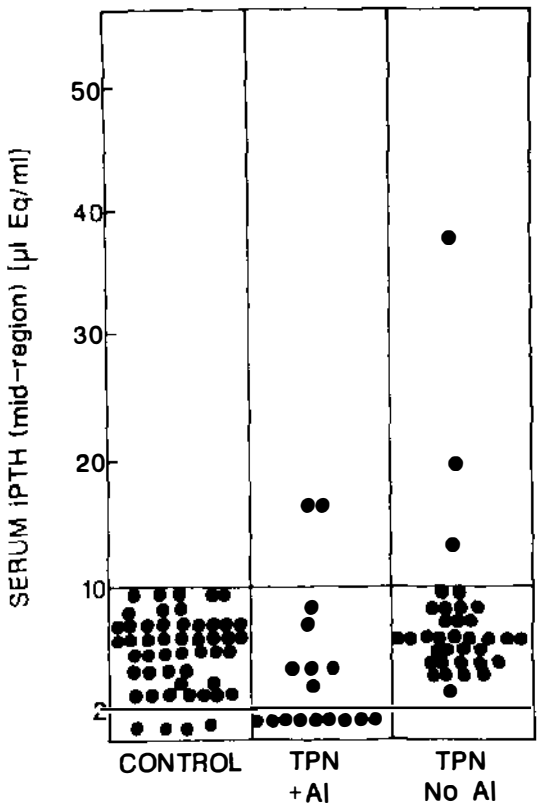

Figure 3 Serum concentration and immunoreactive parathyroid hormone (PTH) by mid-region assay (74) in normal controls, total parenteral nutrition patients (TPN) with tissue aluminum loading (TPN + Al), and total parenteral nutrition patients without evidence of tissue aluminum loading (TPN no Al). Data are modified from Slatopolsky et al (74) and Vargas et al (76).

solution than when it was present; also, the fractional urinary phosphate excretion did not correlate with the serum PTH levels (G. L. Klein and J. W. Coburn, unpublished data). In a group of ten patients receiving parenteral nutrition, removal of calcium from the parenteral solution for 2-4 days resulted in a fall in fractional urinary excretion of calcium but no detectable change in serum PTH concentration (27). Thus, it is not certain that urinary calcium excretion falls as a result of PTH action on the kidney.

Vitamin D Metabolism

As a fat-soluble vitamin, vitamin D_2 (ergocalciferol) is normally absorbed in the upper small intestine (19). In the presence of a steatorrheic condition, such as cholestatic liver disease in childhood, the formation of mixed micelles for absorption of fat and fat-soluble vitamins is reduced; consequently vitamin D and fat are both malabsorbed. If such a patient is not exposed to adequate sunlight, this malabsorption of vitamin D can lead to decreased serum concentrations of 25(OH)D. Calcium is often malabsorbed along with the vitamin D, with resultant hypocalcemia and secondary hyperparathyroidism. Serum calcium concentrations may increase to normal owing to skeletal resorption and increased tubular reabsorption of calcium; serum concentrations of $1,25(OH)_2D$ may range from normal to increased because of the high PTH levels.

In a patient receiving parenteral nutrition, there is no apparent need for intestinal calcium absorption since all calcium is supplied parenterally. In fact, neonatologists have recommended a reduced requirement for vitamin D in infants receiving parenteral nutrition (16), and the content of vitamin D in the multivitamin preparation used for adults receiving parenteral nutrition has also been lowered (40, 76). Some early reports of metabolic bone disease in patients on parenteral nutrition suggested that vitamin D may in fact have been responsible (70, 72), but those observations have not been confirmed (40, 71, 76).

Initial reports of patients on parenteral nutrition and with metabolic bone disease described low serum levels of $1,25(OH)_2D$ and normal serum concentrations of 25(OH)D (29, 72) and $24,25(OH)_2D$ (29). To explain these findings, researchers originally hypothesized that the maintenance of normal serum calcium concentration by continuous or cyclic calcium-containing infusions gave rise to a physiologic hypoparathyroidism, with reduced stimulation of the 25(OH)D-1-α hydroxylase (72). However, although the induction of hypocalcemia by removing calcium from the parenteral solution in a group of parenteral nutrition patients was followed by a rise in serum PTH levels, the low or undetectable serum concentrations of $1,25(OH)_2D$ did not change (29, 29a). Furthermore, one patient with low serum $1,25(OH)_2D$ levels and normal concentrations of 25(OH)D and $24,25(OH)_2D$ continued to

exhibit low serum levels of $1,25(OH)_2D$ for six weeks after the parenteral nutrition was discontinued; only then did the levels of $1,25(OH)_2D$ rise into the normal range (29). Taken together, these findings suggested a toxic effect of a component of the parenteral nutrition solution on the 25(OH)D-1-α hydroxylase. This group of patients was later found to have aluminum loading as a consequence of aluminum in the parenteral nutrition solution that contained casein hydrolysate (26). Following a reduction of aluminum content of the parenteral solutions, the serum levels of $1,25(OH)_2D$ rose to normal in these patients (76). A small rise in serum $1,25(OH)_2D$ concentrations was also demonstrated following treatment of aluminum-loaded patients with end-stage renal disease with deferoxamine for the chelation of aluminum (12). Also, other patients treated with parenteral nutrition solution of low-aluminum content have demonstrated no aluminum accumulation in tissues and have had normal serum levels of $1,25(OH)_2D$ and PTH. These data provide strong evidence that aluminum accumulation was responsible for the low levels of $1,25(OH)_2D$, an observation confirmed in experimental animals (20). However, the biological action or necessity of $1,25(OH)_2D$ in patients receiving parenteral nutrition support is not clear. The existence of receptors for $1,25(OH)_2D$ in many metabolically active tissues (19) suggests that vitamin D may be an important hormone precursor, even when there is no need for calcium absorption. The consequences of the total withdrawal of vitamin D from parenteral solutions over very long-term periods are uncertain.

Finally, the predominant circulating form of vitamin D in parenteral nutrition patients is ergocalciferol, or vitamin D_2, the medicinal form derived from a plant precursor (22, 29). In normal individuals, the predominant circulating form is vitamin D_3, or cholecalciferol, which is generated in the skin from sunlight exposure (19). In humans, the two forms show no apparent differences in physiologic activity (34).

Other Factors Involved in Calcium Homeostasis

Parenteral nutrition patients have normal serum concentrations of calcitonin (L. J. Deftos and J. W. Coburn, unpublished data), a hormone that can oppose certain skeletal resorbing effects of PTH in animals (8b), of vitamin D–binding protein (J. Haddad and J. W. Coburn, unpublished data), and of pyrophosphate, an inhibitor of mineralization (45).

Another theoretical effect of parenteral nutrition on calcium and phosphate homeostasis could arise from the effect of gastrointestinal hormones. In animals, the ingestion of calcium, the administration of gastrin and cholecystokinin, and perhaps other factors can stimulate the secretion of calcitonin, which could theoretically interfere with PTH-mediated skeletal resorption but not with the renal actions of PTH. Parenteral nutrition patients have in-

significant enteral calcium absorption and decreased production of gastrointestinal hormones, including gastrin and cholecystokinin (63). Therefore, the interaction between the gastrointestinal tract and calcium-regulating hormones may be inoperative in these patients who receive no or negligible enteral intake. Whether the reduced production of gastrointestinal hormones has any effect on bone and mineral metabolism is unknown.

PARENTERAL NUTRITION COMPONENTS: EFFECTS ON MINERAL HOMEOSTASIS

Having examined the effects of route of nutrition, oral versus parenteral, on calcium and phosphate homeostasis, we now turn to the known effects on mineral homeostasis of several individual components of the parenteral nutrition solutions. The major facets of mineral homeostasis that are directly affected by parenteral nutrition include urinary mineral excretion and bone metabolism; both are considered.

Urinary Calcium Excretion

VOLUME EXPANSION WITH SALINE In animals, volume expansion with saline infusions leads to increased urinary excretion of both calcium and sodium; this may be due in part to increased glomeruler filtration but is also due to inhibition of proximal tubular calcium and sodium reabsorption (11). Kleeman et al (25a) demonstrated that an oral load of sodium chloride given to normal human volunteers increased urinary excretion of sodium and calcium without changes in creatinine clearance. In adult patients receiving cyclic parenteral nutrition, Klein et al (27) demonstrated that creatinine clearance was 33% higher during the hours of parenteral nutrition infusion than during the noninfusion hours and that the fractional excretions of calcium and sodium (calcium clearance/creatinine clearance, sodium clearance/creatinine clearance) were approximately fourfold higher during the hours of infusion than during the period without any infusion. Thus, volume expansion and increased glomerular filtration contributed to urinary calcium excretion in parenteral nutrition patients. In these parenteral nutrition patients, the ratio of fractional excretion of calcium to that of sodium differed little between infusion and noninfusion hours; however, the fractional calcium excretion remained eight- to ten-fold higher than the fractional sodium excretion, which suggests that volume expansion was only partially responsible for the increased quantity of calcium excreted by these patients.

EFFECT OF GLUCOSE Inasmuch as a 100-g oral glucose load can increase the fractional excretion of calcium from 2 to 5% in normal adults (35, 38), the effect of changing the concentration of infused glucose on urinary calcium

excretion was studied in parenteral nutrition patients by Klein et al (27). Changing the infused glucose load from 300 to 600 g per day produced no change in the fractional excretion of calcium. However, the large amounts of glucose administered in all these studies may have overwhelmed the effects observed with the lower doses used in oral glucose loading. Augmentation of urinary calcium excretion is an unlikely effect of insulin because the antinatriuretic effect of insulin combined with its calciuric effect (9) should have increased the urinary calcium-sodium excretion ratio during the infusion hours compared to the periods with no infusion; however, this did not occur (27). Also, some patients exhibited hypercalciuria in the absence of infused glucose, which indicates that calciuresis can occur during parenteral nutrition independent of the presence of either glucose or insulin.

PROTEIN Variation of protein intake can alter urinary calcium excretion in patients receiving parenteral nutrition. When crystalline amino acid concentration was reduced from 3.0 to 0.6% in the same patient, the fractional excretion of calcium decreased. Conversely, when the infused amino acid concentration was raised from 0.6 to 3% in the same patient, fractional calcium excretion increased (27). Lipkin et al (39) found a positive correlation between parenteral protein intake and urinary calcium excretion, and Vargas et al (76) found a decrease in fractional calcium excretion when infused amino acid nitrogen was reduced by 50%. Bengoa and colleagues (3) reported similar observations and suggested that the urinary calcium excretion was related to the amount of sulfur-containing amino acids in the parenteral solution. Although the underlying mechanism for this effect is unknown, it is suggested that the amino acids play a role in decreasing renal tubular reabsorption of calcium (3).

CALCIUM Another component of parenteral nutrition solutions that influences urinary calcium excretion is the parenteral load of calcium. As discussed above, Klein et al (27) reported that removal of calcium from parenteral solutions resulted in a concomitant decrease in fractional excretion of calcium. Similarly, both Klein et al (27) and Lipkin et al (39) found that urinary calcium excretion was directly related to the parenteral intake in parenteral nutrition patients. This relationship is most likely due to small but unmeasurable changes in filtered calcium load. Inasmuch as the patients of Klein et al (27) were aluminum loaded and those of Lipkin et al (39) were not, these data suggest that the calcium intake contributes to urinary calcium excretion regardless of any effect aluminum may have on calcium metabolism (see below). However, in the absence of aluminum loading, the relationship between calcium intake and urinary calcium excretion in the parenteral nutrition patients was very similar to that observed between absorbed calcium and

urinary calcium in normal individuals consuming calcium in the diet as shown in Figure 1.

PHOSPHATE The phosphate content of parenteral solutions may affect urinary calcium excretion. Although the data are few, Wood and colleagues (79) reported that urinary calcium excretion could be reduced by increasing the phosphate content of the parenteral nutrition solution. Further, in unpublished studies of two patients, Klein and Coburn found that removal of phosphate from the parenteral solution of one patient led to an increase in fractional calcium excretion, whereas adding phosphate to the parenteral solution in another patient led to a decrease in fractional calcium excretion. The mechanism of this effect is unclear; it may be due to the action of PTH, either directly or indirectly, or it may be a local renal mechanism.

VITAMIN D The only reports suggesting that vitamin D may contribute to the hypercalciuria of parenteral nutrition come from Shike et al when studying parenteral nutrition patients in Toronto (72). In those patients, removal of vitamin D from the parenteral nutrition solution was associated with reduced urinary calcium excretion. This result was somewhat surprising because serum calcium concentrations were only slightly elevated and the levels of $1,25(OH)_2D$ were low (72). Physiologic and small pharmacologic doses of exogenous $1,25(OH)_2D_3$ cause hypercalciuria and a tendency to hypercalcemia (75), but the levels of $1,25(OH)_2D$ have generally been low in these reports of parenteral nutrition patients (29, 72). Thus, the basis for the vitamin D-associated increase in urinary calcium excretion in these patients is not clear.

ALUMINUM As noted above, many of the parenteral nutrition patients who were reported to be in negative calcium balance and/or exhibit hypercalciuria had large quantities of aluminum in bone, serum, and urine (26). Most of the aluminum in adult patients came from contamination of the casein hydrolysate used as the protein source (26). Aluminum can come from other sources in the parenteral solutions, particularly the salts of calcium and phosphate; and substantial loading has occurred in premature infants (69). Such patients and patients with impaired renal function are those at greatest risk for aluminum loading. The premature infants, like the adult parenteral nutrition patients with aluminum loading, exhibit hypercalciuria (21, 64), but it is not certain that there is a cause-and-effect relationship between aluminum loading and hypercalciuria.

Henry et al found that a single very large injection of aluminum into dogs increased urinary calcium excretion, and repeated injections led to impaired renal function (18). A relationship between aluminum loading and renal

excretion of calcium could occur owing to the effect of aluminum on bone. Thus, aluminum may impede the deposition of both calcium and phosphate into bone matrix (46) and may inhibit bone matrix formation itself (55). Therefore, the infused calcium will not be taken up by bone but is available for excretion in the urine. When there is little or no intake of aluminum, urinary aluminum excretion probably reflects the tissue content of aluminum (69, 76); with the slow release of a larger amount of aluminum from tissues, the aluminum excretion in the urine would be greater. Such an explanation could account for the findings of Vargas et al (76), who studied urinary calcium excretion in parenteral nutrition patients whose solutions were changed from aluminum-loaded casein hydrolysate to crystalline amino acids and in other patients who had received only crystalline amino acids in their solutions. For the total group of patients, there was a significant positive relationship between urinary aluminum excretion and the excretion of calcium.

Urinary Phosphate Excretion

GLUCOSE Varying the parenteral glucose load apparently does not affect urinary calcium excretion but does affect renal phosphate excretion. Klein et al (27) found that the removal of glucose from cyclically administered parenteral nutrition solutions was associated with significantly lower fractional phosphate excretion during the noninfusion hours compared to the infusion hours. In contrast, no change was found in the fractional excretion of phosphate in patients given cyclic parenteral nutrition solutions that contained standard amounts of glucose. This observation was confirmed by Lipkin et al, who found no change in phosphate excretion during periods with or without infusion of glucose-containing solutions (39). The lack of changes may be explained if glucose both enhances the renal tubular reabsorption of phosphate and enhances the cellular uptake of phosphate by other tissues. These two events would prevent the increase in serum phosphorus level and the subsequent rise in urinary phosphate during the infusion.

PHOSPHATE Not surprisingly, the total phosphate intake was the single most important determinant of urinary phosphate excretion in the patients of Klein et al (27). With a reduced phosphate load, the fractional urinary phosphate excretion fell (27), but a negative phosphate balance was not observed. The negative phosphate balances reported by Shike et al (71) in parenteral nutrition patients remains unexplained.

VITAMIN D Shike et al (72) measured the 24-h urinary phosphate excretion in eight patients while they received parenteral nutrition that contained vitamin D_2 and six months after vitamin D_2 had been removed from the solutions.

No significant differences in urinary phosphate excretion were detected. No other studies have examined the role of vitamin D in urinary phosphate excretion.

OTHER COMPONENTS There are no data to suggest that aluminum loading or changes in amino acid content have any affect on urinary phosphate excretion.

Effects on Bone Metabolism

Components of parenteral nutrition may potentially affect various aspects of bone metabolism such as matrix synthesis or the mineralization of bone per se.

BONE MATRIX FORMATION Matrix formation is initiated by the osteoblast, which is derived from presursor cells in the marrow stroma and the endothelial lining of bone (60). Osteoblasts synthesize and secrete collagen as a glycosylated triple helix. When the collagen fibrils aggregate to form cross-linkages, a stagger arrangement leaves holes for the initial deposition of mineral (60). A number of the components of parenteral nutrition solutions could potentially affect matrix formation: they include aluminum, 1,25 $(OH)_2D$, and acetate.

Aluminum Data suggesting that aluminum can affect matrix formation come from both in vitro and in vivo studies in experimental animals; human data is very limited. The in vitro data regarding the effect of aluminum on bone matrix formation are contradictory. Leiberherr et al (37) report that the effects of aluminum on osteoblast function were dose related: low aluminum concentrations stimulate, while high concentrations reduce, collagen production. In addition, aluminum decreased the osteoblastic production of alkaline phosphatase. Kasai et al (25) found that DNA synthesis was reduced when aluminum and transferrin were added in short-term incubations of the osteoblast-like cell line UMR-106. Using chemically defined media or fetal calf serum, Quarles et al (58) found that aluminum stimulated DNA synthesis in the mouse pre-osteoblast cell line MC3T3. Furthermore, Simmons et al (73) studying rat marrow stromal cells, which have the potential to differentiate into osteoblasts, failed to detect an effect of aluminum on proliferation of stromal cells grown in fetal calf serum. Thus, the effects of aluminum can vary according to the specific conditions reported in the studies.

With in vivo studies, the effects have been more consistent. Thus, Sedman et al (68) found that the parenteral administration of aluminum to piglets was associated with reduced bone formation because of the reduced number of sites of active formation. At some sites, the osteoblasts seemed to function

with normally active bone formation, and yet there were fewer sites of cells and bone formation, which suggests a reduced osteoblast number. In rats with chronic renal failure, similar data for aluminum loading were obtained by Robertson et al (61) and by Rodriguez et al (62). Furthermore, the short-term intraperitoneal injections of aluminum into rats led to decreased collagen production prior to a disturbance in bone mineralization and without histologic evidence of osteomalacia (15). In contrast to these findings, Quarles et al (59) reported aluminum-associated neoosteogenesis in beagle pups, although the newly formed bone was qualitatively abnormal.

Vitamin D No evidence directly links vitamin D to matrix formation, but the active sterol $1,25(OH)_2D_3$ can affect osteoblast function and may therefore affect matrix synthesis, a major function of the osteoblasts. Thus, $1,25(OH)_2D_3$ has been shown in vitro to increase osteoblastic synthesis of osteocalcin, the bone gamma carboxyglutamic acid protein (BGP). The specific role of this protein is not clear, but, as discussed above, the serum concentrations of BGP are in equilibrium with bone levels and correlate with rates of bone formation in a number of circumstances, including parenteral nutrition (41, 56, 57). $1,25(OH)_2D_3$ has also been demonstrated to stimulate alkaline phosphate activity of osteoblasts in vitro (37).

Acetate No clinical evidence directly implicates acetate in the pathogenesis of metabolic bone disease. However, an in vitro study of chick osteoblasts and pre-osteoblasts that were grown in concentrations of acetate present in parenteral nutrition solutions demonstrated impaired proliferation of both osteoblasts and pre-osteoblasts, as measured by cell number and by DNA synthesis (66). Thus, acetate could potentially decrease bone matrix formation, but further studies are necessary to clarify any possible pathogenic role of acetate in the observed metabolic bone disease.

BONE MINERALIZATION Matrix mineralization occurs as phosphate and calcium deposit onto collagen, eventually forming crystals of hydroxyapatite. Mineralization occurs at the junction of mineralized bone and unmineralized matrix, an area referred to as the "mineralization front." The rate of mineralization is measured by the length of bone surface taking up tetracycline and by the distance between two separate fluorescent bands of tetracycline observed in bone after two different courses of tetracycline that are separated by a predetermined interval (usually 10–17 days). Decreased mineralization may occur because of interference with the process of calcium phosphate deposition onto collagen or because of a deficit in matrix formation. It is often difficult to distinguish between these two possibilities; however, if reduced separation of tetracycline labels is accompanied by increased

unmineralized osteoid, the mineralization is reduced far more than the osteoid synthesis.

Calcium and Phosphate Calcium and phosphate are the two major components of mineralized bone matrix. Evidence for the importance of phosphate for matrix mineralization comes from observations in adults who develop hypophosphatemia from consuming large quantities of aluminum-containing antacids over long periods of time. Such individuals develop phosphate depletion and osteomalacia (7). Several conditions of infancy that result in calcium and/or phosphate deficiency lead to rickets or osteopenia. These include inadequate dietary calcium in certain groups of children in South Africa (44) and phosphate deficiency during breast feeding (65). The osteopenia that occurs with or without roentgenographic evidence of rickets in premature infants receiving parenteral nutrition may be germane to this discussion. This condition is probably multifactorial, but the contributing factors most generally agreed upon are inadequate intake of calcium and/or phosphate (21). Most neonatologists consider the in utero accretion rates of calcium and phosphate to be the standard for the administration rates for these substances ex utero. However, the parenteral nutrition solutions that are given to premature infants contain quantities of calcium and phosphate that are limited because the solubility of calcium phosphate is exceeded, with the likelihood of precipitation in the container (10). The addition of cysteine and hydrochloric acid (67) or the use of monobasic phosphate salts (8) increases the solubility of calcium and phosphate in the parenteral solutions and may permit administration of larger and more adequate amounts of calcium and phosphate.

Aluminum Excess aluminum may also lead to reduced mineralization. Aluminum accumulates along the mineralization front of bone in (*a*) adults receiving parenteral nutrition with casein hydrolysate as the protein source (52), (*b*) infants receiving parenteral nutrition with large quantities of aluminum derived from calcium and phosphate salts (32), and (*c*) patients with end-stage renal disease who are exposed to aluminum-contaminated water during hemodialysis treatment or who have received large oral doses of aluminum-containing gels (51). Bone biopsies in adult parenteral nutrition patients and in dialysis patients have exhibited osteomalacia and a reduced rate of bone formation that are directly related to the presence of aluminum along the bone surface (51, 52).

The exact mechanism for this defective mineralization is uncertain. Rodriguez et al (62) dissociated the adverse effect of aluminum on osteoblasts from the defective mineralization by demonstrating that exogenous PTH can increase the osteoblastic surface in bone without improving the mineralization

of osteoid in aluminum-loaded rats with renal failure. The ability of aluminum to prevent the growth of hydroxyapatite crystals (55) and to prevent calcium phosphate precipitation (46) provides major evidence that aluminum can impair mineralization. However, the aluminum-mediated impairment of mineralization and the reduction in matrix production may not be mutually exclusive; thus both factors may be operative in aluminum-loaded patients receiving treatment with parenteral nutrition.

The bone disease associated with parenteral nutrition in premature infants is thought to be multifactorial (21), and the role of aluminum is uncertain. However, the appearance of hypocalcemia during deferoxamine treatment of an aluminum-loaded infant receiving long-term parenteral nutrition suggests that the chelation of aluminum can permit the uptake of calcium by bone at the expense of the serum calcium concentration (30). Similar observations were made during deferoxamine treatment of dialysis patients with aluminum-related dialysis osteomalacia (50). Furthermore, rickets has been reported in aluminum-loaded infants and children (28), osteomalacia has been produced by the parenteral administration of aluminum in dogs (15a), piglets (68), and rats (61), and rickets has been produced in growing rats with uremia (77).

Vitamin D The biologically active form of vitamin D, $1,25(OH)_2D$, promotes the mineralization of bone by raising the amounts of plasma calcium and phosphate to normal levels largely via its ability to enhance their intestinal absorption. However, the role of $1,25(OH)_2D$ in bone mineralization is less certain in patients in whom the intestine is bypassed as a source of calcium and phosphate. Shike et al (72) reported that the osteomalacia observed in long-term parenteral nutrition patients from Toronto improved when vitamin D was withdrawn from the parenteral nutrition solutions. However, osteomalacia has not been reported in any group of parenteral nutrition patients receiving vitamin D unless they had coexistent evidence of aluminum accumulation. This includes the patients of Shike et al in New York (71), Lipkin et al in Seattle, (40) and Vargas et al in Los Angeles (76). Moreover, some of the patients reported from Toronto had histochemical evidence of excess aluminum in their bone biopsies (52); however, the relationship between this finding and the occurrence of osteomalacia was not established.

D-Lactic Acidosis Although D-lactic acid is not a component of parenteral solutions, D-lactic acidosis developed in two adult patients treated with aluminum-free parenteral nutrition solutions. They coincidentally had secondary hyperparathyroidism and osteomalacia with low or low-normal serum ionized calcium concentrations and normal serum phosphorus levels (24). An association between D-lactic acidosis and secondary hyperparathyroidism is possible, but requires further study.

BONE MASS Bone mass, as measured by photon absorptiometry, is a very general measure of calcified bone matrix. An abnormally low bone mass may arise from decreased synthesis of matrix, reduced mineralization of bone, or increased bone resorption. The finding of low bone mass does not distinguish between osteoporosis and osteomalacia but indicates the presence of relative osteopenia. Studies that examined bone mass during parenteral nutrition therapy were mostly population studies. One group has examined patients longitudinally; they found either a decrease in bone mass or stabilization of bone mass at a low level (17). This study is discussed below under the section on vitamin D.

Aluminum Faugere et al found that cancellous bone mass, as determined by histomorphometry, was lower in patients with chronic renal failure and with aluminum deposition in bone; and the bone mass increased following aluminum chelation with deferoxamine (13). The effects of aluminum on bone mass in patients receiving parenteral nutrition have not been studied. Photon absorptiometry showed decreased vertebral bone density in the patients of Lipkin et al (39), who were not receiving aluminum. In addition, Moukarzel et al used computerized tomography to detect subnormal vertebral bone density in children receiving long-term parenteral nutrition without aluminum contamination; the results were compared with age- and sex-matched controls (48).

Vitamin D The relationship between vitamin D and bone mass is unclear. The patients on long-term parenteral nutrition with reduced bone mass were subsequently reported to have low serum levels of $1,25(OH)_2D$. The removal of vitamin D from the parenteral solutions in one subgroup of patients was associated with improved osteomalacia but did not affect the subnormal bone density [as determined by neutron activation analysis (17)]. In these patients, serum $1,25(OH)_2D$ concentrations increased somewhat after vitamin D was removed from the parenteral solutions. Reduced vertebral bone mass was observed by Lipkin et al in adults (39) and by Moukarzel et al (48) in children receiving long-term parenteral nutrition; both groups of patients had normal serum levels of $1,25(OH)_2D$. Thus, data on these patients and those of Shike et al (71) demonstrate that osteopenia can occur independently of aluminum contamination or vitamin D treatment.

SUMMARY: EFFECTS OF PARENTERAL NUTRITION ON BONE AND MINERAL METABOLISM

The effects of parenteral nutrition on calcium and phosphate homeostasis include the bypass of intestinal modulation of calcium and phosphate absorption and the continuous intake of nutrients as opposed to periodic dietary intake.

Can alteration of calcium and phosphate homeostasis by an unknown mechanism(s) associated with the bypass of intestinal regulation contribute to the metabolic bone diseases described during parenteral nutrition? Before approaching this question, it is necessary to rule out exogenous factors that may be responsible for disease.

Aluminum appears to have a toxic effect on bone and may upset various aspects of calcium and phosphate homeostasis. It may decrease bone matrix formation and almost certainly interferes with mineralization. Bone formation and mineralization are both decreased, leading to osteomalacia or aplastic bone disease. The administration of exogenous calcium cannot improve this condition, and the administered calcium is taken up poorly by the bone. This probably contributes to the exaggerated urinary calcium losses seen in these patients. Aluminum loading may reduce serum concentrations of $1,25(OH)_2D$, with uncertain consequences for bone and calcium metabolism, and it may impair PTH synthesis and secretion. The latter may contribute to low bone formation rates.

Exogenous vitamin D was postulated to be the cause of an osteomalacic low-turnover bone disease; low serum levels of $1,25(OH)_2D$ and decreased bone mass were observed. Removal of vitamin D was associated with the resolution of the osteomalacia and with increased serum $1,25(OH)_2D$ levels, but the reduced bone mass did not improve. Finally, aluminum was detected in bone biopsy specimens of some of these patients, but the relationship of this finding to bone disease is unknown. Other studies of patients on long-term parenteral nutrition, who received vitamin D but not aluminum, failed to detect osteomalacia, and the serum concentrations of $1,25(OH)_2D$ were found to be normal. Thus, the contribution of exogenous vitamin D to bone disease in parenteral nutrition is uncertain.

Secondary hyperparathyroidism arising from malabsorption of fat-soluble vitamins and calcium and the action of medications, such as steroids for inflammatory bowel disease or aluminum-containing antacids for chronic peptic disease, can contribute to bone disease that may only be detected during the course of parenteral nutrition therapy. Finally, many parenteral nutrition patients are postmenopausal, and the degree to which postmenopausal osteoporosis may antedate the therapy with parenteral nutrition is unknown.

During the acute stages of severe illness, immobilization may also contribute to bone loss.

The homeostatic regulation of calcium and phosphate, despite bypass of the gut by parenteral nutrition, appears reasonably intact according to the available literature. The pathogenesis of metabolic bone disease is still poorly understood. In the absence of various militating factors, it is difficult to postulate that altered homeostatic control renders the parenteral nutrition patients more susceptible to metabolic bone disease. Care must be taken to

rule out preexisting bone disease, the presence of toxins or deficiencies in the parenteral solutions, themselves, and the adverse effect of treatment of coexisting medical conditions that could predispose these patients to metabolic bone diseases.

The reports of Shike et al (71), Lipkin et al (39), and Moukarzel et al (48) suggest that parenteral nutrition predisposes patients to osteopenic bone disease, although no obvious mechanism can account for the alterations of calcium and phosphate homeostasis that are produced by parenteral nutrition.

The data of Shike et al (71) and Lipkin et al (39) suffer from a lack of information regarding baseline bone histology either immediately prior to or shortly after the initiation of parenteral nutrition therapy. Bone histology is lacking in the data of Moukarzel et al (48). Thus, it is uncertain whether or not low-turnover bone disease contributed to the low bone mineral density in the pediatric patients.

If further studies exclude preexisting osteoporosis and/or osteomalacia, one would be forced to conclude that the intestinal bypass produced by continuous or cyclic administration of parenteral nutrition solutions is not innocuous with regard to bone and mineral homeostasis.

Literature Cited

1. Al-Jurf, A. S., Chapman-Furr, F. 1986. Phosphate balance and distribution during total parenteral nutrition: effect of calcium and phosphate additives. *J. Parenter. Enter. Nutr.* 10:508–12
2. Andress, D., Felsenfeld, A., Voigts, A., Llach, F. 1983. Parathyroid hormone response to hypocalcemia in hemodialysis patients with osteomalacia. *Kidney Int.* 24:364–70
3. Bengoa, J. M., Stirin, M. D., Wood, R. J., Rosenberg, I. H. 1983. Amino acid-induced hypercalciuria in patients on total parenteral nutrition. *Am. J. Clin. Nutr.* 38:264–69
4. Brenner, B. B., Meyer, T. W., Hostetter, T. H. 1982. Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *New Engl. J. Med.* 307:652–59
5. Brickman, A. S., Sherrard, D. J., Jowsey, J., Singer, F. R., Baylink, D. J., et al. 1975. 1,25-dihydroxycholecalciferol: Effect on skeletal lesions and plasma parathyroid hormone levels in uremic osteodystrophy. *Arch. Int. Med.* 134:883–88
6. Brumbaugh, P. F., Hughes, M. R., Haussler, M. R. 1975. Cytoplasmic and nuclear binding components for 1α,25-dihydroxyvitamin D_3 in chick parathyroid glands. *Proc. Natl. Acad. Sci. USA* 72:4871–75
7. Carmichael, K. A., Fallon, M. D., Dalinka, M., Kaplan, F. S., Axel, L., et al. 1984. Osteomalacia and osteitis fibrosa in a man ingesting aluminum hydroxide antacid. *Am. J. Med.* 76:1137–43
8. Chessex, P., Pineault, M., Brisson, G., Delvin, E. E., Glorieux, F. H. 1990. Role of the source of phosphate salt in improving the mineral balance of parenterally fed low birth weight infants. *J. Pediatr.* 116:765–72

8a. Coburn, J. W., Klein, G. L. 1985. *Metabolic Bone Disease in Total Parenteral Nutrition.* Baltimore/Munich: Urban & Schwarzenberg. 146 pp.

8b. Cooper, C. W., Peng, T-C., Toverud, S. U., Vander Wiel, C. J., Talmage, R. V. 1981. Calcitonin and feeding. In *Hormonal Control of Calcium Metabolism,* ed. D. V. Cohn, R. V. Talmage, J. L. Matthews, pp. 271–80. Amsterdam: Excerpta Medica. 506 pp.

9. DeFronzo, R. A., Goldberg, M., Agus, Z. S. 1976. The effect of glucose and

insulin on renal electrolyte transport. *J. Clin. Invest.* 58:83–90
10. Eggert, L. D., Rusho, W. J., McKay, M. W., Chan, G. M. 1982. Calcium and phosphorus compatability in parenteral nutrition solutions for neonates. *Am. J. Hosp. Pharm.* 39:49–53
11. Epstein, F. H. 1968. Calcium and the kidney. *Am. J. Med.* 45:700–14
12. Fanti, P., Faugere, M. C., Smith, A. J., Malluche, H. H. 1987. Removal of aluminum (Al) is associated with increased production of $1,25(OH)_2$ vit-D in dialysis patients. *Kidney Int.* 31:346 (Abstr.)
13. Faugere, M. C., Arnala, I. O., Ritz, E., Malluche, H. H. 1986. Loss of bone resulting from accumulation of aluminum in bone of patients undergoing dialysis. *J. Lab. Clin. Med.* 107:481–87
14. Fontaine, O., Matsumoto, T., Goodman, D. B. P., Rasmussen, H. 1981. Liponomic control of Ca^{2+} transport: relationship to mechanism of action of 1,25-dihydroxyvitamin D_3. *Proc. Natl. Acad. Sci. USA* 78:1751–54
15. Goodman, W. G. 1984. Short-term aluminum administration in the rat: Reduction in bone formation without osteomalacia. *J. Lab. Clin. Med.* 103:749–57
15a. Goodman, W. G., Henry, D. A., Horst, R., Nudelman, R. K., Alfrey, A. C., et al. 1984. Parenteral aluminum administration in the dog: II. Induction of osteomalacia and effect on vitamin D metabolism. *Kidney Int.* 25:370–75
16. Greene, H. L., Hambidge, K. M., Schanler, R., Tsang, R. C. 1988. Guidelines for the use of vitamins, trace elements, calcium, magnesium, and phosphorus in infants and children receiving total parenteral nutrition: report of the Subcommittee on Pediatric Parenteral Nutrient Requirements from the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition. *Am. J. Clin. Nutr.* 48:1324-42
17. Harrison, J. E., Jeejeebhoy, K. N., Track, N. S. 1985. The effect of total parenteral nutrition (TPN) on bone mass. See Ref. 8a, pp. 55–61
18. Henry, D. A., Goodman, W. G., Nudelman, R. K., DiDomenico, N. D., Alfrey, A. C., et al. 1984. Parenteral aluminum administration in the dog. I. Plasma kinetics, tissue distribution and effects on calcium metabolism and parathyroid hormone. *Kidney Int.* 25:362–69
19. Henry, H. L., Norman, A. W. 1984. Vitamin D: Metabolism and biological actions. *Annu. Rev. Nutr.* 4:493–520
20. Henry, H. L., Norman, A. W. 1985. Interactions between aluminum and the actions and metabolism of vitamin D_3 in the chick. *Calcif. Tissue Int.* 37:484–87
21. Hillman, L. S. 1990. Nutritional factors affecting mineral homeostasis and mineralization in the term and preterm infants. In *Nutrition and Bone Development*, ed. D. J. Simmons, pp. 55–92. New York/Oxford: Oxford. 383 pp.
22. Jones, G., Byrnes, B., Duthie, B., Jeejeebhoy, K. N. 1979. Contribution of skin vitamin D_3 synthesis in patients receiving TPN. In *Vitamin D: Basic Research and its Clinical Application*, ed. A. W. Norman, K. Schaefer, D. von Herrath, H-G. Grigoleit, pp. 169–72. Berlin: de Gruyter
23. Juan, D., Liptak, P., Gray, T. K. 1976. Absorption of inorganic phosphate in the human jejunum and its inhibition by salmon calcitonin. *J. Clin. Endocrinol. Metab.* 43:517–22
24. Karton, M. A., Rettmer, R. A., Lipkin, E. W., Ott, S. M., Chait, A. 1989. D-lactate and metabolic bone disease in patients on long-term parenteral nutrition. *J. Parenter. Enter. Nutr.* 13:132–35
25. Kasai, K., Hori, M., Goodman, W. 1989. Transferrin-mediated inhibition of DNA synthesis by metals in osteoblast-like cells. *J. Bone Miner. Res.* 4:S122 (Suppl.)
25a. Kleeman, C. R., Bohannan, J., Bernstein, D., Ling, S., Maxwell, M. H. 1964. Effect of variations in sodium intake on calcium excretion in normal humans. *Proc. Soc. Exp. Biol. Med.* 115:29–32
26. Klein, G. L., Alfrey, A. C., Miller, N. L., Sherrard, D. J., Hazlet, T. K., et al. 1982. Aluminum loading during total parenteral nutrition. *Am. J. Clin. Nutr.* 35:1425–29
27. Klein, G. L., Ament, M. E., Slatopolsky, E., Coburn, J. W. 1985. Urinary mineral excretion during total parenteral nutrition. See Ref. 8a, pp. 103–28
28. Klein, G. L., Cannon, R. A., Diament, M., Kangarloo, H., Ament, M. E., et al. 1982. Infantile vitamin D resistant rickets associated with total parenteral nutrition. *Am. J. Dis. Child.* 136:74–76
29. Klein, G. L., Horst, R. L., Norman, A. W., Ament, M. E., Slatopolsky, E., et al. 1981. Reduced serum levels of $1\alpha,25$-dihydroxyvitamin D during long-term total parenteral nutrition. *Ann. Intern. Med.* 94:638–43
29a. Klein, G. L., Horst, R. L., Slatopolsky, E., Kurokawa, K., Alfrey, A. C., et al. 1985. Attempts to modify PTH and

vitamin D status in patients receiving long-term parenteral nutrition. See Ref. 8a, pp. 89–100
30. Klein, G. L., Snodgrass, W. R., Griffin, M. P., Miller, N. L., Alfrey, A. C. 1989. Hypocalcemia complicating deferoxamine therapy in an infant with parenteral nutrition-associated aluminum overload: evidence for a role of aluminum in the bone disease of infants. *J. Pediatr. Gastroenterol. Nutr.* 9:400–3
31. Klein, G. L., Targoff, C. M., Ament, M. E., Sherrard, D. J., Bluestone, R., et al. 1980. Bone disease associated with total parenteral nutrition. *Lancet* 2:1041–44
32. Koo, W. W. K., Kaplan, L. A., Bendon, R., Succop, P., Tsang, R. C., et al. 1986. Response to aluminum in parenteral nutrition during infancy. *J. Pediatr.* 109:883–87
33. Kraut, J. A., Shinaberger, J. H., Singer, F. R., Sherrard, D. J., Saxton, J., et al. 1983. Parathyroid gland responsiveness to acute hypocalcemia in dialysis osteomalacia. *Kidney Int.* 23:725–30
34. Lawson, D. E. M. 1980. Metabolism of Vitamin D. In *Vitamin D: Molecular Biology and Clinical Nutrition*, ed. A. W. Norman, pp. 117–18. New York: Marcel Dekker
35. Lemann, J. Jr., Lennon, E. J., Piering, W. R., Prien, E. L. Jr., Ricanati, E. S. 1970. Evidence that glucose ingestion inhibits net renal tubular reabsorption of calcium and magnesium in man. *J. Lab. Clin. Med.* 75:578–85
36. Levine, B. S., Kurokawa, K., Coburn, J. W. 1984. Early renal adaptation to dietary phosphorus restriction. *Adv. Exp. Med. Biol.* 178:93–101
37. Lieberherr, M., Grosse, B., Cournot-Witmer, G., Herman-Erlee, M., Balsan, S. 1987. Aluminum action of mouse bone cell metabolism and response to PTH and $1,25(OH)_2D_3$. *Kidney Int.* 31:736–43
38. Lindeman, R. D., Adler, S., Yiengst, M. J., Beard, E. S. 1967. Influence of various nutrients on urinary divalent cation excretion. *J. Lab. Clin. Med.* 70:236–45
39. Lipkin, E. W., Ott, S. M., Chesnut, C. H. III, Chait, A. 1988. Mineral loss in the parenteral nutrition patient. *Am. J. Clin. Nutr.* 47:515–23
40. Lipkin, E. W., Ott, S. M., Klein, G. L. 1987. Heterogeneity of bone histology in parenteral nutrition patients. *Am. J. Clin. Nutr.* 46:673–80
41. Lipkin, E. W., Ott, S. M., Klein, G. L., Deftos, L. J. 1990. Serum markers of bone metabolism and bone formation in parenteral nutrition patients. *Calcif. Tissue Int.* 47:75–81
42. Lutz, J., Linkswiler, H. M. 1981. Calcium metabolism in postmenopausal and osteoporotic women consuming two levels of dietary protein. *Am. J. Clin. Nutr.* 34:2178–86
43. Margen, S., Chu, J. Y., Kaufmann, N. A., Calloway, D. H. 1974. Studies in calcium metabolism I. The calciuretic effect of dietary protein. *Am. J. Clin. Nutr.* 27:584–89
44. Marie, P. J., Pettifor, J. M., Ross, F. P., Glorieux, F. H. 1982. Histological osteomalacia due to dietary calcium deficiency in children. *New Engl. J. Med.* 307:584–88
45. McGuire, M. K. B., Klein, G. L., Russell, R. G. G., Ament, M. E., Coburn, J. W. 1982. Plasma pyrophosphate levels in osteomalacia. *Kidney Int.* 21:230 (Abstr.)
46. Meyer, J. L., Thomas, W. C. Jr. 1986. Aluminum and aluminum complexes. Effect on calcium phosphate precipitation. *Kidney Int.* 29:S20–23 (Suppl.)
47. Morrissey, J., Rothstein, M., Mayor, G., Slatopolsky, E. 1983. Suppression of parathyroid hormone secretion by aluminum. *Kidney Int.* 23:699–704
48. Moukarzel, A., Ament, M. E., Vargas, J., McDiarmid, S., Reyen, L., et al. 1990. Non-aluminum dependent osteopathy in children on long-term parenteral nutrition. *Am. J. Clin. Nutr.* 51:520 (Abstr.)
49. Neer, R. M. 1989. Calcium and inorganic phosphate homeostasis. In *Endocrinology*, ed. L. J. DeGroot, pp. 927–53. Philadelphia: Saunders. 2nd ed.
50. Ott, S. M., Andress, D. L., Nebeker, H. G., Milliner, D. S., Maloney, N. A., et al. 1986. Changes in bone histology after treatment with desferrioxamine. *Kidney Int.* 29 (Suppl. 18):S108–13
51. Ott, S. M., Maloney, N. A., Coburn, J. W., Alfrey, A. C., Sherrard, D. J. 1982. The prevalence o f bone aluminum deposition in renal osteodystrophy and its relation to the response to calcitriol therapy. *New Engl. J. Med.* 307:709–13
52. Ott, S. M., Maloney, N. A., Klein, G. L., Alfrey, A. C., Ament, M. E., et al. 1983. Aluminum is associated with low bone formation in patients receiving chronic parenteral nutrition. *Ann. Intern. Med.* 98:910–14
53. Portale, A. A., Halloran, B. P., Morris, R. C. Jr., 1989. Physiologic regulation of serum concentration of 1,25-dihydroxyvitamin D by phosphorus in normal men. *J. Clin. Invest.* 83:1494–99

54. Portale, A. A., Halloran, B. P., Murphy, M. M., Morris, R. C. Jr. 1986. Oral intake of phosphorus can determine the serum concentration of 1,25-dihydroxyvitamin D by determining its production rate in humans. *J. Clin. Invest.* 77:7–12
55. Posner, A. S., Blumenthal, N. C., Boskey, A. L. 1986. Model of aluminum-induced osteomalacia: Inhibition of apatite formation and growth. *Kidney Int.* 29:S17–19 (Suppl.)
56. Price, P. A., Baukol, S. A. 1980. 1,25-dihydroxyvitamin D_3 increases synthesis of the vitamin K-dependent bone protein by osteosarcoma cells. *J. Biol. Chem.* 255:11660–63
57. Price, P. A., Parthemore, J. G., Deftos, L. J. 1980. New biochemical marker for bone metabolism. Measurement by radioimmunoassay of Bone GLA Protein in the plasma of normal subjects and patients with bone diseases. *J. Clin. Invest.* 66:878–83
58. Quarles, L. D., Castillo, S. A., Drezner, M. K. 1989. Aluminum-induced replication of osteoblast precursors: a potential mechanism underlying neo-osteogenesis. *J. Bone Miner. Res.* 4:S131 (Suppl.)
59. Quarles, L. D., Gitelman, H. J., Drezner, M. K. 1988. Induction of de novo bone formation in the beagle: A parathyroid hormone-dependent event. *J. Clin. Invest.* 83:1644–50
60. Raisz, L. G., Kream, B. E. 1983. Regulation of bone formation. *New Engl. J. Med.* 309:29–35
61. Robertson, J. A., Felsenfeld, A., Haygood, C., Llach, F. 1983. An animal model of aluminum-induced osteomalacia: Role of chronic renal failure and parathyroid hormone. *Kidney Int.* 23:327–35
62. Rodriguez, M., Felsenfeld, A. J., Llach, F. 1990. Aluminum administration in the rat separately affects the osteoblast and bone mineralization. *J. Bone Miner. Res.* 5:59–67
63. Rossi, T. M. 1986. Effects of total parenteral nutrition on the digestive organs. In *Total Parenteral Nutrition: Indications, Utilization, Complications, and Pathophysiological Considerations,* ed. E. Lebenthal, pp. 173–84. New York: Raven. 514 pp.
64. Rowe, J. C., Adams, N. D. 1989. *What is hypercalciuria in VLBW premature infants and what does it mean?* Presented at the Ann. Meet. North Am. Pediatr. Bone and Miner. Work. Group, 6th, Montreal
65. Rowe, J. C., Wood, D. H., Rowe, D. W., Raisz, L. G. 1979. Nutritional hypophosphatemic rickets in a premature infant fed breast milk. *New Engl. J. Med.* 300:293–96
66. Saitta, J. C., Lipkin, E. W., Howard, G. A. 1989. Acetate inhibition of chick bone cell proliferation and bone growth *in vitro*. *J. Bone Miner. Res.* 4:379–86
67. Schmidt, G. L., Baumgartner, T. G., Fischlschweiger, W., Sitren, H. S., Thakker, K. M., et al. 1986. Cost containment using cysteine HCl acidification to increase calcium/phosphate solubility in hyperalimentation solutions. *J. Parenter. Enter. Nutr.* 10:203–7
68. Sedman, A. B., Alfrey, A. C., Miller, N. L., Goodman, W. G. 1987. Tissue and cellular basis for impaired bone formation in aluminum-related osteomalacia in the pig. *J. Clin. Invest.* 79:86–92
69. Sedman, A. B., Klein, G. L., Merritt, R. J., Miller, N. L., Weber, K. O., et al. 1985. Evidence of aluminum loading in infants receiving intravenous therapy. *New Engl. J. Med.* 312:1337–43
70. Shike, M., Harrison, J. E., Sturtridge, W. C., Tam, C. S., Bobechko, P. E., et al. 1980. Metabolic bone disease in patients receiving long-term parenteral nutrition. *Ann. Intern. Med.* 92:343–50
71. Shike, M., Shils, M. E., Heller, A., Alcock, N., Vigorita, V., et al. 1986. Bone disease in prolonged parenteral nutrition: osteopenia without mineralization defect. *Am. J. Clin. Nutr.* 44:89–98
72. Shike, M., Sturtridge, W. C., Tam, C. S., Harrison, J. E., Jones, G., et al. 1981. A possible role of vitamin D in the genesis of parenteral nutrition-induced metabolic bone disease. *Ann. Intern. Med.* 95:560–68
73. Simmons, D. J., Seitz, P. K., Kidder, L., Klein, G. L., Waeltz, M., et al. 1991. Partial characterization of rat marrow stromal cells. *Calcif. Tissue Int.* In press
74. Slatopolsky, E., Hruska, K., Martin, K., Freitag, J. 1979. Physiologic and metabolic effects of parathyroid hormone. In *Hormonal Function and the Kidney,* ed. B. M. Brenner, J. Stein, pp. 169–92. New York: Churchill Livingstone
75. Smothers, R. L., Levine, B. S., Singer, F. R., Bryce, G. F., Mallon, J. P., et al. 1986. Relationship between urinary calcium and calcium intake during calcitriol administration. *Kidney Int.* 29:578–83

76. Vargas, J. H., Klein, G. L., Ament, M. E., Ott, S. M., Sherrard, D. J., et al. 1988. Metabolic bone disease of total parenteral nutrition: course after changing from casein to amino acids in parenteral solutions with reduced aluminum content. *Am. J. Clin. Nutr.* 48:1070–78
77. Vukicevic, S., Krempien, B., Stavljenic, A. 1987. Effects of 1α,25- and 24R,25-dihydroxyvitamin D_3 on aluminum-induced rickets in growing uremic rats. *J. Bone Miner. Res.* 2:533–45
78. Wood, R. J., Bengoa, J. M., Sitrin, M. D., Rosenberg, I. H. 1985. Calciuretic effect of cyclic versus continuous total parenteral nutrition. *Am. J. Clin. Nutr.* 41:614–19
79. Wood, R. J., Sitrin, M. D., Cusson, G. J., Rosenberg, I. H. 1986. Reduction of total parenteral nutrition-induced urinary calcium loss by increasing the phosphorus in the total parenteral nutrition prescription. *J. Parenter. Enter. Nutr.* 10:188–90
80. Zemel, M. B., Schuette, S. A., Hegsted, M., Linkswiler, H. M. 1981. Role of the sulfur-containing amino acids in protein-induced hypercalciuria in man. *J. Nutr.* 111:545–52